Title	Prospective Observational Study to Evaluate Usage of XGEVA®(denosumab) 120 mg for Prevention of Skeletal Related Events (SREs) in Patients with Bone Metastases and Solid Tumors in Routine Clinical Practice (X-TREME)
Version Identifier of the Final Study Report	20101312 Final 26 February 2018
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Active Substance	M05BX04 (denosumab)
Medicinal Product	XGEVA®
Product Reference:	EU/1/11/703/001 EU/1/11/703/002 EU/1/11/703/003
Marketing Authorization Holder(s)	Amgen Europe B.V. Minervum 7061 NL-4817 ZK Breda The Netherlands
Research Question and Objectives	The primary objective of this observational study was to estimate the persistence with XGEVA® at 24 weeks in patients with solid tumors accompanied by bone metastases and treated as per routine clinical practice.
Country of Study	Germany
Author	[redacted] AMGEN GmbH München Germany Tel.: [redacted]

Marketing Authorization Holder

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1. ABSTRACT

- **Title**

Prospective Observational Study to Evaluate Usage of XGEVA® (denosumab) 120 mg for Prevention of Skeletal Related Events (SREs) in Patients with Bone Metastases and Solid Tumors in Routine Clinical Practice (X-TREME)

- **Keywords**

Persistence after 24 weeks, XGEVA® treatment, solid tumors, bone metastases, observational study

- **Rationale and Background**

Despite treatment guidelines recommending the use of BP/XGEVA® for the prevention of SRE in advanced cancer patients with bone metastases, the proportion of patients receiving these in clinical practice is low. Suboptimal compliance and/or persistence with therapy for the prescribed duration may impact the therapeutic potential of XGEVA® treatment demonstrated in the clinical trials. Low adherence and high discontinuation rates can lead to suboptimal efficacy, putting patients at an increased risk of experiencing SREs. There is a paucity of data on persistence with XGEVA® for the prevention of SREs in adults with bone metastases from solid tumors in daily routine.

- **Research Question and Objectives**

This non-interventional Medical Practice Evaluation Program (MPEP) was descriptive in nature and there was no a priori hypothesis. Data collected in this study provided information to estimate persistence with XGEVA® at 24 and 48 weeks in routine clinical practice. Further secondary objectives were to estimate time to non-persistence to XGEVA®, to describe the primary and secondary persistence outcomes by tumor type, to describe demographics, disease characteristics, concomitant anticancer therapy and medical history of patients treated with XGEVA® as per routine clinical practice, to describe dose and frequency of calcium and vitamin D supplementation of patients treated with XGEVA® as per routine clinical practice.

- **Study Design**

This multi-center non-interventional prospective study of advanced cancer patients with bone metastases treated in routine clinical practice involved collection of patient-related information on the use of XGEVA®.

- **Setting**

Patient data were collected during routine scheduled hospital visits (both in- and out-patient). The duration of the entire study was approximately 88 months, i.e. from the first patient enrolled until the last visit of the last patient.

- **Subjects and Study Size, Including Dropouts**

Overall, 1276 patients were enrolled in 88 sites in Germany and 1128 patients could be included in the analysis. Patients were excluded from the analysis if the previous antiresorptive therapy was longer than 6 months ago (55 patients), had received no XGEAVA® or more than 2 XGEVA® treatments before inclusion (21 and 15 patients) or for other reasons (57 patients).

- **Variables and Data Sources**

Observational data were recorded via an e-CRF in a web-based secured electronic data capture system, at baseline and every 4 weeks thereafter for a maximum of 52 weeks during routinely scheduled hospital visits.

- **Results**

Of the 1128 patients included in the statisitcal analysis, 1008 patients could be assessed for persistency of XGEVA® use. The persistence with XGEVA® at 24 weeks (defined as receipt of at least 6 XGEVA® injections no more than 4 weeks (+7 days) apart, with permissible time windows of +2 weeks after the 24 weeks endpoint and ± 7 days for each injection relative to the previous injection) was 61.5% (620 of 1008 patients, 95% CI: [58.4%-64.5%]) across all solid tumor types. The most frequent reason for non-persistence at 24 weeks (defined as not meeting the aforementioned persistence at 24 weeks definition and associated permissible gaps) was violation of the time window, which was reported in 342 patients (33.9%). Only few patients were non-persistent due to premature termination (4.3%, 43/1008) or to not enough injections (0.3%, 3/1008). Enlarging the time window resulted in a higher value for persistency with XGEVA® at 24 weeks: 76.2% (n=990; 95% CI: [73.4%-78.8%]) across all tumor types. Kaplan-Meier analyses for the time to non-persistence yielded comparable estimates of patients being persistent at 24 weeks. Among the 928 patients who were assessed for persistency of XGEVA® use, persistence with XGEVA® at 48 weeks was found to be 37.7% (350/928, 95%CI: [34.6%-40.9%]) across all tumor types. Patients with lung and other cancer types tended to be less often persistent than patients with prostate and breast cancer. Kidney cancer patients showed highest rate of patients being persistent at 24 and 48 week.

- **Discussion**

In this study evaluating usage of XGEVA® (denosumab) 120 mg for prevention of skeletal related events (SREs) in patients with bone metastases and solid tumors in routine clinical practice, the persistence across all tumor types was 61.5 % (95% CI: [58.4%-64.5%]) at 24 weeks after treatment start and 37.7 % (95%CI: [34.6%-40.9%]) at 48 weeks across all tumor types. Using Kaplan-Meier methods, the estimated overall median time to non-persistence with XGEVA® in all enrolled 1128 patients was 33.3 weeks (95%CI: 31.7 weeks to 37.1 weeks), and the estimated probability of persistence with XGEVA® at 24 weeks was 61.4% which was well comparable to the calculated incidence of persistence with XGEVA® at 24 weeks. The risk of non-persistence with XGEVA® was greater in patients with visceral metastases (HR, 1.355; 95% CI: 1.138, 1.614; p=0.0006, Wald test). The median number of XGEVA® injections administered to study patients was 13. XGEVA® was well tolerated with only 6.4% of patients reporting at least one ADR and only very few leading to discontinuation.

- **Marketing Authorization Holder(s)**

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2. LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
ADR	Adverse Drug Reaction
AE	Adverse Events
AQA	Analgesics Score
CI	Confidence Interval
ECOG	Eastern Cooperative Oncology Group
e-CRF	electronic Case Report Form
EOS	End of Study
EQ-5D	EuroQol five Dimensions Questionnaire
FAS	Full Analysis Set
GFR	Glomerular Filtration Rate
HR	Hazards Ratio
IV	intravenous
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MPEP	Medical Practice Evaluation Program
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SD	Standard Derivation
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SRE	Skeletal-Related Events
TA/GCSM	Therapeutic Area Global Clinical Study Management
PRO	Patient-Reported Outcome
PT	Preferred term
VAS	Visual Analog Scale

3. INVESTIGATORS

A list of all collaborating institutions and investigators will be made available upon request.

4. OTHER RESPONSIBLE PARTIES

Sponsor	AMGEN GmbH Riesstraße 24 80992 München Germany
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Management of Adverse Events	[redacted] AMGEN GmbH München Germany Tel.: [redacted]
Statistical Analysis and Data Management	Metronomia Clinical Research GmbH Paul-Gerhardt-Allee 42 81245 München Germany

5. MILESTONES

Milestone	Planned Date	Actual Date	Comments
Start of data collection	January 2012	07 May 2012	First Patient In
End of data collection	December 2016	12 January 2017	Last Patient Out
Database hard lock	NA	05 May 2017	
Interim report		28 November 2014	Synoptic Report
Final report of study results		26 February 2018	Complete Report

6. RATIONALE AND BACKGROUND

Patients with metastatic bone disease or multiple myeloma frequently experience osteoclast-mediated bone destruction, resulting in clinically important complications such as fracture, need for radiation or surgery to bone, spinal cord compression, or hypercalcemia (Coleman 2004, Vogel et al 2004). These complications, collectively known as skeletal-related events (SREs) (Colemand 2001, Cook and Major 2001, Kosteva and Langer 2008, Yeh and Berenson 2006), lead to pain and decreased quality of life (Weinfurt et al 2005).

Denosumab, marketed under the name XGEVA®, is a human monoclonal antibody that binds to and neutralizes the receptor activator of nuclear factor kappa-B ligand, subsequently inhibiting osteoclast function and preventing generalized bone resorption and local bone destruction. Denosumab has been investigated in two phase 2 trials in patients with advanced cancer accompanied by bone metastasis and in one phase 2 trial in patients with multiple myeloma. These trials have shown that treatment with denosumab in a 30–180 mg dose range, administered every 4 or 12 weeks, was associated with a rapid and sustained suppression of bone turnover markers and a delay in manifestation of SREs, similar to that seen with intravenous bisphosphonates.

In three pivotal, phase 3 trials that compared the effectiveness of XGEVA® versus zoledronic acid in delaying SREs, XGEVA® was found to result in a more clinically meaningful improvement in comparison with zoledronic acid. The dose regimen of XGEVA® and zoledronic acid in these trials was once every four weeks, the former as a 120 mg subcutaneous injection, and the latter via a 15-minute intravenous infusion after adjusting the dose for kidney function in patients. In patients with breast or prostate cancer accompanied by bone metastases, XGEVA® was superior to zoledronic acid in reducing the risk of SREs (Stopeck et al 2010, Fizazi et al 2011). In patients with bone metastases due to other solid tumors or multiple myeloma, XGEVA® was non-inferior to zoledronic acid in reducing the risk of SREs (Henry et al 2011). An integrated analysis of all three studies revealed that XGEVA® was superior to zoledronic acid in delaying time to first on-study SRE by 8.2 months [median time to first skeletal related event of 27.6 months for XGEVA® and 19.4 months for zoledronic acid, ($p<0.0001$)]. Moreover, XGEVA® was also found to be superior to zoledronic acid in delaying time to first-and-subsequent on-study SRE by 18 percent ($p<0.0001$). In patients with mild or no pain at baseline, time to worsening pain was delayed for XGEVA® compared to zoledronic acid (198 versus 143 days) ($p=0.0002$). The time to pain improvement was similar for

XGEVA® and zoledronic acid in each single study and the integrated analysis. Overall rates of adverse events (AEs) and serious AEs were generally similar between XGEVA® and zoledronic acid. Osteonecrosis of the jaw was seen in approximately 1–2 percent of patients, with no statistically significant difference between treatment arms. Hypocalcemia was more frequent in the XGEVA® treatment group. Overall survival and progression-free survival were similar between arms in all three trials (Lipton et al 2010).

Despite treatment guidelines recommending the use of BP/XGEVA® for the prevention of SRE in advanced cancer patients with bone metastases, the proportion of patients receiving these in clinical practice is low (Oster et al 2013). Oral bisphosphonates are associated with low compliance and are contraindicated in patients with disease of the upper gastrointestinal tract. In addition, discontinuation rates of over 50% and low treatment persistence have been reported with intravenous (IV) bisphosphonates. Suboptimal compliance and/or persistence with therapy for the prescribed duration may impact the therapeutic potential of XGEVA® treatment demonstrated in the clinical trials. Low adherence and high discontinuation rates can lead to suboptimal efficacy, putting patients at an increased risk of experiencing SREs (Hagiwara et al 2014). There is a paucity of data on persistence with XGEVA® for the prevention of SREs in adults with bone metastases from solid tumors in daily routine. This multi-center, non-interventional, prospective study was conducted to evaluate the usage of XGEVA® for the prevention of SREs in adults with bone metastases from solid tumors in routine clinical practice.

7. RESEARCH QUESTION AND OBJECTIVES

This non-interventional Medical Practice Evaluation Program (MPEP) was descriptive in nature and there was no a priori hypothesis. The MPEP was initiated in order to collect information about the use of XGEVA® in routine clinical practice in treatment of adults with bone metastases in solid tumors. Data collected in this study provided information to estimate persistence with XGEVA® at 24 and 48 weeks in routine clinical practice. Moreover, the MPEP collected data on demographics, disease characteristics, medical history, and concomitant anticancer therapy in solid tumor patients with bone metastases. Most of the data were collected along routine clinical care, and any collection of patient reported outcomes were kept at minimum and did not expose the patient to extensive burden.

7.1 Primary Objective

The primary objective of this observational study was to estimate the persistence with XGEVA® at 24 weeks in patients with solid tumors and bone metastases treated as per routine clinical practice.

7.2 Secondary Objective

The secondary objectives of this study were to:

- Estimate the persistence with XGEVA® at 48 weeks as per routine clinical practice.
- Estimate time to non-persistence to XGEVA®.
- Describe the primary and secondary persistence outcomes by tumor type.
- Describe demographics, disease characteristics, concomitant anticancer therapy and medical history of patients treated with XGEVA® as per routine clinical practice.
- Describe dose and frequency of calcium and vitamin D supplementation of patients treated with XGEVA® as per routine clinical practice.

7.3 Exploratory Objective

The exploratory objectives of this study were to:

- Describe changes in individual pain scores between baseline and week 24 during use of XGEVA® as per routine clinical practice.

- Describe changes in individual pain medication between baseline and week 24 during use of XGEVA® as per routine clinical practice.
- Collect patient-reported outcomes describing problems with mobility, self-care, daily activities, pain/discomfort, and anxiety/depression (EuroQol five Dimensions Questionnaire [EQ-5D]).
- Collect data on adverse drug reactions (ADR) to XGEVA®

8. AMENDMENTS AND UPDATES

The original observational plan was dated on 14 December 2011. There were 5 updates of the observational plan as detailed in the table below.

Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
2	29 November 2012	Title page	• Change in responsibilities for project coordination and ADR handling.	NA
		Section 6	• Definitions of ADRs, SAEs, SADRs, AEs of special interest and other events relevant to the safety of XGEVA® were clarified. • Instructions which of these events need to be reported within which timelines were clarified. • Examples for questionnaires to report exposure XGEVA® during pregnancy or nursing were added.	
3	27 February 2014	Title page	• Change in responsibilities for project coordination and ADR handling.	NA
		Abstract and Section 3.4 Section 7.4	• Prolongation of project end from December 2015 to December 2017, of inclusion of last patient to October 2015 and of completion of last patient to December 2016 • Recruitment was prolonged from 2 to 4 years	
4	14 March 2014	Sections 3.4, 5.5.2 and 5.5.3 Section 6	• The planned duration of the project was extended. The last patient was planned to be included end of 2015 and the end of the observation time was estimated to the end of 2016 • Specification of Other events relevant to the safety of XGEVA® was clarified. The reporting timeline of these other relevant events was explicitly specified to be 1 working day after gaining knowledge of the event.	NA

Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
5	9 May 2016	Cover page	• Change in responsibilities for project coordination, deletion of [redacted]	NA
		Synopsis-sample size and sections 5.2	• Information about actual sample size until end of recruitment in December 2015 was added: Until the end of recruitment in December 2015, 1257 patients were included in a total of 88 recruiting centers in this observational study.	The number of patients is lower than originally planned. Therefore, the number of actual patients was added.
		6.2.1	• A statement was added, why collection of AEs that are not related to XGEVA®, is not required for this study.	NA
6	10 October 2016	Cover page	• Change in sponsor address	Move of sponsor
		Synopsis-sample size and sections 5.2	• Sample size actually recruited was amended to 1258 patients.	

9. RESEARCH METHODS

9.1 Study Design

This multi-center non-interventional prospective study of advanced cancer patients with bone metastases treated in routine clinical practice involved collection of patient-related information on the use of XGEVA® and data on demographic information, disease characteristics, concomitant anti-cancer therapy and medical history of these patients. Patient data were collected at enrolment into the study and during oncologic treatment, along routine clinical practice. Collection of patient-reported outcomes were kept at minimum and did not expose the patient to extensive burden.

9.1.1 Primary Endpoint

- Persistence (yes/no) to XGEVA® at 24 weeks.

9.1.2 Secondary Endpoint

- Persistence (yes/no) to XGEVA® at 48 weeks.
- Time to non-persistence.
- Primary and secondary persistence outcomes by tumor type.
- Patient characteristics at baseline assessed for description of patients treated with XGEVA® as per clinical routine and their association with persistence / non-persistence.
- Dose and frequency of calcium and vitamin D supplementation at baseline and throughout treatment with XGEVA®.

9.1.3 Exploratory Endpoint

- Pain scores on a 10-item visual analog scale (VAS) at baseline and every 4 weeks for up to 24 weeks [or end-of-study (EOS), whichever came first].
- Pain medication and 8-point scale analgesics score (AQA) at baseline and every 4 weeks for up to 24 weeks (or at EOS, whichever came first).
- EQ-5D at baseline and every 12 weeks for up to 52 weeks (or at EOS, whichever came first).
- ADRs during the time period starting with the first XGEVA® application and after each subsequent application for up to 52 weeks (or at EOS, whichever came first).

9.2 Setting

This observational study was conducted at 88 sites in Germany. All participating sites were selected by the medical team (TA/GCSM) following the existing Amgen quality standards for observational research. Selection was based on estimated number of patients, the type of site, and their geographical location. The site selection process ensured a geographically balanced distribution across Germany. For all potential sites, a mandatory site evaluation visit was conducted and a monitoring plan was implemented.

Sites that were inactive for 6 months from the time of initiation were considered to be closed. Details on all centers that were selected but did not participate were recorded, including the primary reason for non-participation.

Upon independent ethic committee approval of the project plan, patients were recruited across 88 sites over a period of approximately 76 months.

Patient data were collected during routine scheduled hospital visits (both in- and out-patient), using a secure web-based electronic data capture system, at baseline and at every 4 weeks thereafter for a maximum of 52 weeks.

The duration of the entire study was approximately 88 months, i.e. from the first patient enrolled until the last visit of the last patient.

At the individual centers, patients fulfilling the inclusion and exclusion criteria were included in the study. An enrolment log file was used to collect basic patient information (age, sex, tumor, planned chemotherapy, outcome of screening, and reasons for non-enrolment, if applicable) of all patients meeting the selection criteria.

Subject enrollment began on 07 May 2012 and the last subject last visit was on 12 January 2017. Patient data were collected at enrolment and during oncologic treatment up to 30 days after the latest dose of XGEVA® or until the patient completed the study, died, was ‘lost to follow-up’, or withdrew informed consent, whichever occurred first.

No laboratory, diagnostic, or therapeutic procedures other than those currently performed as part of the patient’s routine care were performed.

The study ended when the last patient remaining on the study either completed the observation period, died, was ‘lost to follow-up’, or withdrew informed consent, whichever occurred first.

9.3 Subjects

The study population of this observational study was defined according to the summary of product characteristics (SmPC) of XGEVA® as patients with solid tumors and bone metastases. At each participating site, patients who met the selection criteria were enrolled as a study subject. Overall, 1276 patients were enrolled in 88 sites in Germany. Since this is a non-interventional study, the decision to treat with XGEVA® was freely undertaken by the clinician prior to consideration of the patient to be included into the observational study. Therefore, treatment administration was independent and dissociated from participation in the study.

9.3.1 Inclusion Criteria

- Patients aged 18 years or older,
- Patients diagnosed with bone metastasis of breast, prostate, lung cancer, and other solid tumors,
- Patients currently treated with XGEVA® (at most 2 injections prior to enrolment)
- Patients with Eastern Cooperative Oncology Group (ECOG) staging 0-2,
- Written informed consent to allow transfer of personal data.

9.3.2 Exclusion Criteria

- Patients diagnosed with multiple myeloma,
- Patients that previously received XGEVA® for more than 3 months in investigational clinical studies or clinical routine,
- Patients previously treated for more than 6 months with antiresorptive treatments in clinical studies or clinical routine,
- Patients previously treated with radionuclides (e.g. strontium-98, samarium-153, radion-223),
- Parallel enrolment of the patient in an investigational drug trial for the treatment / prevention of bone metastases and SREs.
- Patients with severe, untreated hypocalcemia (e.g. Common Terminology Criteria for Adverse Events [CTCAE] Grade 3 or higher); pre-existing hypocalcemia must have been corrected prior to initiating therapy with XGEVA®,
- Hypersensitivity to the active substance or any of the excipients of XGEVA®.

9.4 Variables

The following data was collected during this observational study. Except for the patient reported outcome (questionnaire) all data were collected on the electronic Case Report Form (e-CRF).

- Investigator's specialty, type of institution (practice / clinic), number of patients with metastasized solid tumors treated in the last year
- In- and exclusion criteria
- Demographics: year of birth, sex
- Tumor type: breast, prostate, lung, kidney, other and Classification of Malignant Tumors (TNM) status at initial diagnosis, further staging for lung cancer (extended or limited disease)
- Details on visceral and bone metastases
- Previous and on-study antineoplastic therapy: surgeries, radiotherapies, chemotherapies, anti-hormonal therapies
- Presence of previous and on-study bone pain and tumor–induced hypercalcemia
- Occurrence and treatment of previous and on-study SREs (skeletal complications defined as one or more of the following: radiation therapy to bone including use of radioisotopes, surgery to bone, pathological fracture or spinal cord compression).
- ECOG status before XGEVA® treatment start
- Concomitant disease
- Previous antiresorptive therapies and concomitant therapies (e.g., vitamin D and calcium supplementation, bisphosphonate therapy [in categories: "yes" versus "no"]).
- History of renal impairment and on-study renal function [e.g. creatinine, calculated clearance, serum calcium, glomerular filtration rate (GFR) as per clinical routine]
- Pain score (10-item VAS)
- Usage of analgesic medication and 8-point scale analgesics score (AQA)

- Healthcare interactions (e.g., emergency room/trauma center/urgent care, outpatient and home visits, hospitalizations), concomitant medications, imaging procedures and other information
- Reported adverse drug reactions (ADR) to XGEVA®
- Details of treatment with XGEVA® including reasons for patient ending treatment with XGEVA®
- Reason for study termination
- Study patients were asked to complete a patient-reported outcome (PRO) questionnaire. The validated questionnaire EQ-5D (i.e. 5 questions and 1 VAS) was used; the assumed burden for patients to complete these questionnaires was 10-15 min.

An overview on the schedule of data collection is provided in the observational plan (see Annex 2)

9.5 Data Sources and Measurement

Upon enrolment into the study, basic patient information (age, sex, tumor, planned chemotherapy, outcome of screening, and reasons for non-enrolment, if applicable) were collected in an enrolment log file for all patients. Observational data were recorded via an e-CRF in a web-based secured electronic data capture system “Clincase” (by Quadratec Data Solutions Ltd., www.clincase.com), at baseline and every 4 weeks thereafter for a maximum of 52 weeks during routinely scheduled hospital visits.

9.6 Bias

For this observational study measures to avoid bias have been taken.

All participating sites were selected by the Amgen medical team according to internal quality standards. The site selection ensured a (i) geographically balanced distribution of German sites, (ii) representative of practice (not excluding difficult patients), (iii) different center sizes, and (iv) different physician specialties (oncologists, gyneco-oncologists, uro-oncologists). In all sites, a site evaluation visit was mandatory and a monitoring plan was implemented. Moreover, since treatment administration was independent and dissociated from participation in the study, it was assumed to not impart bias on patient selection.

9.7 Study Size

It was planned to enroll around 1400 patients at approximately 80 sites in Germany in order to minimize bias, and accurately estimate the primary and secondary endpoints.

The actual sample size for this study was 1276 patients who were enrolled in 88 sites across Germany.

No formal hypothesis was tested and the primary analysis was descriptive in nature. The sample size therefore has not been assessed in terms of statistical power but rather the expected level of precision for the incidence of patients persisting with XGEVA® at any time point and by tumor type. It was assumed that studied tumor types breast cancer, prostate cancer, lung cancer and other solid tumors take respectively 35%, 35%, 20% and 10% of the enrolled population. Different tumor type populations were expected to show different dropout rates on target time points (24 weeks and 48 weeks after initiation of the therapy). For breast cancer, the proportions were assumed to be 15% for 24 weeks and 30% for 48 weeks, for prostate cancer 25% and 50%, for other lung cancer and other solid tumors 50% and 90%, respectively.

The planned sample size was based on the objective to estimate the 95% confidence interval (CI) around the proportion of persistence. The proportion of persistent patients was determined by not taking patients into account who dropped out of the study. A precision (half-width of the 95% CI) of 3.1% was deemed appropriate for the chosen primary endpoint in the overall patient population, which resulted in a sample size of approximately 1400 patients for an assumed proportion of 60% of patients persistent to XGEVA® after 24 weeks from start of treatment.

The sample size allowed for an estimate of precision for each of the covariates; prostate cancer, breast cancer, lung cancer and other solid tumors.

This sample size also allowed the estimation of the key secondary endpoint proportion of patients persistent to XGEVA® after 48 weeks from start of treatment: The assumed proportion of 30% of patients persistent to XGEVA® after 48 weeks could be estimated with a precision of 3.6% when an overall drop-out rate of 55% after 48 weeks was taken into account. The sample size allowed for an estimate of precision for each of the covariates; prostate cancer, breast cancer, lung cancer and other solid tumor.

9.8 Data Transformation

The principal aim of this prospective observational study was to demonstrate the persistence with XGEVA®, when prescribed according to SmPC, in routine clinical practice in Germany in different therapeutic indications. Therefore, the statistical analyses performed for the study were descriptive in nature. No formal prospective hypotheses were tested.

Collected data were analyzed through Statistical Analysis Software (SAS) programming according to Metronomia standards as defined in BM-08-SOP "Statistical Analysis and Programming" and related work instructions. Continuous outcomes were summarized by number of non-missing values, mean, median, standard deviation (SD), lower and upper 25th quartiles and minimum and maximum. For categorical outcomes, the number and percentage of patients in each category are presented.

The production environment for statistical analyses consisted of Amgen-supported versions of statistical analysis software, specifically the SAS system in version 9.3 or higher. Data were stored in SAS data sets. Results were stored as Word and PDF files. Both data and results were transferred to Amgen by secure file transfer.

9.9 Statistical Methods

A full description of statistical analysis methods is available in the statistical analysis plan (SAP) (Annex 1).

9.9.1 Main Summary Measures

In general, the analysis of persistence was based on the full analysis set (FAS) but excluded those patients who died, withdrew informed consent or who were lost to follow-up before the persistence assessment. The analyses of the primary and secondary endpoints are provided in Sections 10.3 and 10.4.1. Variables associated with the primary and secondary endpoints were displayed in listings. Assessments of the secondary endpoints were also presented in the listings.

9.9.1.1 Primary Outcome

- Persistence (yes/no) with XGEVA® at 24 weeks – a patient was considered persistent with XGEVA® at 24 weeks if patient received at least 6 XGEVA® injections no more than 4 weeks (+7 days) apart. A time window of +2 weeks was allowed after the 24 weeks endpoint. A time window of ± 7 days will be allowed for each injection relative to the previous injection. Therefore, patients who finished at least 6 XGEVA® injections until week 26 (= up to 182 days) and who had respected the permissible time window for each single injection were defined as persistent at 24 weeks.

In addition to the number of patients being persistence the reason for being non-persistent was analyzed:

- Premature termination (adverse event)
- Premature termination (patient refuses to take medication)
- Premature termination (physician's decision)

- Premature termination (other)
- Not enough injections
- Violation of time windows.

Furthermore, the number of violated time windows (1, 2, 3 or more than 3 time windows) was tabulated.

9.9.1.2 Secondary Outcome

- Persistence (yes/no) with XGEVA® at 48 weeks – a patient was considered persistent with XGEVA® at 48 weeks if patient receives at least 12 XGEVA® injections no more than 4 weeks (+7 days) apart. A time window of +7 weeks was allowed after the 48 weeks endpoint. A time window of ± 7 days was allowed for each injection relative to the previous injections. Therefore, patients who finished at least 12 XGEVA® injections until week 55 (= up to 385 days) and who had respected the permissible time window for each single injection were defined as persistent at 48 weeks.
- Time to non-persistence was calculated as the time in days between the date of the first injection and the date of last injection received during the period where the patient was still classified as persistent plus 4 weeks (28 days) for patients who are non-persistent at any time during the study as defined below:
    - Patients refused to receive further XGEVA® treatment.
    - Physician had decided to stop treatment.
    - Treatment had been stopped because of an ADR
    - Patients showed lack of compliance with the scheduled treatment visits (see 9.9.1.1).
    - Patients were lost to follow-up.

  Patients were regarded as censored if:

    - they had died (censoring date was equal to date of death).
    - they had finished treatment per protocol after 52 weeks (censoring date was equal to date of last injection).
    - they had withdrawn informed consent (censoring date was equal to date of withdrawal of consent).

Patients were only censored if the censoring day was before time to non-persistence.

- Primary and secondary persistency outcomes by tumor type – The outcome calculations were repeated for each tumor type
- Patient characteristics at baseline assessed for description of patients treated with XGEVA® as per clinical routine and their association with persistence/non-persistence
- The dose and frequency of calcium and vitamin D supplementation at baseline and throughout treatment with XGEVA® were tabulated, and displayed in the listings.

9.9.1.3 Exploratory Outcomes:

- Pain scores on a 10-item VAS at baseline and 4-weekly for up to 24 weeks (or at EOS, whichever came first) were tabulated, and displayed in the listings.
- Pain medication and 8-point scale analgesics score (AQA) at baseline and 4-weekly for up to 24 weeks (or at EOS, whichever came first) were tabulated, and displayed in the listings.
- EQ-5D patient-reported outcomes of quality of life at baseline for up to 52 weeks (or at EOS, whichever came first) were tabulated, and displayed in the listings.
- Adverse drug reactions from first XGEVA® injection up to 52 weeks (or at end of study, whichever comes first) were tabulated. The Medical Dictionary for Regulatory Activities (MedDRA) version 15.1 was used to code all adverse drug reactions (ADRs) to a system organ class (SOC) and a preferred term (PT). Serious ADRs, fatal ADRs, ADRs leading to withdrawal of product and adverse events which were suspected osteonecrosis of the jaw events were tabulated by SOC and PT in descending order of frequency. Furthermore, the time from XGEVA® initiation to suspected osteonecrosis of the jaw event was summarized by Kaplan-Meier methods.

9.9.2 Main Statistical Methods

This was an observational study to estimate the persistence [including 95% confidence intervals (CI)] with XGEVA® at 24 or 48 weeks in the study population consisting of patients with solid tumors and bone metastases treated as per routine clinical practice.

The statistical analyses were based in general on the FAS. For the evaluation of the primary and the first secondary outcome measure the basis of analysis was the FAS as well, but excluding patients who died, withdrew informed consent or who are lost to

follow-up before the respective persistence assessment. All analyses were descriptive only.

The FAS was defined as the set of all patients who were documented in the e-CRF and who received at least one injection of XGEVA®.

Summary statistics were provided for all outcomes for:

- Overall
- Covariates

Covariates were defined in context of the observational study as:

- Tumor type (breast cancer, prostate cancer, lung cancer, kidney cancer, other solid tumors)
- Previous antiresorptive therapy (yes/no)
- Systemic antineoplastic therapy (by type).

Endpoints of a categorical nature (e.g. yes/no) were summarized as the frequencies and proportions (percentages) based on the appropriate analysis set denominator. For the primary and secondary endpoints, a 95% confidence interval (CI) (exact 2-sided Clopper-Pearson) was calculated around the proportions responding categories, as a measure of precision.

Endpoints of continuous nature were described by number of non-missing values, mean, median, standard deviation (SD), lower and upper 25th quartiles and minimum and maximum.

Detailed statistical methods used in this study are provided in the SAP Section 10 (Annex 1).

9.9.3 Missing Values

In general, missing or incomplete data were not replaced or imputed. Further details are provided in the Statistical Analysis Plan (SAP; Annex 4). The actual responses from the individual variables in the standardized data collection form were displayed in the Listings, including missing if applicable.

9.9.4 Sensitivity Analyses

Sensitivity analyses were conducted on data used to summarize persistence at scheduled time-points i.e. 24 and 48 weeks, as well as on data used to calculate time to non-persistence and proportional hazards analysis of time to non-persistence.

- A time window of ± 14 days (instead of ± 7 days) was allowed for each injection relative to the previous injection for persistence (yes/no) to XGEVA® at 24 weeks and after 48 weeks.
- A time window of +4 weeks (instead of +2 weeks) was allowed after the 24 weeks endpoint.
- A time window of +10 weeks (instead of +7 weeks) was allowed after the 48 weeks endpoint.

For time to non-persistence, two sensitivity analyses were performed, whereby the same definition as for time to non-persistence was valid except for the following:

- Sensitivity analysis 1: Lost to follow-up patients were censored at time of last XGEVA® injection.
- Sensitivity analysis 2: For 'patient is still classified as persistent' the definition of 'persistence – sensitivity analysis' (see above) was used and lost to follow-up patients were censored at time of last XGEVA® injection.

9.9.5 Amendments to the Statistical Analysis Plan

There were no amendments to the SAP.

9.10 Quality Control

Study data was entered by investigators and/or their delegates directly into the e-CRF. An investigator manual was provided as a reference document describing the functionalities of the e-CRF. Consistency and plausibility of data was controlled and verified by programmed rules (constraints, edit checks, derivations) and manual checks. In addition, data were reviewed for adherence to the observational plan and Good Clinical Practice guidelines (as applicable by local law). Constraints enabled specific data items or sets of data items if specific conditions were met, e.g. Stop date of a concomitant medication was requested only if ongoing = "no". Programmed edit checks ran automatically during data entry. The checks indicated inconsistent and implausibility data as "failed edit checks". A manual and medical data review was performed by qualified staff members, utilizing specific data views and listings. E.g. all text entries were scrutinized for the occurrence of adverse events and inconsistencies within the e-CRF. If necessary, manual data queries were created. To resolve any questions arising from the clinical data management review process, data queries and/or study center, queries were created in the electronic data capture system database for study center resolution and closed by qualified reviewers. Data could only be edited by users

with the according access rights to the e-CRF. All data entries and modifications were tracked in the audit trail.

Special attention was paid to planning and performance of quality control measures as documented in the QC plan for the analysis of this study (see BM-08-WIN03 “How to Plan and Document QC for Statistical Analysis”). Tables, figures and listings were produced with validated standard macro programs where standard macros produce the specified outputs.

10. RESULTS

10.1 Participants

A total of 1276 patients were enrolled in the study from 88 sites across Germany. Of these, 1128 (88.4%) patients were included in the full analysis set (FAS) (Table 2). Patients with known tumor type were nearly all included in the FAS, whereas patients with missing tumor type were not included in the FAS (N=148). The most frequent reason for exclusion from FAS was “previous antiresorptive therapy was longer than 6 month” (55 patients), followed by “other” (30 patients) (see Table 1).

In general, this analysis set was used to analyze all of the outcomes in this study. For the evaluation of the primary and the first secondary outcome measure, the basis of analysis was the FAS as well; but patients who had died, had withdrawn informed consent or who were lost to follow-up before the respective persistence assessment were excluded from these analyses.

The most common cancer type for patients in the FAS was breast cancer (509 patients, 45.1%). In addition, patients with prostate cancer (294 patients, 26.1%), lung cancer (159 patients, 14.1%), kidney cancer (50 patients, 4.4%), and other cancer types (116 patients, 10.3%) were included in the study (Table 3). The specifications of other cancer types are summarized in Table 15.2.2.2 (Annex 1).

Out of the 1128 patients included in FAS, 78.4% (884 patients) and 59.0% (665 patients) of the patients across all solid tumor types were still receiving treatment with XGEVA® at 24 weeks and 48 weeks after enrolment, respectively. Among the tumor types still on-treatment, the proportion of breast, prostate and kidney cancer patients remained relatively high, with 71.5% (at 48 weeks) vs 86.6% (at 24 weeks), 69.7% (at 48 weeks) vs 88.1% (at 24 weeks), 50.0% (at 48 weeks) vs 76.0% (at 24 weeks), respectively. In contrast, the proportion of lung cancer patients still on-treatment was 22.6% (at 48 weeks) vs 49.7% (at 24 weeks) (Table 4).

A total of 54.6% patients across all solid tumor types in the FAS completed their observation period, which was planned to be 52 weeks for each patient. 19.0% of patients terminated the study prior to completing 24 weeks of treatment, 1.6% of patients between 24 and 26 weeks, 16.5% of patients later than 26 weeks and prior to 48 weeks, and 8.3% of patients at 48 weeks or later. The proportion of patients who completed the observation period was relatively high for breast, prostate and kidney cancer patients, with 68.2%, 63.6%, 46.0%, respectively. In contrast, the proportion of patients who

completed the study within the group of patients with lung cancer or other cancer type was only 17.6%, 26.7%, respectively.

The most common reason for study termination in patients who did not complete the study was death (25.0%) followed by patient not showing up any more (6.9%). The reasons were similar for those patients who terminated already during the first 24 weeks. The different tumor cohorts were comparable with respect to the reason for termination.

10.2 Descriptive Data

Demographics and other Baseline Characteristics

10.2.1.1 Demographics

Patient demographic data on age and gender are presented in Table 5.

Overall, 55.6% women and 44.4% men were included in FAS. A majority (32.6%) of the patients were in the age range 65 to <75 years, followed by 27.4% in the range ≥75 years and 25.6% in the range 55 to <65 years.

In the breast cancer cohort, patients enrolled were 99.0% women and 1.0% men. A majority (29.3%) of the patients were in the age range 55 to <65 years, followed by 28.9% in the range 65 to <75 years and 19.4% in the range ≥75 years.

In the prostate cancer cohort, patients enrolled were 100.0% men and 0.0% women as expected. A majority (50.7%) of the patients were in the age range ≥75 years, followed by 35.0% in the range 65 to <75 years and 13.3% in the range 55 to <65 years.

In the lung cancer cohort, patients enrolled were 66.7% men and 33.3% women. A majority (37.1%) of the patients were in the age range 65 to <75 years, followed by 33.3% in the range 55 to <65 years and 16.4% in the range ≥75 years.

In the kidney cancer cohort, patients enrolled were 66.0% men and 34.0% women. A majority (40.0%) of the patients were in the age range 65 to <75 years, followed by 30.0% in the range 55 to <65 years and 18.0% in the range ≥75 years.

In the cohort with other cancer types, patients enrolled were 54.3% men and 45.7% women. A majority (33.6%) of the patients were in the age range 65 to <75 years, followed by 28.4% in the range 55 to <65 years and 22.4% in the range ≥75 years.

10.2.1.2 Tumor Diagnosis and Metastases

The duration from the initial tumor diagnosis to the first XGEVA® application is summarized in years categorized by tumor type for the FAS (Table 6). Across all solid tumor types, a total of 484 patients (42.9%) had been diagnosed with the tumor less than 1 year before first XGEVA® application. Three patients (0.3%) were diagnosed with prostate cancer during the course of the study. Of the 640 patients (56.8%) who had had their tumor diagnosis more than 1 year prior to start of XGEVA® therapy, the duration from tumor diagnosis from tumor diagnosis to start of XGEVA® was between 1 and 2 years for 9.1% (n=103) patients, between 2 and 5 years for 17.4% (n=196) patients, between 5 and 10 years for 16.8% (n=189) patients and 10 years or longer for 13.5% (n=152) patients.

For patients with breast cancer, the tumor diagnosis tended to be longer ago compared to patients with other solid tumors. In this group, 30.5% (n=155) of patients had had the initial diagnosis within the year preceding the start of XGEVA® therapy, and it was more than 5 years ago for 44.2% (n=225) of patients with breast cancer.

Around 40% of patients with prostate cancer, kidney cancer and other cancer types had had the initial tumor diagnosis less than 1 year prior to the start of XGEVA® therapy and the diagnosis was more than 5 years ago for 29.3% (n=86) for patients with prostate cancer, 22.0% (n=11) for patients with kidney cancer, and 15.5% (n=18) for patients with other cancer types.

Patients with lung cancer had by far the shortest duration from the tumor diagnosis to start of XGEVA®. In this patient cohort, 87.4% (n=139) patients had had the initial tumor diagnosis within the year preceding the start of XGEVA® therapy.

The durations from the diagnosis of any metastases and of bone metastases to the first XGEVA® application are summarized in years in Table 7 and Table 8, respectively.

For the substantial majority of patients in the FAS (82.5%, n=929), the diagnosis of **any** metastases had taken place during the last year prior to the first XGEVA® application. The proportions of patients with the diagnosis of metastases between 1 and 2 years ago, between 2 and 5 years ago, and between 5 and 10 years ago were 6.2% (n=70), 6.1% (n=69), and 2.9% (n=33), respectively (Table 7). The diagnosis of **bone** metastases had taken place during the last year prior to the first XGEVA® application for nearly all (90.1%, n=1015) of patients in the FAS (Table 8).

The duration from initial diagnosis of any metastases and of bone metastases was similar across the different tumor types. However as seen for the initial tumor diagnosis, patients with lung cancer had the shortest times between diagnosis and start of XGEVA® therapy, whereas in kidney cancer patients, there were 14 patients with a duration from diagnosis of any metastases and start of XGEVA® therapy between 2 and 5 years (Table 7).

Bone metastases were diagnosed by asymptomatic imaging in a majority (968 patients, 85.9%) of the FAS across all tumor types, as well in solid tumor type cohorts. The remaining 133 patients (11.8%) with known type of diagnosis were diagnosed via symptomatic presentation. Distribution of bone metastases was largely oligometastatic i.e. with >3 metastases per region, irrespective of solid tumor type as reported in a total of 646 patients (57.3%). This pattern was also observed in patients with breast and prostate cancer with oligometastatic distribution in 62.3% (n=317) and 63.9% (n=188) of patients, respectively. In contrast, patients in the lung cancer, kidney cancer, and other cancer type cohorts had a singular distribution pattern in 47.8% (n=76), 60.0% (n=30), and 52.6% (n=61) of patients within the respective tumor-specific cohorts (Table 9).

In the FAS, the most frequent locations of bone metastases were reported to be in the thoracic spine (53.8%, n=587), ribs (48.1%, n=525), lumbar spine (47.9%, n=523), and the pelvis (43.2%, n=472) (Table 10).

In patients with lung cancer, most often the pelvis, the ribs and the lumber spine were affected by metastases (pelvis: 63.9%, n=184; ribs: 55.9% n=161; lumbar spine (53.5%, n=161) (Table 10).

10.2.1.3 Previous Skeletal-Related Event and Tumor-Induced Hypercalcemia

Previous tumor-induced hypercalcemia was not considered as an SRE; the latter being defined as SREs without tumor-induced hypercalcemia.

In the FAS, a total of 9.3% patients (n=105) had experienced only previous SRE(s) prior to enrolment into the study. The proportion of previous SREs within the tumor-specific cohorts differed; with a reported rate of 10.4% patients (n=53) within the breast cancer cohort, 11.9% patients (n=19) within the lung cancer cohort, 4.8% patients (n=14) within the prostate cancer cohort, 6.9% patients (n=8) within other cancer types and 22% patients (n=11) within the kidney cancer cohort (Table 11).

Only very few patients (0.5%, n=6) had experienced previous tumor–induced hypercalcemia prior to the study and similarly, only 0.5% of patients (n=6) had reported both prior tumor-induced hypercalcemia and SREs prior to the study.

A majority (86.4%, n=89) of the patients with previous SRE had the SRE diagnosed within the year prior to enrolment, and this pattern was observed irrespective of tumor type (Table 12).

10.2.1.4 ECOG Performance Status and Concomitant Diseases

About one third (31.5%, n=347) of the patients in FAS had an ECOG status of '0' before start of therapy. More than half (54.8%, n=604) had an ECOG performance status of '1'. ECOG performance status was well comparable for patients with breast cancer, prostate cancer, lung cancer and other cancer types. In patients with kidney cancer an ECOG status of '0' was observed only in 10.4% (n=5), and of '1' in 79.2% (n=38) of patients (Table 13).

At least one concomitant diseases were reported in 38.7% of patients in the FAS (n=437). The lowest proportion of patients reporting any concomitant disease was seen in patients with breast cancer (25.9%, n=132); and the highest proportion was seen in patients with lung cancer (60.4%, n=96) (Table 13).

Concomitant diseases are summarized on a preferred term level in Table 14. As required by the inclusion criteria, all patients in the FAS had a tumor diagnosis. The most common other concomitant diseases in FAS patients were diabetes (16.9%, n=191), moderate to severe kidney disease (9.9%, n=112), and chronic lung disease (9.1%, n=102). Prevalence of chronic lung disease was the highest (32.1%, n=51) in patients with lung cancer while prevalence of moderate to severe kidney disease was the highest (36.0%, n=18)) in patients with kidney cancer. Other diseases having a notable prevalence were peripheral artery occlusive disease in lung cancer patients (10.7%, n=17) and in the other cancer type cohort (9.5%, n=11), and cardiac infarction in patients with prostate cancer (7.2%, n=21).

10.2.1.5 Previous Antiresorptive and Antineoplastic Therapy

Documented antiresorptive and antineoplastic therapies are analyzed as previous therapies if

- the start date of the therapy or date of surgery was prior to the first XGEVA® application or

- the start date was missing and the end date was prior to the first XGEVA® application or completely missing.
- The corresponding tickbox in the e-CRF was ticked.

Use of previous antiresorptive therapy was reported in 6.4% (n=72) of the FAS patients. The cohorts defined by different solid tumor type were quite similar with respect to use of previous antiresorptive therapy (Table 15).

Details of previous antineoplastic therapy are summarized in Table 16. Chemotherapy was the most common previous antineoplastic therapy, reported for 41.3% (n=466) of the FAS patients, followed by antihormonal therapy (37.0%, n=417) and radiotherapy (25.9%, n=292). Please note that one patient could report more than one type of previous antineoplastic therapy previous to enrolment.

Antihormonal therapy was the most common antineoplastic therapy for patients with breast cancer (42.8%, n=218) and for prostate cancer patients (65.3%, n=192). The proportion of patients who had received prior chemotherapy was substantially higher in patients with lung cancer (71.1%, n=113), patients with kidney cancer (68.0%, n=34) and patients with other cancers (58.6%, n=68) compared to patients with prostate cancer (21.8%, n=64) and with breast cancer (36.7%, n=187).

Details of chemotherapeutic agents used in prior chemotherapy are given in Table 17. Percentages were based on those patients who received any chemotherapy prior to the study (N=466 in the FAS).

Agents most frequently administered to study patients were docetaxel (20.2%, n=94), paclitaxel (20.2%, n=94), bevacizumab (17.2%, n=80), and carboplatin (15.9%, n=74).

In the different tumor cohorts, different chemotherapeutic agent had been used predominantly. Patients with prostate cancer had mostly received docetaxel (79.7%, n=51). Patients with breast cancer had received a variety of agents with the most common being paclitaxel (33.2%, n=62), bevacizumab (27.8%, n=52), trastuzumab (25.1%, n=47), and docetaxel (19.3%, n=36). Patients with lung cancer had received mostly carboplatin (46.0%, n=52), cisplatin (38.9%, n=44), and patients with other cancer types had mostly received cisplatin (29.4%, n=20). Patients with kidney cancer had mostly received everolimus (26.5%, n=9), sunitinib malate (23.5%, n=8), and pazopanib hydrochloride (23.5%, n=8) (Table 17).

Details of previous antihormonal therapy are summarized in Table 18.

In the FAS, the antihormonal agents most frequently administered to study patients, relative to the number of patients who had received any kind of antihormonal therapy, were leuprorelin acetate (21.1%, n=88), letrozole (19.4%, n=81), anastrozole (18.9%, n=79), and bicalutamide (17.7%, n=74). Antihormonal therapy had largely been prescribed to patients in the breast and prostate cancer cohorts (410 out of 417 patients prescribed antihormonal therapy).

In patients with breast cancer, the antihormonal agents most frequently administered were letrozole (37.2%, n=81), anastrozole (36.2%, n=79), tamoxifen (21.1%, n=46), and exemestane (18.8%, n=41).

In patients with prostate cancer, the antihormonal agents most frequently prescribed were leuproreline acetate (45.8%, n=88), bicalutamide (38.0%, n=73), buserelin acetate (10.4%, n=20), and leuprorelin (7.3%, n=14).

10.3 Main Data

10.3.1 Persistence at 24 weeks

The analysis of persistence at 24 weeks was based on the FAS but excluded those patients who could not be evaluated for persistence at 24 weeks, i.e. who had died, had withdrawn informed consent or had been lost to follow-up prior to the persistence assessment . Reasons for non-persistence were

- premature termination of XGEVA® therapy due to an ADR, due to refusal of further XGEVA® injections, due to the physician's decision or due to other reasons
- less than 6 XGEVA® injections within 24 weeks
- violations of time windows for injections, which were defined as a duration of no more than 4 weeks (± 7 days) between injections and a permissible duration of +2 weeks after the 24 weeks endpoint and ±7 days for each injection relative to the previous injection.

Persistence at 24 weeks was thus defined as receipt of at least 6 XGEVA® injections no more than 4 weeks (±7 days) apart, with permissible time windows of +2 weeks after the 24 weeks endpoint and ±7 days for each injection relative to the previous injection.

Among the 1008 patients included in this non-interventional prospective study and who were assessable for persistency of XGEVA® use, persistence with XGEVA® at 24 weeks

was found to be 61.5% (620 of 1008 patients; 95% CI: [58.4%-64.5%]) across all solid tumor types (Table 19).

Differences in persistence with XGEVA® at 24 weeks (with the aforementioned definition and permissible gaps) were noted in specific tumor type cohorts. 52% of patients in the lung and 50% of patients in the other cancer type cohorts were persistent at 24 weeks, 61.2% of patients in the prostate and 65% in the breast cancer cohort were persistent at 24 weeks respectively, and 71.7% of the kidney cancer patients were persistent at 24 weeks.

The most frequent reason for non-persistence at 24 weeks (defined as not meeting the aforementioned persistence at 24 weeks definition and associated permissible gaps) was violation of the time window, which was reported in 342 patients (33.9%). Of the 342 patients non-persistent at 24 weeks due to violation of time windows, 283 patients violated one time window with one of the 6 XGEVA® injections outside of the aforementioned permissible gap for persistence with XGEVA® at 24 weeks. Only few patients were non-persistent due to premature termination (4.3%, 43/1008) or to not enough injections (0.3%, 3/1008). 2.2% (22/1008) of patients terminated prematurely because the patient refused further XGEVA® injections, 0.8% (8/1008) of patients terminated prematurely because of other reasons, 0.7% (7/1008) of patients terminated prematurely because of physician's decision, and 0.6% (6/1008) of patients terminated prematurely because of ADRs (Table 20).

A sensitivity analysis for persistency with XGEVA® at 24 weeks was conducted, with a wider permissible gap than the aforementioned definition for persistence at 24 weeks; i.e. with a permissible time window of +4 weeks (instead of +2 weeks) after the 24 weeks endpoint and of ± 14 days (instead of ± 7 days) for each injection relative to the previous injection. Doubling the permissible time windows resulted in a higher value for persistency with XGEVA® at 24 weeks: 76.2% (754/990; 95% CI: [73.4%-78.8%]) across all tumor types versus 61.5% (620/1008; 95% CI: [58.4%-64.5%]) across all tumor types (Table 21 and Table 20). Similarly, persistence with XGEVA® at 24 weeks (using the wider permissible gaps) was higher in specific tumor type cohorts; 67.0% and 71.4% of patients in the lung and other cancer type cohorts, respectively were persistent at 24 weeks, 76.3% of patients in the prostate and 79.2% of the breast cancer cohort were persistent at 24 weeks. 73.9% of patients with kidney cancer were persistent at 24 weeks using this definition with wider permissible gaps.

The most frequent reason for non-persistence at 24 weeks using the wider permissible gap remained violation of time window, which was reported in 184 patients (Table 22). Of the 184 patients non-persistent at 24 weeks (using the wider permissible gaps) due to violation of time windows, 167 patients violated only one time window with one of the 6 XGEVA® injections outside of the aforementioned wider permissible gaps for persistence with XGEVA® at 24 weeks (Table 22).

10.3.2 Persistence at 48 weeks

The analysis of persistence at 48 weeks was based on the FAS but excluded those patients who could not be evaluated for persistence at 48 weeks, i.e. who had died, had withdrawn informed consent or had been lost to follow-up prior to the persistence assessment. Reasons for non-persistence were

- premature termination of XGEVA® therapy due to an ADR, due to refusal of further XGEVA® injections, due to the physician's decision or due to other reasons
- less than 12 XGEVA® injections within 48 weeks
- violations of time windows for injections, which were defined as a duration of no more than 4 weeks (± 7 days) between injections and a permissible duration of +7 weeks after the 48 weeks endpoint and ±7 days for each injection relative to the previous injection.

Among the 928 patients included in this non-interventional prospective study and who were assessable for persistency of XGEVA® use, persistence with XGEVA® at 48 weeks was found to be 37.7% (350/928, 95%CI: [34.6%-40.9%]) across all tumor types (Table 23).

Differences in persistence with XGEVA® at 48 weeks (with the aforementioned definition and permissible gaps) were noted in specific tumor type cohorts. The highest persistence was observed in patients with breast cancer (43.5%), followed by patients with kidney cancer (38.5%) and prostate cancer (35.6%). 29.5% of patients in lung cancer and 20.3% of patients with other cancer type were persistent at 48 weeks.

The most frequent reason for non-persistence at 48 weeks (defined as not meeting the aforementioned persistence at 48 weeks definition and associated permissible gaps) was violation of time window, which was reported in 501 of 928 patients (54.0%)

(Table 24). Of the 501 patients non-persistent at 48 weeks due to violation of time windows, 308 patients had violated only single time window (Table 24).

A sensitivity analysis for persistency with XGEVA® at 48 weeks was conducted, with a wider permissible gap than the aforementioned definition for persistence at 48 weeks; i.e. with permissible time windows of +10 weeks (instead of +7 weeks) after the 48 weeks endpoint and ± 14 days (instead of ± 7 days) for each injection relative to the previous injection. Doubling the permissible time windows resulted in a higher value for persistency with XGEVA® at 48 weeks: 55.8% (488/875; 95% CI: [52.4%-59.1%]) across all tumor types versus 37.7% (350/928; 95% CI: [34.6%-40.9%]) across all tumor types (Table 25 and Table 23). Similarly, persistence with XGEVA® at 48 weeks (using the wider permissible gaps) was higher in specific tumor type cohorts; 60.6% of patients in breast cancer, 56.5% of patients with prostate cancer, 45.8% of patients with lung cancer, 43.2% of patients with kidney cancer and 39.1% of patients with other cancer type were persistent at 48 weeks.

The most frequent reason for non-persistence at 48 weeks using the wider permissible gaps remained violation of time window, which was reported in 290 patients (33.1%) (Table 26). Of the 290 patients non-persistent at 48 weeks (using the wider permissible gaps) due to violation of time windows, 224 patients violated one time window with one of the 12 XGEVA® injections outside of the aforementioned wider permissible gap for persistence with XGEVA® at 48 weeks (Table 26).

10.3.3 Time to non-persistence

Time to non-persistence was calculated as the time from the date of the first XGEVA® injection

- to the date of last injection received during the period where the patient was still classified as persistent plus 28 days, if the patient was considered non-persistent at any time during the study, i.e. the patient had an event
- to the date of last injection received if the patient was considered persistent and was thus censored for this analysis
- to the date of death if the patient was considered persistent until he/she died and was thus censored for this analysis

- to the date of withdrawal if the patient was considered persistent until he/she withdrew and was thus censored for this analysis.

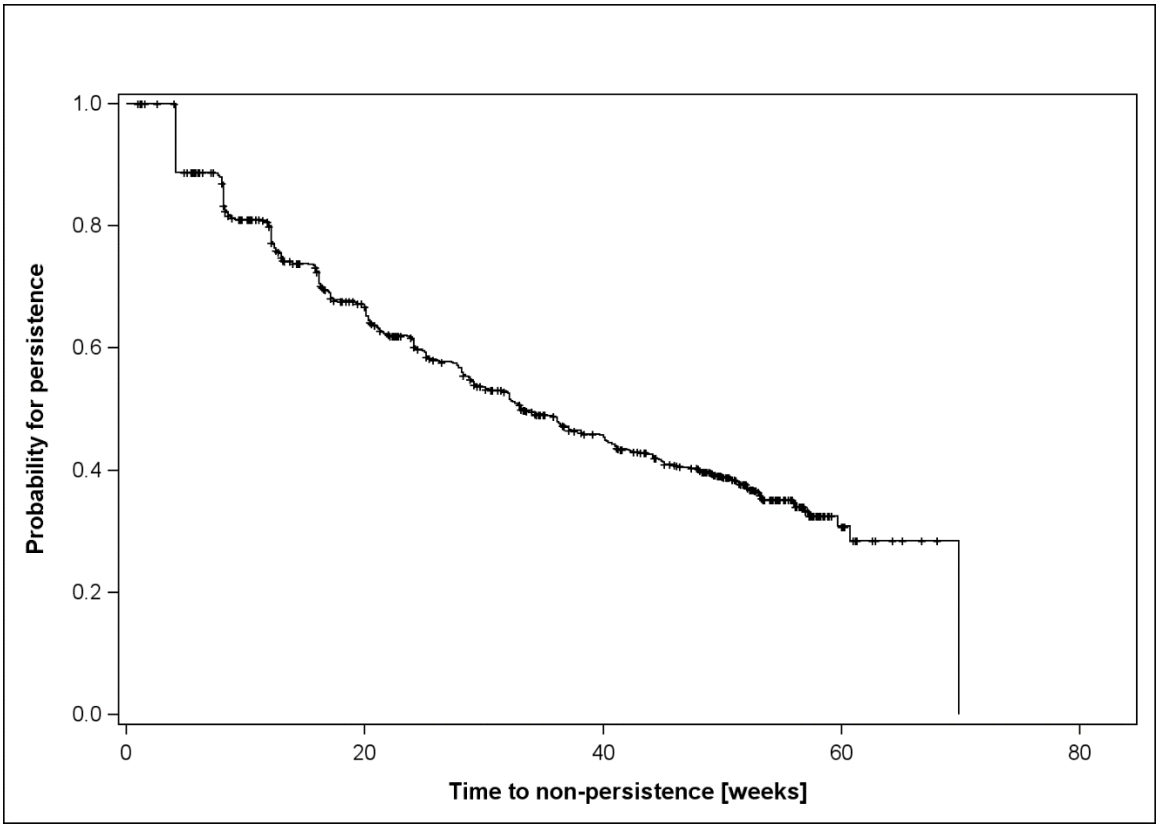
The overall median time to non-persistence, estimated by Kaplan-Meier methods, was 33.3 weeks (N=1128; 95%CI: [31.7 weeks; 37.1 weeks]) across all solid tumor types (see Table 27 and Figure 1). Median time to non-persistence estimated by Kaplan-Meier methods by tumor type ranged from 24.1 weeks (n=116; 95%CI: [19.9 weeks; 36.1 weeks]) in patients with other cancer type to 37.3 weeks (n=509; 95%CI: [33.1 weeks; 44.1 weeks]) in patients with breast cancer (see Table 28). The results for time to non-persistence were very similar in the sensitivity analysis, which censored patients who were lost to follow-up instead of evaluating these patients as having non-persistence (Tables 15.3.7.1.1, 15.3.7.1.2, 15.3.7.2.1, 15.3.7.2.2, and 15.3.8, see Annex 1). The overall median time to non-persistence estimated by Kaplan-Meier methods for the sensitivity analysis was 36.4 weeks (N=1128; 95%CI: 32.6 weeks to 40.7 weeks) compared to 33.3 weeks (N=1128; 95%CI: 31.7 weeks to 37.1 weeks) for the original analysis.

In another sensitivity analysis for time to non-persistence, which doubled the permissible time window from ± 7 days to ± 14 days and censored patients who were lost to follow-up instead of evaluating these patients as having non-persistence, the median time to non-persistence was not estimable. In this analysis, the 1st quartile of the time to non-persistence estimated by Kaplan-Meier methods was estimated to 27.7 weeks (N=1128, 95%CI: 24.0 weeks to 30.4 weeks) compared to the original analysis of a 1st quartile of 13.0 weeks (N=1128, 95%CI: 12.1 weeks to 16.1 weeks) (Tables 15.3.9.1.1 and 15.3.9.1.2, see Annex 1).

The estimated probability of persistence at 24 weeks (with permissible time windows of +2 weeks after the 24 weeks endpoint and ± 7 days for each injection relative to the previous injection) using Kaplan-Meier methods was 61.4%. This was comparable to the calculated persistence with XGEVA® at 24 weeks (according to the same persistence definition and associated permissible gaps) based on data from1008 patients included in this non-interventional prospective study and who were assessed for persistency of XGEVA® use: 61.5% (620/1008; 95% CI: [58.4%-64.5%]) across all solid tumor types. Similarly, the estimated tumor-specific probability of persistence with XGEVA® at 24 weeks using Kaplan-Meier methods was comparable to that estimated using data from each tumor type cohort within the 1008 study participants assessed for persistency of XGEVA® use (Table 29, see Section 10.3.1).

A sensitivity analysis was performed by applying a time window of +/- 14 days instead of +/- 7 days between injections to determine persistence and censoring for patients who were lost to follow up. In this Kaplan-Meier analysis, the overall probability of being persistent at 24 weeks (using the wider permissible gaps) was 77.5% (Table 29).

Figure 1. Time to non-persistence estimated by Kaplan-Meier method – overall study patients



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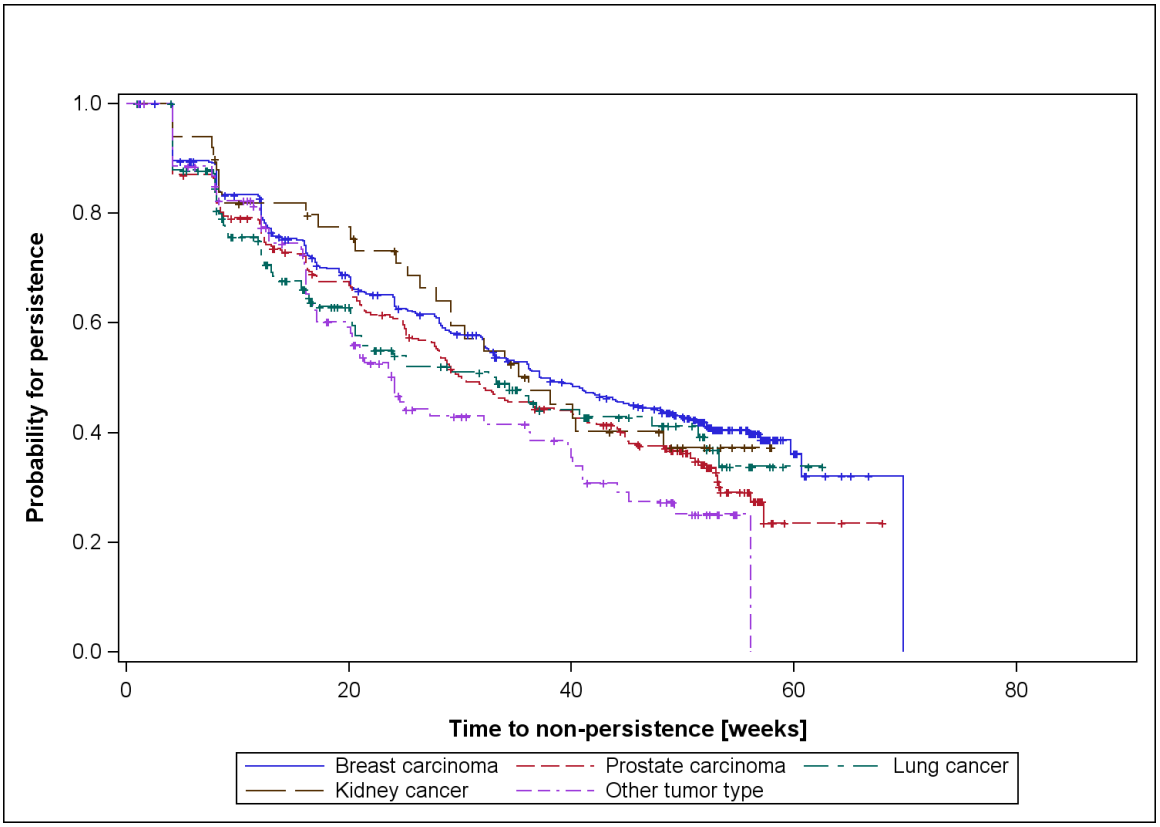
Source: Annex 1, Figure 15.3.5.1.1

Using a Cox proportional hazards model, the presence of visceral metastases and the ECOG score (p=0.0381, Wald test) were found to be significantly associated with time to non-persistence with XGEVA® (with permissible time windows of +2 weeks after the 24 weeks endpoint and ± 7 days for each injection relative to the previous injection). The risk of non-persistence with XGEVA® was greater in patients with visceral metastases (hazards ratio [HR], 1.355; 95% CI: [1.138, 1.614]; p=0.0006, Wald test) than those without visceral metastases (Table 30). The risk of non-persistence with XGEVA® was

lower in patients with ECOG status '0' (HR, 0.716; 95% CI: [0.552, 0.929]) than those with ECOG status '2'. Furthermore, the risk of non-persistence with XGEVA® was lower in patients with ECOG status '1' (HR, 0.828; 95% CI: [0.653, 1.051]) than those with ECOG status '2' (Table 30). A sensitivity analysis was performed by applying a time window of +/- 14 days instead of +/- 7 days between injections to determine persistence and censoring for patients who were lost to follow up. In the Cox proportional hazard model (using the wider permissible gap), the presence of visceral metastases was again found to be significantly associated with time to non-persistence (Table 31). The risk of non-persistence with XGEVA® (using the wider permissible gap) was greater in patients with visceral metastases (hazards ratio [HR], 1.286; 95% CI: [1.035, 1.597]; p=0.0230, Wald test). In addition, the variable age (p=0.011, Wald test) was found to be significantly associated with time to non-persistence; the risk of non-persistence increases with the age of patients.

Figure 2. Time to non-persistence by Kaplan-Meier estimates – overall study patients



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Source: Annex 1, Figure 15.3.5.2.1

10.4 Other Analysis

10.4.1 Dose and Frequency of Calcium and Vitamin D supplementation

Vitamin D supplementation was prescribed to 890 (82.4%) patients at Visit 1 and this percentage increased slightly over the study (Table 32). The number of evaluable patients decreased throughout the study from 1080 at Visit 1 to 1 at Visit 21 whereby the number of patients with missing information on Vitamin D supplementation ranged from 0 to 8. The median daily dose of Vitamin D was 400 IU during the whole study (Table 33). The daily dose of Vitamin D ranged from 13 IU to 41600 IU during the whole study.

The number of patients with Calcium supplementation was similar to the number of patients with Vitamin D supplementation. Calcium supplementation was prescribed to 893 (82.6%) of the patients at Visit 1 and also increased very slightly during the course of the study whereby the number of evaluable patients decreased (Table 34). The median daily dose of Calcium supplementation was 600 mg during the whole study (Table 35).

10.4.2 Change in Pain Score and Medication

Pain scores on a 10-item VAS were evaluated at every visit until Visit 7 and a summary of this data is presented in Table 36. The VAS ranges from 0 (no pain) to 100 (highest pain).

Overall, average (±SD) pain score decreased from 25.9 (±23.2) at Visit 1 (n=852) to 24.2 (±22.0) at Visit 7 (n=440). By tumor type, at Visit 1, the highest average pain score (±SD) was in patients with other cancer type (30.3±22.1, n=83) and the lowest average pain score (±SD) was in patients with prostate cancer (21.9±22.6, n=240). For the other cancer types the following was observed at Visit 1 (mean±SD): 26.2±23.5 for patients with breast cancer (n=380), 29.5±24.4 for patients with lung cancer (n=107) and 27.8±21.0 for patients with kidney cancer (n=42). There were patients without pain at all visits and for all tumor type (minimum VAS=0).

A summary of absolute changes in pain score from Visit 1 is provided in Table 15.5.2, Annex 1.

10.4.3 Extent of Exposure

Extent of exposure was analyzed over the whole study period on 52 weeks. Patients should receive 12 injections of XGEVA® during this time frame according to prescription information.

The median number of XGEVA® injections administered to the study patients was 13, the lower quartile was 7 and the upper quartile was 14 (Table 44). Overall, average (±SD) number of XGEVA® injections administered was 10.6 (±4.4). The median number of XGEVA® injections administered was the highest in patients with breast and prostate cancer (13, each) and the lowest in patients with lung cancer (6). The minimum number of XGEVA® injections administered was 2 for patients with kidney cancer. For the patients with the other solid tumor types a minimum of 1 injection was administered.

10.4.4 Quality of Life

The quality of life was measured by EQ-5D whereby problems with mobility, self-care, daily activities, pain/discomfort, and anxiety/depression were collected at Visit 1, Visit 4, Visit 7, Visit10 and EOS. Patient response on QoL questions related to mobility is summarized in Table 37.

Overall, >50.0% of the study patients responded that they had no problems in walking about from Visit 1 all throughout till EOS (overall number of patients at Visit 1: n=810, Visit 4: n=618, Visit 7: n=498, Visit 10: n=422, EOS: n=272). A small fraction (<2.0%) of the patients reported being confined to bed (Visit 1: 1.2%, n=10; Visit 4: 1.6%, n=10; Visit 7: 1.8%, n=9; Visit 10: 0.5%, n=2; EOS: 0.4%, n=1). This pattern was also observed for patients with breast and prostate cancer. In patients with lung cancer only at Visit 4 the proportion of patients without problems with mobility was below 50% (41.0%, n=25). In patients with kidney cancer 50.0% (n=20) of the study patients had no problems with mobility at Visit 1. At Visit 4 42.3% (n=11), at Visit 7 47.4% (n=9), at Visit 10 50% (n=6) and at EOS 54.5% (n=6) of the study patients had no problems with mobility. In patients with other cancer type 53.9% (n=41) of the study patients had no problems with mobility at Visit 1. At Visit 4 49.1% (n=26), at Visit 7 40.0% (n=12), at Visit 10 36.4% (n=8) and EOS 62.5% (n=10) of study patients had no problems with mobility.

Patient response on QoL questions related to self-care is summarized in Table 38.

Overall, ≥70.0% of the study patients responded that they had no problems in caring for self from Visit 1 till EOS (overall number of patients at Visit 1: n=810, Visit 4: n=620, Visit

7: n=497, Visit 10: n=423, EOS: n=273). A smaller fraction (≤4.5%) of overall patients reported an inability to take care of self (Visit 1: 3.6%, n=29; Visit 4: 3.5%, n=22; Visit 7: 3.0%, n=15; Visit 10: 4.3%, n=18; EOS: 2.9%, n=8). This pattern was also observed for patients with breast and prostate cancer (except for EOS in prostate cancer: percentage of patients without problems was slightly below 70%). The proportion of patients with lung cancer or with other cancer type who had no problems with self-care at Visit 1 was <70.0% (lung cancer: 69.2%, n=74; other cancer type: 69.7%, n=53). In addition, the proportion of patients who were unable to perform self-care in these groups was higher than the others (>5.0%). The proportion of patients with kidney cancer who had no problems in caring for self was above 70.0% for all visits. At Visit 1, Visit 4 and Visit 7 4% or less of patients with kidney cancer reported an inability to take care of self. At Visit 10 and EOS the proportion increased (Visit 10: 8.3%, n=1; EOS: 9.1%, n=1). The number of patients was quite low for these visits (n=12 at Visit 10 and n=11 at EOS).

Patient response on QoL questions related to performing usual activities are given in Table 39. Overall, at Visit 1, a majority (47.3%) of the study patients had some problems with performing usual activities and 8.3% of the total cohort was unable to perform usual activities (overall number of patients at Visit 1: n=811). However, from Visit 4 to EOS, a majority of the patients reported no problems with performing usual activities (Visit 4: 46.3%, n=286; Visit 7: 47.8%, n=237; Visit 10: 51.2%, n=215; EOS: 52.4%, n=143). This pattern was also noticed in patients with breast cancer. Over half of the patients with prostate cancer had no problems with performing usual activities all through till EOS. In patients from the other groups, the proportion of patients who had problem with performing usual activities remained higher than that with no problems performing usual activities all throughout till EOS. At EOS patients with kidney cancer, lung cancer and other cancer type the proportion of patients without problems with performing usual activities increased (kidney cancer: 54.5%, n=6; lung cancer: 55.6%, n=5; other cancer type: 50%, n=8) (Table 39).

Patient response on QoL questions related to pain or discomfort are summarized in Table 40. Overall, >60.0% of the study patients responded that they had moderate pain or discomfort from Visit 1 all through to EOS (overall number of patients at Visit 1: n=809, Visit 4: n=617, Visit 7: n=502, Visit 10: n=423, EOS: n=273). In most cases, this pattern was also observed for patients irrespective of type of cancer. But less than 60% of the patients with prostate cancer responded that they had moderate pain or discomfort at Visit 1 (53.6%, n=119) and Visit 4 (51.8%, n=99) (Table 40).

Patient response on QoL questions related to anxiety or depression are given in Table 41. Overall, of majority of the study patients responded that they were not depressed from Visit 1 all throughout till EOS (overall number of patients at Visit 1: n=805, Visit 4: n=616, Visit 7: n=496, Visit 10: n=423, EOS: n=270). This pattern was also observed for patients with breast and prostate cancer and lung cancer. Overall, a small fraction (<4.5%) of the patients reported having extreme anxiety or depression. Except for Visit 1 and EOS a majority of the patients with kidney cancer reported moderate anxiety or depression all throughout till EOS. Except for Visit 10 a majority of the patients with other cancer type reported that they were not depressed all throughout till EOS (Table 41).

Data on self-rated health measurement by EQ-5D VAS is summarized in Table 42. Overall, average (±SD) EQ-5D VAS scores in study patients increased from 63.9 (±21.0) at Visit 1 (n=804) to 68.0 (±21.3) at EOS (n=268). This trend was observed across the different cohort based on cancer type. Calculation of absolute change from Visit 1 at other points of evaluation showed that the largest increase in average VAS scores between Visit 1 and EOS occurred in patients with lung cancer (6.1±17.6) and kidney cancer (5.9±15.2) (Table 43).

10.4.5 Concomitant Medication

Overall, the concomitant antineoplastic therapy of choice was chemotherapy followed by antihormonal therapy (including antibodies and small molecules), prescribed to 60.4% (n=681) and 50.7% (n=572) of the study patients, respectively (Table 45).

The types of concomitant antineoplastic therapy differed between the different types of solid tumor. Antihormonal therapy was prescribed to a majority of patients with breast cancer (63.3%, n=322) and prostate cancer (82.7%, n=243). In cohorts with lung cancer, kidney cancer, and other cancer types, chemotherapy was the major concomitant antineoplastic therapy, prescribed to 81.8% (n=130), 88.0% (n=44), and 82.8% (n=96) of the patients, respectively.

A summary of concomitant chemotherapy by WHO Drug Dictionary preferred term is given in Table 46 (abridged) and Table 15.7.3, Annex 1 (complete). Similarly, a summary of concomitant antihormonal therapy by WHO DRL preferred term is given in Table 47 (abridged) and Table 15.7.4, Annex 1 (complete).

Overall, the top three chemotherapeutic agents of choice were docetaxel, paclitaxel, and bevacizumab, prescribed to 22.3% (n=152), 21.3% (n=145), and 18.8% (n=128) of the patients who received any chemotherapy during the study (n=681), respectively. The top three antihormonal agents of choice were leuprorelin acetate, letrozole, and anastrazole, prescribed to 24.3% (n=139), 20.6% (n=118), and 20.5% (n=117) of the patients who received any antihormonal therapy (n=572), respectively (Table 47).

10.4.5.1 Concomitant therapy of breast cancer patients

In patients with breast cancer who received chemotherapy (n=288), the top three chemotherapeutic agents were paclitaxel (33.3%, n=96), bevacizumab (30.2%, n=87), and trastuzumab (23.6%, n= 68). Also capecitabine (18.1%, n=52), docetaxel (13.5%, n=39) and pertuzumab (10.1%, n=29) were two agents, which were given to more than 10% of patients with breast cancer, who were prescribed at least one chemotherapeutic agent during the study. The most common antihormonal therapies prescribed to patients with breast cancer were letrozole (36.6%, n=118), anastrazole (36.0%, n=116), exemestane (21.7%, n=70), and tamoxifen (17.7%, n=57).

10.4.5.2 Concomitant therapy of prostate cancer patients

In patients with prostate cancer who received chemotherapy (n=123), common chemotherapeutic agents were docetaxel (74.0%, n=91), abiraterone acetate (17.1%, n=21), cabazitaxel (17.1%, n=21), and prednisolone (13.8%, n=17). Common antihormonal therapies prescribed to patients with prostate cancer (n=243) were leuprorelin acetate (56.4%, n=137), bicalutamide (33.7%, n=82), abiraterone acetate (15.2%, n=37), and buserelin acetate (14.0%, n=34). Further 24 patients with prostate cancer received other antineoplastic agents during the study.

10.4.5.3 Concomitant therapy of lung cancer patients

In patients with lung cancer who received chemotherapy (n=130), common chemotherapeutic agents were carboplatin (44.6%, n=58), cisplatin (33.1%, n=43), paclitaxel (23.1%, n=30), and pemetrexed disodium (20.8%, n=27). Further chemotherapeutic agents prescribed at least 10 patients with lung cancer were bevacizumab (n=24), vinorelbine (n=22), pemetrexed (n=20), etoposide (n=19), docetaxel (n=17), topotecan (n=13), erlotinib hydrochloride (n=13), and gemcitabine (n=12). No antihormonal, antibody or small molecule therapy was prescribed to patients with lung cancer.

10.4.5.4 Concomitant therapy of kidney cancer patients

In patients with kidney cancer who received chemotherapy (n=44), the common agents were everolimus (27.3%, n=12), temsirolimus (25.0%, n=11), sunitinib malate (22.7%, n=10), pazopanib hydrochloride (18.2%, n=8), axitinib (11.4% n=5), and pazopanib (11.4%, n=5).

10.4.5.5 Concomitant therapy of patients with other cancer types

In patients with other cancer types for whom any kind of chemotherapy was documented (n=96), the prescribed agents were cisplatin (22.9% n=22), fluorouracil (19.8%, n=19), and paclitaxel (18.8%, n=18), gemcitabine (16.7%, n=16), carboplatin (16.7%, n=16), bevacizumab (15.6%, n=15), combinations of antineoplastic agents (12.5%, n=12), and capecitabine (10.4%, n=10).

10.4.6 Analgesic drug use and analgesic score (AQA)

Overall, 51.8% (n=584) of the patients in the FAS were prescribed any analgesic drug during the course of the study (Table 48). The proportion of patients receiving analgesic medication was the highest in patients with other cancer type (74.1%, n=86) and the lowest in patients with prostate cancer (42.2%, n=124).

The analgesic score (AQA) of pain medications was provided directly as such in the e-CRF together with the documentation of analgesic medication. The AQA is summarized in Table 49 for each medication, i.e. with multiple medications with different AQA scores is counted more than once. 42.2% (n=476) of all patients received non-opioid analgesics. The proportion of patients who received non-opioid analgesics in the FAS was 60.3% (n=70) in patients with other cancer types, which was the highest percentage in all patient cohorts. The lowest percentage was observed in patients with prostate cancer (35.7%, n=105).

In the FAS, patients with lung cancer, kidney cancer and other cancer types tended to receive more often opoidsopioids in weak doses, or at dose levels 1, 2 and 3 compared to patients with breast or prostate cancer. The proportion of all patients in FAS who received weak opoidsopioids was 13.6% (n=153). It was highest in lung cancer patients (20.1%, n=32), and also high for patients with other cancer types (17.2%, n=20) and patients with kidney cancer (16.0%, n=8). 24.1% of patients in the FAS (n=272) received strong opoidsopioids dose level 1. 39.6% (n=63) of lung cancer patients, 47.4% (n=55) of patients with other cancer types and 38.0% (n=19) of kidney cancer patients received this class of medication (Table 49).

Summaries of the worst and the best AQA score analyzed as numeric value by study period can be found in Table 50 and Table 51 for all patients in the FAS and in Annex 1 (Tables 15.7.11 to 15.7.14) for the different tumor cohorts. AQA scores tended to be highest in patients with lung cancer, other cancer types and kidney cancer and were slightly lower in patients with breast or prostata cancer.

10.4.7 Laboratory Results

Calcium and creatinine in serum as well as creatinine clearance are summarized by visit and tumor type/overall in Tables 15.8.1, 15.8.2, and 15.8.3 (see Annex 1), respectively. Mean and median laboratory results did not change considerably during the study and were also comparable within each tumor type cohort.

10.5 Adverse Events/Adverse Reactions

Overall, a total of 95 ADRs (except suspected osteonecrosis of the jaw events) were reported in 72 patients (6.4% of patients in the FAS) and all were assessed to be related to XGEVA® (Table 52). While none of the ADRs were fatal, a total of 12 ADRs in 10 patients led to the withdrawal of XGEVA®. In detail, the reported terms were hypocalcemia (3 patients), rash (2 patients, one in combination with general physical health deterioration and circulatory collapse), and nausea, decreased appetite, vasculitis, arthralgia, bone pain in one patient each (Table 15.9.6, Annex 1). In addition, for 15 patients suspected osteonecrosis of the jaw was reported (Table 15.9.7, Annex 1), in 6 patients suspected ONJ led to the withdrawal of XGEVA® (Patient Data Listing 16.2.1.3, Annex 1).

Occurrence of documented ADRs differed by tumor type: 43 events in 33 (6.5%) patients with breast cancer, 22 events in 14 (8.8%) lung cancer patients, 16 events in 15 (5.1%) patients with prostate cancer, 5 events in 3 (6.0%) kidney cancer patients, and 9 events in 7 (6.0%) patients with other cancer types (Table 52).

A total of 4 serious ADRs were reported in 4 patients (2 patients with breast cancer and 2 patients with lung cancer). No serious ADRs were reported for patients with prostate cancer, kidney cancer and other cancer type (Table 53). Two of these serious events were hypocalcemia, one event was thrombocytopenia and another event was respiratory tract infection.

The summary of reported ADRs related to XGEVA® by tumor type is presented in Table 54. The most commonly reported ADR in overall patients and in cohorts based on tumor type was hypocalcemia (62 events in 48 patients; 4.3%).

11. Discussion

11.1 Key Results

This study was conducted to evaluate usage of XGEVA® (denosumab) 120 mg for prevention of skeletal related events in patients with bone metastases and solid tumors in routine clinical practice. The primary objective was to estimate persistence with XGEVA® at 24 weeks in patients with solid tumors and bone metastases and treated as per routine clinical practice.

- The primary analysis of persistence at 24 weeks was based on the FAS excluding those patients who had died, had withdrawn informed consent or who had been lost to follow-up prior to the persistence assessment. Among the 1008 patients included in this non-interventional prospective study and assessed for persistency of XGEVA® use, persistence with XGEVA® at 24 weeks (defined as receipt of at least 6 XGEVA® injections no more than 4 weeks (+7 days) apart, with permissible time windows of +2 weeks after the 24 weeks endpoint and ± 7 days for each injection relative to the previous injection) was 61.5% (620 of 1008 patients, 95% CI: [58.4%-64.5%]) across all solid tumor types.
- The most frequent reason for non-persistence at 24 weeks (defined as not meeting the aforementioned persistence at 24 weeks definition and associated permissible gaps) was violation of the time window, which was reported in 342 patients (33.9%). Of the 342 patients non-persistent at 24 weeks due to violation of time windows, 283 patients violated one time window with one of the 6 XGEVA® injections outside of the aforementioned permissible gap for persistence with XGEVA® at 24 weeks. Only few patients were non-persistent due to premature termination (4.3%, 43/1008) or to not enough number of injections (0.3%, 3/1008).
- Doubling the permissible time windows in sensitivity analyses [permissible time windows of +4 weeks (instead of +2 weeks) after the 24 weeks endpoint and ± 14 days (instead of ± 7 days) for each injection relative to the previous injection] resulted in a higher value for persistency with XGEVA® at 24 weeks: 76.2% (n=990; 95% CI: [73.4%-78.8%]) across all tumor types compared to 61.5% (n=1008; 95% CI: [58.4%-64.5%]) across all tumor types in the primary analysis.
- Persistency with XGEVA® at 48 weeks and time-to-non-persistence were estimated as secondary objectives. Among the 928 patients who were assessed for persistency of XGEVA® use, persistence with XGEVA® at 48 weeks (defined in the

primary analysis as receipt of at least 12 XGEVA® injections no more than 4 weeks (±7 days) apart, with permissible time windows of +7 weeks after the 48 weeks endpoint and of ± 7 days for each injection relative to the previous injection) was found to be 37.7% (350/928, 95%CI: [34.6%-40.9%]) across all tumor types. The most frequent reason for non-persistence at 48 weeks was violation of time window, which was reported in 501 patients (54.0% of the 928 evaluable patients).

- Doubling the permissible time windows in sensitivity analyses [permissible time windows of +10 weeks (instead of +7 weeks) after the 48 weeks endpoint and ± 14 days (instead of ± 7 days) for each injection relative to the previous injection] resulted in a higher value for persistency with XGEVA® at 48 weeks: 55.8% (488/875; 95% CI: [52.4%-59.1%]) across all tumor types versus 37.7% (350/928; 95% CI: [34.6%-40.9%]) across all tumor types
- Using Kaplan-Meier methods, the estimated overall median time to non-persistence with XGEVA® was 33.3 weeks (N=1128; 95%CI: [31.7 weeks; 37.1 weeks]) across all solid tumor types, and the estimated probability of persistence with XGEVA® at 24 weeks was 61.4% in FAS. This was well comparable to the calculated incidence of persistence with XGEVA® at 24 weeks (according to the same persistence definition and associated permissible gaps but without taking into account censoring information) of 61.5% (n=1008; 95% CI: [58.4%-64.5%]) across all solid tumor types.
- Using Cox proportional hazards model, the risk of non-persistence with XGEVA® was greater in patients with visceral metastases (HR, 1.355; 95% CI: 1.138, 1.614; p=0.0006, Wald test) than those without visceral metastases.
- The median number of XGEVA® injections administered to the study patients was 13, the lower quartile was 7 and the upper quartile was 14.
- The number of patients who reported at least one ADR was 6.4%, overall, a total of 95 ADRs were reported (except suspected osteonecrosis of the jaw events). Only very few of these led to the discontinuation of XGEVA® administration (12 ADRs in 10 (0.9%) patients. 4 of the ADRs in 4 (0.4%) patients were serious. No fatal ADR was reported. No new or unexpected ADRs compared to the SmPC were reported in the study, which included 1128 patients overall.

11.2 Limitations

The main limitation of the study is the lack of the control group. Therefore, no direct comparison to any other treatment is possible.

11.3 Interpretation

This study reflects the persistency of XGEVA® use in patients with bone metastases and solid tumors in real live. The percentage of patients under treatment was examined for 24 weeks and 48 weeks with each two different large time windows.

11.4 Generalizability

Comparing these data with other studies, there is to notice that in this analysis those patients were excluded who had died, had withdrawn informed consent or who had been lost to follow-up prior to the persistence assessment.

On the other hand all kinds of solid tumors with bone metastases are represented like in clinicians´ daily practice.

12. OTHER INFORMATION

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13. CONCLUSION

In this study evaluating usage of XGEVA® (denosumab) 120 mg for prevention of skeletal related events (SREs) in patients with bone metastases and solid tumors in routine clinical practice, the persistence across all tumor types was 61.5 % (95% CI: [58.4%-64.5%]) at 24 weeks after treatment start and 37.7 % (95%CI: [34.6%-40.9%]) at 48 weeks across all tumor types. Using Kaplan-Meier methods, the estimated overall median time to non-persistence with XGEVA® in all enrolled 1128 patients was 33.3 weeks (95%CI: 31.7 weeks to 37.1 weeks), and the estimated probability of persistence with XGEVA® at 24 weeks was 61.4% which was well comparable to the calculated incidence of persistence with XGEVA® at 24 weeks. The risk of non-persistence with XGEVA® was greater in patients with visceral metastases (HR, 1.355; 95% CI: 1.138, 1.614; p=0.0006, Wald test). The median number of XGEVA® injections administered to study patients was 13. XGEVA® was well tolerated with only 6.4% of patients reporting at least one ADR and only very few leading to discontinuation.

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15. SUMMARY TABLES, FIGURES, AND LISTINGS

Table 1. Reason for exclusion from FAS

	Total (N=148)	
	n	(%)
Previous antiresorptive therapy was longer than 6 month	55	(37.2%)
Other	30	(20.3%)
No previous application of Denosumab	21	(14.2%)
More than 2 Densoumab (XGEVA®) treatments before inclusion	15	(10.1%)
No confirmed bone metastases due to mamma, prostate, lung cancer or other solid tumor	11	(7.4%)
Previous therapy of Denosumab (XGEVA®) was longer than 3 month	6	(4.1%)
Former treatment of the patient with radionuclide	5	(3.4%)
Serious hypocalcemia	2	(1.4%)
Withdrawal of informed consent	2	(1.4%)
Not available	1	(0.7%)

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Source: Annex 1, Patient data listing 16.2.1.6 and 16.2.1.4

Table 2. Overall enrolment and inclusion in the full analysis set

	Missing tumor type (N=144)		Breast cancer (N=511)		Prostate cancer (N=296)		Lung cancer (N=159)	
	n	(%)	n	(%)	N	(%)	n	(%)
Documented in e-CRF	144	(100.0%)	511	(100.0%)	296	(100.0%)	159	(100.0%)
Not included in FAS*#	144	(100.0%)	2	(0.4%)	2	(0.7%)	0	(0.0%)
Included in FAS*	0	(0.0%)	509	(99.6%)	294	(99.3%)	159	(100.0%)

	Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1276)	
	n	(%)	n	(%)	N	(%)
Documented in e-CRF	50	(100.0%)	116	(100.0%)	1276	(100.0%)
Not included in FAS*	0	(0.0%)	0	(0.0%)	148	(11.6%)
Included in FAS*	50	(100.0%)	116	(100.0%)	1128	(88.4%)

* FAS: Full Analysis Set. Patients who violated inclusion/exclusion criteria, were screening failures, had not received any XGEVA injection, or had no valid date of informed consent were excluded from the FAS.
# 144 screening failures and 4 violations of exclusion criteria EC3
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Source: Annex 1, Table 15.1.1

Table 3. Patient enrolment by type of tumor, full analysis set

	Total (N=1128)	
Type of tumor	**n**	**(%)**
Breast cancer	509	(45.1%)
Prostate cancer	294	(26.1%)
Lung cancer	159	(14.1%)
Kidney cancer	50	(4.4%)
Other cancer type	116	(10.3%)

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Source: Annex 1, Table 15.2.2.1

Table 4. Patient disposition and reasons for withdrawal, full analysis set

	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Patients who are still on-treatment at 24 weeks												
No	68	(13.4%)	35	(11.9%)	80	(50.3%)	12	(24.0%)	49	(42.2%)	244	(21.6%)
Yes	441	(86.6%)	259	(88.1%)	79	(49.7%)	38	(76.0%)	67	(57.8%)	884	(78.4%)
Patients who are still on-treatment at 48 weeks												
No	145	(28.5%)	89	(30.3%)	123	(77.4%)	25	(50.0%)	81	(69.8%)	463	(41.0%)
Yes	364	(71.5%)	205	(69.7%)	36	(22.6%)	25	(50.0%)	35	(30.2%)	665	(59.0%)
Study termination												
Observation completed	347	(68.2%)	187	(63.6%)	28	(17.6%)	23	(46.0%)	31	(26.7%)	616	(54.6%)
Prior to 24 weeks	59	(11.6%)	32	(10.9%)	70	(44.0%)	9	(18.0%)	44	(37.9%)	214	(19.0%)
Between 24 weeks and 26 weeks	6	(1.2%)	2	(0.7%)	5	(3.1%)	1	(2.0%)	4	(3.4%)	18	(1.6%)
More than 26 weeks and prior to 48 weeks	65	(12.8%)	40	(13.6%)	39	(24.5%)	13	(26.0%)	29	(25.0%)	186	(16.5%)
48 weeks or later	32	(6.3%)	33	(11.2%)	17	(10.7%)	4	(8.0%)	8	(6.9%)	94	(8.3%)
Reason for study termination												
Reported event	5	(1.0%)	6	(2.0%)	1	(0.6%)	3	(6.0%)	0	(0.0%)	15	(1.3%)
Death	76	(14.9%)	43	(14.6%)	98	(61.6%)	14	(28.0%)	51	(44.0%)	282	(25.0%)
Patient did not show up any more	28	(5.5%)	18	(6.1%)	16	(10.1%)	5	(10.0%)	11	(9.5%)	78	(6.9%)
Patient's wish	22	(4.3%)	20	(6.8%)	5	(3.1%)	3	(6.0%)	13	(11.2%)	63	(5.6%)
Withdrawal of informed consent	2	(0.4%)	1	(0.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	3	(0.3%)
Investigator's decision	18	(3.5%)	12	(4.1%)	7	(4.4%)	2	(4.0%)	3	(2.6%)	42	(3.7%)
Other	11	(2.2%)	7	(2.4%)	4	(2.5%)	0	(0.0%)	7	(6.0%)	29	(2.6%)

	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Reason for study termination prior to 24 weeks												
Reported event	3	(0.6%)	3	(1.0%)	0	(0.0%)	1	(2.0%)	0	(0.0%)	7	(0.6%)
Death	25	(4.9%)	13	(4.4%)	48	(30.2%)	6	(12.0%)	28	(24.1%)	120	(10.6%)
Patient did not show up any more	9	(1.8%)	5	(1.7%)	13	(8.2%)	1	(2.0%)	6	(5.2%)	34	(3.0%)
Patient's wish	8	(1.6%)	9	(3.1%)	3	(1.9%)	1	(2.0%)	8	(6.9%)	29	(2.6%)
Withdrawal of informed consent	2	(0.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.2%)
Investigator's decision	5	(1.0%)	1	(0.3%)	4	(2.5%)	0	(0.0%)	0	(0.0%)	10	(0.9%)
Other	7	(1.4%)	1	(0.3%)	2	(1.3%)	0	(0.0%)	2	(1.7%)	12	(1.1%)

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Source: Annex 1, Table 15.1.2

Table 5. Demographic–sex and age by tumor type, full analysis set

	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)	
	n	(%)	n	(%)	n	(%)
Sex						
Male	5	(1.0%)	294	(100.0%)	106	(66.7%)
Female	504	(99.0%)	0	(0.0%)	53	(33.3%)
Age in categories						
18–<25 y	1	(0.2%)	0	(0.0%)	0	(0.0%)
25–<35 y	1	(0.2%)	0	(0.0%)	0	(0.0%)
35–<45 y	23	(4.5%)	0	(0.0%)	4	(2.5%)
45–<55 y	89	(17.5%)	3	(1.0%)	17	(10.7%)
55–<65 y	149	(29.3%)	39	(13.3%)	53	(33.3%)
65–<75 y	147	(28.9%)	103	(35.0%)	59	(37.1%)
≥75 y	99	(19.4%)	149	(50.7%)	26	(16.4%)
Geriatric age group 1						
<65 y	263	(51.7%)	42	(14.3%)	74	(46.5%)
≥65 y	246	(48.3%)	252	(85.7%)	85	(53.5%)
Geriatric age group 2						
<75 y	410	(80.6%)	145	(49.3%)	133	(83.6%)
≥75 y	99	(19.4%)	149	(50.7%)	26	(16.4%)

	Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
	n	(%)	n	(%)	n	(%)
Sex						
Male	33	(66.0%)	63	(54.3%)	501	(44.4%)
Female	17	(34.0%)	53	(45.7%)	627	(55.6%)
Age in categories						

	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)	
	n	(%)	n	(%)	n	(%)
18–<25 y	0	(0.0%)	0	(0.0%)	1	(0.1%)
25–<35 y	0	(0.0%)	1	(0.9%)	2	(0.2%)
35–<45 y	1	(2.0%)	5	(4.3%)	33	(2.9%)
45–<55 y	5	(10.0%)	12	(10.3%)	126	(11.2%)
55–<65 y	15	(30.0%)	33	(28.4%)	289	(25.6%)
65–<75 y	20	(40.0%)	39	(33.6%)	368	(32.6%)
≥75 y	9	(18.0%)	26	(22.4%)	309	(27.4%)
Geriatric age group 1						
<65 y	21	(42.0%)	51	(44.0%)	451	(40.0%)
≥65 y	29	(58.0%)	65	(56.0%)	677	(60.0%)
Geriatric age group 2						
<75 y	41	(82.0%)	90	(77.6%)	819	(72.6%)
≥75 y	9	(18.0%)	26	(22.4%)	309	(27.4%)

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Source: Annex 1, Table 15.2.1.1

Table 6. Duration (years in categories) since initial tumor diagnosis by tumor type, full analysis set

Duration since initial tumor diagnosis (years)	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
	n	(%)	n	(%)	n	(%)	N	(%)	n	(%)	n	(%)
During study	0	(0.0%)	3	(1.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	3	(0.3%)
<1 y	155	(30.5%)	120	(41.0%)	139	(87.4%)	19	(38.0%)	51	(44.0%)	484	(42.9%)
1–<2 y	38	(7.5%)	33	(11.3%)	10	(6.3%)	6	(12.0%)	16	(13.8%)	103	(9.1%)
2–<5 y	91	(17.9%)	51	(17.4%)	9	(5.7%)	14	(28.0%)	31	(26.7%)	196	(17.4%)
5–<10 y	120	(23.6%)	52	(17.7%)	1	(0.6%)	5	(10.0%)	11	(9.5%)	189	(16.8%)
10–<20 y	86	(16.9%)	31	(10.6%)	0	(0.0%)	4	(8.0%)	5	(4.3%)	126	(11.2%)
>= 20 y	19	(3.7%)	3	(1.0%)	0	(0.0%)	2	(4.0%)	2	(1.7%)	26	(2.3%)
Missing	0		1		0		0		0		1	

Duration since initial tumor diagnosis as documented at study start.
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Source: Annex 1, Table 15.2.2.3

Table 7. Duration since initial diagnosis of metastases to first XGEVA® application, full analysis set

Duration since initial diagnosis of metastases (years)	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
	n	(%)	n	(%)	n	(%)	N	(%)	n	(%)	n	(%)
During study	9	(1.8%)	7	(2.4%)	1	(0.6%)	0	(0.0%)	1	(0.9%)	18	(1.6%)
<1 y	438	(86.1%)	227	(77.7%)	147	(92.5%)	30	(60.0%)	87	(75.0%)	929	(82.5%)
1–<2 y	19	(3.7%)	27	(9.2%)	7	(4.4%)	4	(8.0%)	13	(11.2%)	70	(6.2%)
2–<5 y	23	(4.5%)	19	(6.5%)	3	(1.9%)	14	(28.0%)	10	(8.6%)	69	(6.1%)
5–<10 y	16	(3.1%)	10	(3.4%)	1	(0.6%)	2	(4.0%)	4	(3.4%)	33	(2.9%)
10–<20 y	4	(0.8%)	2	(0.7%)	0	(0.0%)	0	(0.0%)	1	(0.9%)	7	(0.6%)
Missing	0		2		0		0		0		2	

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Source: Annex 1, Table 15.2.3.1

Table 8. Duration since initial diagnosis of bone metastases

Duration since initial diagnosis of bone metastases (years)	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
	n	(%)	n	(%)	n	(%)	N	(%)	n	(%)	n	(%)
During study	16	(3.1%)	7	(2.4%)	6	(3.8%)	1	(2.0%)	5	(4.3%)	35	(3.1%)
<1 y	476	(93.5%)	242	(82.6%)	152	(95.6%)	42	(84.0%)	103	(88.8%)	1015	(90.1%)
1–<2 y	5	(1.0%)	24	(8.2%)	1	(0.6%)	3	(6.0%)	4	(3.4%)	37	(3.3%)
2–<5 y	8	(1.6%)	10	(3.4%)	0	(0.0%)	4	(8.0%)	4	(3.4%)	26	(2.3%)
5–<10 y	3	(0.6%)	9	(3.1%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	12	(1.1%)
10–<20 y	1	(0.2%)	1	(0.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.2%)
Missing	0		1		0		0		0		1	

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Source: Annex 1, Table 15.2.3.6

Table 9. Distribution pattern and diagnosis of bone metastases, full analysis set

	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
	n	(%)	n	(%)	n	(%)	N	(%)	n	(%)	n	(%)
Distribution pattern												
Singular / region	179	(35.2%)	100	(34.0%)	76	(47.8%)	30	(60.0%)	61	(52.6%)	446	(39.5%)
Oligometastatic (>3) / region	317	(62.3%)	188	(63.9%)	74	(46.5%)	18	(36.0%)	49	(42.2%)	646	(57.3%)
Not determined	13	(2.6%)	6	(2.0%)	9	(5.7%)	2	(4.0%)	6	(5.2%)	36	(3.2%)
Type of diagnosis												
Symptoms	61	(12.0%)	28	(9.6%)	13	(8.2%)	12	(24.0%)	19	(16.4%)	133	(11.8%)
Imaging (asymptomatic)	439	(86.2%)	258	(88.1%)	142	(89.3%)	38	(76.0%)	91	(78.4%)	968	(85.9%)
Unknown	9	(1.8%)	7	(2.4%)	4	(2.5%)	0	(0.0%)	6	(5.2%)	26	(2.3%)
Missing	0		1		0		0		0		1	

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Source: Annex 1, Table 15.2.3.8

Table 10. Localization of bone metastases, full analysis set

	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
	n	(%)	n	(%)	n	(%)	N	(%)	n	(%)	n	(%)
Cranium												
No	402	(81.0%)	244	(84.7%)	138	(92.0%)	44	(91.7%)	96	(87.3%)	924	(84.6%)
Yes	94	(19.0%)	44	(15.3%)	12	(8.0%)	4	(8.3%)	14	(12.7%)	168	(15.4%)
Missing	13		6		9		2		6		36	
Humerus												
No	459	(92.5%)	247	(85.8%)	138	(92.0%)	46	(95.8%)	103	(93.6%)	993	(90.9%)
Yes	37	(7.5%)	41	(14.2%)	12	(8.0%)	2	(4.2%)	7	(6.4%)	99	(9.1%)
Missing	13		6		9		2		6		36	
Scapula												
No	440	(88.7%)	236	(81.9%)	133	(88.7%)	42	(87.5%)	98	(89.1%)	949	(86.9%)
Yes	56	(11.3%)	52	(18.1%)	17	(11.3%)	6	(12.5%)	12	(10.9%)	143	(13.1%)
Missing	13		6		9		2		6		36	
Ribs												
No	258	(52.0%)	127	(44.1%)	87	(58.0%)	25	(52.1%)	70	(63.6%)	567	(51.9%)
Yes	238	(48.0%)	161	(55.9%)	63	(42.0%)	23	(47.9%)	40	(36.4%)	525	(48.1%)
Missing	13		6		9		2		6		36	
Cervical spine												
No	394	(79.4%)	224	(77.8%)	133	(88.7%)	42	(87.5%)	93	(84.5%)	886	(81.1%)
Yes	102	(20.6%)	64	(22.2%)	17	(11.3%)	6	(12.5%)	17	(15.5%)	206	(18.9%)
Missing	13		6		9		2		6		36	
Thoracic spine												
No	202	(40.7%)	128	(44.4%)	81	(54.0%)	31	(64.6%)	63	(57.3%)	505	(46.2%)
Yes	294	(59.3%)	160	(55.6%)	69	(46.0%)	17	(35.4%)	47	(42.7%)	587	(53.8%)
Missing	13		6		9		2		6		36	
Lumbar spine												
No	247	(49.8%)	134	(46.5%)	95	(63.3%)	33	(68.8%)	60	(54.5%)	569	(52.1%)
Yes	249	(50.2%)	154	(53.5%)	55	(36.7%)	15	(31.3%)	50	(45.5%)	523	(47.9%)
Missing	13		6		9		2		6		36	
Sacrum												
No	379	(76.4%)	206	(71.5%)	130	(86.7%)	38	(79.2%)	88	(80.0%)	841	(77.0%)
Yes	117	(23.6%)	82	(28.5%)	20	(13.3%)	10	(20.8%)	22	(20.0%)	251	(23.0%)
Missing	13		6		9		2		6		36	
Pelvis												
No	312	(62.9%)	104	(36.1%)	95	(63.3%)	34	(70.8%)	75	(68.2%)	620	(56.8%)
Yes	184	(37.1%)	184	(63.9%)	55	(36.7%)	14	(29.2%)	35	(31.8%)	472	(43.2%)
Missing	13		6		9		2		6		36	
Femoral												
No	393	(79.2%)	209	(72.6%)	130	(86.7%)	37	(77.1%)	92	(83.6%)	861	(78.8%)
Yes	103	(20.8%)	79	(27.4%)	20	(13.3%)	11	(22.9%)	18	(16.4%)	231	(21.2%)
Missing	13		6		9		2		6		36	

	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
	n	(%)	n	(%)	n	(%)	N	(%)	n	(%)	n	(%)
Other												
No	439	(88.5%)	248	(86.1%)	134	(89.3%)	38	(79.2%)	86	(78.2%)	945	(86.5%)
Yes	57	(11.5%)	40	(13.9%)	16	(10.7%)	10	(20.8%)	24	(21.8%)	147	(13.5%)
Missing	13		6		9		2		6		36	

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Source: Annex 1, Table 15.2.3.10

Table 11. Frequency of previous SREs and tumor-induced hypercalcemia, full analysis set

	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
	n	(%)	n	(%)	n	(%)	N	(%)	n	(%)	n	(%)
Previous tumor-induced hypercalcemia only	3	(0.6%)	1	(0.3%)	1	(0.6%)	1	(2.0%)	0	(0.0%)	6	(0.5%)
Previous SRE only*	53	(10.4%)	14	(4.8%)	19	(11.9%)	11	(22.0%)	8	(6.9%)	105	(9.3%)
Previous skeletal compression	7	(1.4%)	1	(0.3%)	1	(0.6%)	2	(4.0%)	0	(0.0%)	11	(1.0%)
Previous pathologic fracture	38	(7.5%)	11	(3.7%)	11	(6.9%)	6	(12.0%)	6	(5.2%)	72	(6.4%)
Previous surgery to bone	20	(3.9%)	5	(1.7%)	9	(5.7%)	5	(10.0%)	3	(2.6%)	42	(3.7%)
Previous radiation therapy to bone	27	(5.3%)	8	(2.7%)	13	(8.2%)	7	(14.0%)	3	(2.6%)	58	(5.1%)
Previous SRE and tumor-induced hypercalcemia	2	(0.4%)	2	(0.7%)	0	(0.0%)	1	(2.0%)	1	(0.9%)	6	(0.5%)

*Excluding tumor-induced hypercalcemia
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Source: Annex 1, Table 15.2.4.1

Table 12. Duration since diagnosis of previous SREs (years), full analysis set

	Breast cancer (N=58)			Prostate cancer (N=17)			Lung cancer (N=20)		
	N*	n	(%)	N*	n	(%)	N*	n	(%)
Previous SRE only	53			14			19		
During study		5	(9.6%)		2	(14.3%)		1	(5.3%)
<1 y		45	(86.5%)		10	(71.4%)		18	(94.7%)
1–<2 y		1	(1.9%)		1	(7.1%)		0	(0.0%)
2–<5 y		1	(1.9%)		1	(7.1%)		0	(0.0%)
Missing		1			0			0	

	Kidney cancer (N=13)			Other cancer type (N=9)			Total (N=117)		
	N*	n	(%)	N*	n	(%)	N*	n	(%)
Previous SRE only	11			8			105		
During study		1	(9.1%)		0	(0.0%)		9	(8.7%)
<1 y		10	(90.9%)		6	(85.7%)		89	(86.4%)
1–<2 y		0	(0.0%)		0	(0.0%)		2	(1.9%)
2–<5 y		0	(0.0%)		1	(14.3%)		3	(2.9%)
Missing		0			1			2	

Percentages are based on the number of subjects with previous SRE (excluding tumor-induced hypercalcemia) respectively for each tumor type. In each column header 'N' denotes the number of subjects with previous SRE and/or tumor induced hypercalcemia.
* 'N*' denotes the number of subjects in the respective subgroup
Program: s:\Amgen\AM05\SAS\PRG_Analysis\TAB.sas
Output: End of Text Tables Final 2017-07-21 Denosumab (XGEVA) Protocol 20101312 (X-TREME) (AM05).pdf (Date Generated: 20 February 2018)
Source: Annex 1, Table 15.2.4.2

Table 13. ECOG score and presence of concomitant disease before start of therapy, full analysis set

	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
ECOG performance status before start of therapy												
0	193	(38.4%)	82	(29.5%)	37	(23.3%)	5	(10.4%)	30	(26.1%)	347	(31.5%)
1	244	(48.5%)	160	(57.6%)	95	(59.7%)	38	(79.2%)	67	(58.3%)	604	(54.8%)
2	66	(13.1%)	36	(12.9%)	27	(17.0%)	5	(10.4%)	18	(15.7%)	152	(13.8%)
Missing	6		16		0		2		1		25	
Any concomitant diseases (except tumor)?												
No	377	(74.1%)	165	(56.1%)	63	(39.6%)	27	(54.0%)	59	(50.9%)	691	(61.3%)
Yes	132	(25.9%)	129	(43.9%)	96	(60.4%)	23	(46.0%)	57	(49.1%)	437	(38.7%)

Program: s:\Amgen\AM05\SAS\PRG_Analysis\TAB.sas
Output: End of Text Tables Final 2017-07-21 Denosumab (XGEVA) Protocol 20101312 (X-TREME) (AM05).pdf (Date Generated: 20 February 2018)
Source: Annex 1, Table 15.2.6.1

Table 14. Summary of concomitant diseases before start of therapy

Concomitant disease	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Tumor												
Yes	509	(100.0%)	294	(100.0%)	159	(100.0%)	50	(100.0%)	116	(100.0%)	1128	(100.0%)
Diabetes												
No	435	(85.5%)	238	(81.2%)	127	(79.9%)	46	(92.0%)	90	(77.6%)	936	(83.1%)
Yes	74	(14.5%)	55	(18.8%)	32	(20.1%)	4	(8.0%)	26	(22.4%)	191	(16.9%)
Missing	0		1		0		0		0		1	
Moderate to severe kidney disease												
No	476	(93.5%)	260	(88.4%)	144	(90.6%)	32	(64.0%)	104	(89.7%)	1016	(90.1%)
Yes	33	(6.5%)	34	(11.6%)	15	(9.4%)	18	(36.0%)	12	(10.3%)	112	(9.9%)
Chronic lung disease												
No	492	(96.7%)	273	(93.2%)	108	(67.9%)	47	(94.0%)	105	(90.5%)	1025	(90.9%)
Yes	17	(3.3%)	20	(6.8%)	51	(32.1%)	3	(6.0%)	11	(9.5%)	102	(9.1%)
Missing	0		1		0		0		0		1	
Peripheral artery occlusive disease												
No	500	(98.4%)	273	(93.2%)	142	(89.3%)	47	(94.0%)	105	(90.5%)	1067	(94.8%)
Yes	8	(1.6%)	20	(6.8%)	17	(10.7%)	3	(6.0%)	11	(9.5%)	59	(5.2%)
Missing	1		1		0		0		0		2	
Congestive heart failure												
No	500	(98.4%)	273	(93.2%)	152	(95.6%)	50	(100.0%)	109	(94.0%)	1084	(96.3%)
Yes	8	(1.6%)	20	(6.8%)	7	(4.4%)	0	(0.0%)	7	(6.0%)	42	(3.7%)
Missing	1		1		0		0		0		2	
Cardiac infarction												
No	505	(99.4%)	272	(92.8%)	148	(93.1%)	48	(96.0%)	113	(97.4%)	1086	(96.4%)
Yes	3	(0.6%)	21	(7.2%)	11	(6.9%)	2	(4.0%)	3	(2.6%)	40	(3.6%)
Missing	1		1		0		0		0		2	
Mild liver disease												
No	501	(98.4%)	287	(97.6%)	153	(96.2%)	49	(98.0%)	108	(93.1%)	1098	(97.3%)
Yes	8	(1.6%)	7	(2.4%)	6	(3.8%)	1	(2.0%)	8	(6.9%)	30	(2.7%)
Cerebrovascular disease												
No	499	(98.2%)	284	(96.9%)	153	(96.2%)	50	(100.0%)	113	(97.4%)	1099	(97.6%)
Yes	9	(1.8%)	9	(3.1%)	6	(3.8%)	0	(0.0%)	3	(2.6%)	27	(2.4%)
Missing	1		1		0		0		0		2	
Moderate to severe liver disease												
No	500	(98.2%)	290	(98.6%)	155	(97.5%)	50	(100.0%)	113	(97.4%)	1108	(98.2%)
Yes	9	(1.8%)	4	(1.4%)	4	(2.5%)	0	(0.0%)	3	(2.6%)	20	(1.8%)
Lymphoma												
No	508	(99.8%)	286	(97.3%)	158	(99.4%)	47	(94.0%)	116	(100.0%)	1115	(98.8%)
Yes	1	(0.2%)	8	(2.7%)	1	(0.6%)	3	(6.0%)	0	(0.0%)	13	(1.2%)

Concomitant disease	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Diabetes with end organ damages												
No	500	(98.2%)	293	(100.0%)	156	(98.1%)	49	(98.0%)	113	(97.4%)	1111	(98.6%)
Yes	9	(1.8%)	0	(0.0%)	3	(1.9%)	1	(2.0%)	3	(2.6%)	16	(1.4%)
Missing	0		1		0		0		0		1	
Ulcer disease												
No	506	(99.4%)	292	(100.0%)	154	(96.9%)	50	(100.0%)	114	(98.3%)	1116	(99.1%)
Yes	3	(0.6%)	0	(0.0%)	5	(3.1%)	0	(0.0%)	2	(1.7%)	10	(0.9%)
Missing	0		2		0		0		0		2	
Dementia												
No	508	(99.8%)	291	(99.0%)	159	(100.0%)	49	(98.0%)	116	(100.0%)	1123	(99.6%)
Yes	1	(0.2%)	3	(1.0%)	0	(0.0%)	1	(2.0%)	0	(0.0%)	5	(0.4%)
Leukemia												
No	508	(99.8%)	294	(100.0%)	158	(99.4%)	47	(94.0%)	116	(100.0%)	1123	(99.6%)
Yes	1	(0.2%)	0	(0.0%)	1	(0.6%)	3	(6.0%)	0	(0.0%)	5	(0.4%)
Connective tissue disease												
No	507	(99.6%)	292	(100.0%)	159	(100.0%)	50	(100.0%)	116	(100.0%)	1124	(99.8%)
Yes	2	(0.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.2%)
Missing	0		2		0		0		0		2	
Hemiplegia												
No	507	(99.8%)	293	(100.0%)	158	(99.4%)	50	(100.0%)	116	(100.0%)	1124	(99.8%)
Yes	1	(0.2%)	0	(0.0%)	1	(0.6%)	0	(0.0%)	0	(0.0%)	2	(0.2%)
Missing	1		1		0		0		0		2	
AIDS												
No	509	(100.0%)	293	(100.0%)	159	(100.0%)	50	(100.0%)	115	(99.1%)	1126	(99.9%)
Yes	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.9%)	1	(0.1%)
Missing	0		1		0		0		0		1	

Program: s:\Amgen\AM05\SAS\PRG_Analysis\TAB.sas
Output: End of Text Tables Final 2017-07-21 Denosumab (XGEVA) Protocol 20101312 (X-TREME) (AM05).pdf (Date Generated: 20 February 2018)
Source: Annex 1, Table 15.2.6.2

Table 15. Previous antiresorptive therapy, full analysis set

Previous antiresorptive therapy	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
No	469	(92.1%)	280	(95.2%)	151	(95.0%)	45	(90.0%)	111	(95.7%)	1056	(93.6%)
Yes	40	(7.9%)	14	(4.8%)	8	(5.0%)	5	(10.0%)	5	(4.3%)	72	(6.4%)

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Output: End of Text Tables Final 2017-07-21 Denosumab (XGEVA) Protocol 20101312 (X-TREME) (AM05).pdf (Date Generated: 20 February 2018)
Source: Annex 1, Table 15.2.5.1

Table 16. Previous antineoplastic therapy

	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Previous surgery												
No	425	(83.5%)	271	(92.2%)	134	(84.3%)	29	(58.0%)	81	(69.8%)	940	(83.3%)
Yes	84	(16.5%)	23	(7.8%)	25	(15.7%)	21	(42.0%)	35	(30.2%)	188	(16.7%)
Previous radiotherapy												
No	367	(72.1%)	257	(87.4%)	105	(66.0%)	31	(62.0%)	76	(65.5%)	836	(74.1%)
Yes	142	(27.9%)	37	(12.6%)	54	(34.0%)	19	(38.0%)	40	(34.5%)	292	(25.9%)
Previous chemotherapy												
No	322	(63.3%)	230	(78.2%)	46	(28.9%)	16	(32.0%)	48	(41.4%)	662	(58.7%)
Yes	187	(36.7%)	64	(21.8%)	113	(71.1%)	34	(68.0%)	68	(58.6%)	466	(41.3%)
Previous antihormonal therapy (including antibodies and small molecules)												
No	291	(57.2%)	102	(34.7%)	158	(99.4%)	49	(98.0%)	111	(95.7%)	711	(63.0%)
Yes	218	(42.8%)	192	(65.3%)	1	(0.6%)	1	(2.0%)	5	(4.3%)	417	(37.0%)

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Output: End of Text Tables Final 2017-07-21 Denosumab (XGEVA) Protocol 20101312 (X-TREME) (AM05).pdf (Date Generated: 20 February 2018)
Source: Annex 1, Table 15.2.6.3

Table 17. Most comment previous chemotherapy (at least 5% of patients with any chemotherapy and most frequent therapies in kidney cancer patients) by preferred term, full analysis set

	Breast cancer (N=187)		Prostate cancer (N=64)		Lung cancer (N=113)		Kidney cancer (N=34)		Other cancer type (N=68)		Total (N=466)	
Preferred term	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Docetaxel	36	(19.3%)	51	(79.7%)	4	(3.5%)	0	(0.0%)	3	(4.4%)	94	(20.2%)
Paclitaxel	62	(33.2%)	0	(0.0%)	21	(18.6%)	1	(2.9%)	10	(14.7%)	94	(20.2%)
Bevacizumab	52	(27.8%)	0	(0.0%)	15	(13.3%)	2	(5.9%)	11	(16.2%)	80	(17.2%)
Carboplatin	9	(4.8%)	1	(1.6%)	52	(46.0%)	0	(0.0%)	12	(17.6%)	74	(15.9%)
Cisplatin	2	(1.1%)	1	(1.6%)	44	(38.9%)	2	(5.9%)	20	(29.4%)	69	(14.8%)
Trastuzumab	47	(25.1%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	3	(4.4%)	50	(10.7%)
Capecitabine	33	(17.6%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	7	(10.3%)	40	(8.6%)
Cyclophosphamide	28	(15.0%)	1	(1.6%)	3	(2.7%)	0	(0.0%)	1	(1.5%)	33	(7.1%)
Vinorelbine	17	(9.1%)	0	(0.0%)	10	(8.8%)	0	(0.0%)	2	(2.9%)	29	(6.2%)
Gemcitabine	4	(2.1%)	1	(1.6%)	7	(6.2%)	1	(2.9%)	12	(17.6%)	25	(5.4%)
Everolimus	8	(4.3%)	0	(0.0%)	0	(0.0%)	9	(26.5%)	1	(1.5%)	18	(3.9%)
Sunitinib malate	0	(0.0%)	0	(0.0%)	0	(0.0%)	8	(23.5%)	1	(1.5%)	9	(1.9%)
Pazopanib hydrochloride	0	(0.0%)	0	(0.0%)	0	(0.0%)	8	(23.5%)	0	(0.0%)	8	(1.7%)

Program: s:\Amgen\AM05\SAS\PRG_Analysis\TAB.sas
Output: End of Text Tables Final 2017-07-21 Denosumab (XGEVA) Protocol 20101312 (X-TREME) (AM05).pdf (Date Generated: 20 February 2018)
Source: Annex 1, Table 15.2.6.5

Table 18. Most common previous antihormonal therapy* (> 3% of all patients), full analysis set

	Breast cancer (N=218)		Prostate cancer (N=192)		Lung cancer (N=1)		Kidney cancer (N=1)		Other cancer type (N=5)		Total (N=417)	
Preferred term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Leuprorelin acetate	0	(0.0%)	88	(45.8%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	88	(21.1%)
Letrozole	81	(37.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	81	(19.4%)
Anastrozole	79	(36.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	79	(18.9%)
Bicalutamide	0	(0.0%)	73	(38.0%)	0	(0.0%)	0	(0.0%)	1	(20.0%)	74	(17.7%)
Tamoxifen	46	(21.1%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	46	(11.0%)
Exemestane	41	(18.8%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(40.0%)	43	(10.3%)
Buserelin acetate	0	(0.0%)	20	(10.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	20	(4.8%)
Leuprorelin	0	(0.0%)	14	(7.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	14	(3.4%)
Degarelix	0	(0.0%)	13	(6.8%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	13	(3.1%)

* Including antibodies and small molecules
Program: s:\Amgen\AM05\SAS\PRG_Analysis\TAB.sas
Output: End of Text Tables Final 2017-07-21 Denosumab (XGEVA) Protocol 20101312 (X-TREME) (AM05).pdf (Date Generated: 20 February 2018)
Source: Annex 1, Table 15.2.6.6

Table 19. Persistence at 24 weeks by tumor type, full analysis set excluding patients with events before persistence assessment*

	Breast cancer (N=480)			Prostate cancer (N=281)			Lung cancer (N=113)		
	n	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	168	(35.0%)	[30.7%-39.5%]	109	(38.8%)	[33.1%-44.8%]	54	(47.8%)	[38.3%-57.4%]
Yes	312	(65.0%)	[60.5%-69.3%]	172	(61.2%)	[55.2%-66.9%]	59	(52.2%)	[42.6%-61.7%]

	Kidney cancer (N=46)			Other cancer type (N=88)			Total (N=1008)		
	n	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	13	(28.3%)	[16.0%-43.5%]	44	(50.0%)	[39.1%-60.9%]	388	(38.5%)	[35.5%-41.6%]
Yes	33	(71.7%)	[56.5%-84.0%]	44	(50.0%)	[39.1%-60.9%]	620	(61.5%)	[58.4%-64.5%]

*excluding subjects who died, withdrew consent or lost to follow-up **before** persistence assessment, patients who died, withdrew consent or who were lost to follow-up **after** being non-persistent were included.
CI: exact 2-sided Clopper-Pearson 95%-confidence interval
Program: s:\Amgen\AM05\SAS\PRG_Analysis\TAB.sas
Output: End of Text Tables Final 2017-07-21 Denosumab (XGEVA) Protocol 20101312 (X-TREME) (AM05).pdf (Date Generated: 20 February 2018)
Source: Annex 1, Table 15.3.1.1

Table 20. Persistence at 24 weeks by tumor type – reasons for non-persistence, full analysis set excluding patients with events before persistence assessment*

	Breast cancer (N=480)		Prostate cancer (N=281)		Lung cancer (N=113)		Kidney cancer (N=46)		Other cancer type (N=88)		Total (N=1008)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Persistent	312	(65.0%)	172	(61.2%)	59	(52.2%)	33	(71.7%)	44	(50.0%)	620	(61.5%)
Reasons for non-persistence												
Prem. term. (adverse event)	4	(0.8%)	2	(0.7%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	6	(0.6%)
Prem. term. (patient refuses to take medication)	7	(1.5%)	5	(1.8%)	3	(2.7%)	1	(2.2%)	6	(6.8%)	22	(2.2%)
Prem. term. (physician`s decision)	4	(0.8%)	1	(0.4%)	2	(1.8%)	0	(0.0%)	0	(0.0%)	7	(0.7%)
Prem. term. (other)	4	(0.8%)	1	(0.4%)	1	(0.9%)	0	(0.0%)	2	(2.3%)	8	(0.8%)
Not enough injections	1	(0.2%)	0	(0.0%)	1	(0.9%)	0	(0.0%)	1	(1.1%)	3	(0.3%)
Violation of time windows	148	(30.8%)	100	(35.6%)	47	(41.6%)	12	(26.1%)	35	(39.8%)	342	(33.9%)
Number of time windows violated #												
1	121	(25.2%)	83	(29.5%)	40	(35.4%)	11	(23.9%)	28	(31.8%)	283	(28.1%)
2	24	(5.0%)	13	(4.6%)	6	(5.3%)	1	(2.2%)	6	(6.8%)	50	(5.0%)
3	3	(0.6%)	2	(0.7%)	1	(0.9%)	0	(0.0%)	1	(1.1%)	7	(0.7%)
More than 3	0	(0.0%)	2	(0.7%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.2%)

*excluding patients who died, withdrew consent or lost to follow-up **before** persistence assessment, patients who died, withdrew consent or who were lost to follow-up **after** being non-persistent were included.
# A time window of **+/- 7 days** was allowed for each injection relative to the previous injection and of **+ 2 weeks** after 24 weeks endpoint.
Prem.term. = premature termination
Program: s:\Amgen\AM05\SAS\PRG_Analysis\TAB.sas
Output: End of Text Tables Final 2017-07-21 Denosumab (XGEVA) Protocol 20101312 (X-TREME) (AM05).pdf (Date Generated: 20 February 2018)
Source: Annex 1, Table 15.3.1.1

Table 21. Persistence at 24 weeks – sensitivity analysis, full analysis set excluding patients with events before persistence assessment*

	Breast cancer (N=475)			Prostate cancer (N=279)			Lung cancer (N=106)		
	n	(%)	CI	n	(%)	CI	n	(%)	CI
No	99	(20.8%)	[17.3%-24.8%]	66	(23.7%)	[18.8%-29.1%]	35	(33.0%)	[24.2%-42.8%]
Yes	376	(79.2%)	[75.2%-82.7%]	213	(76.3%)	[70.9%-81.2%]	71	(67.0%)	[57.2%-75.8%]
	Kidney cancer (N=46)			**Other cancer type (N=84)**			**Total (N=990)**		
	n	(%)	CI	n	(%)	CI	n	(%)	CI
No	12	(26.1%)	[14.3%-41.1%]	24	(28.6%)	[19.2%-39.5%]	236	(23.8%)	[21.2%-26.6%]
Yes	34	(73.9%)	[58.9%-85.7%]	60	(71.4%)	[60.5%-80.8%]	754	(76.2%)	[73.4%-78.8%]

*excluding subjects who died, withdrew consent or lost to follow-up **before** persistence assessment, patients who died, withdrew consent or who were lost to follow-up **after** being non-persistent were included.
CI: exact 2-sided Clopper-Pearson 95%-confidence interval
Program: s:\Amgen\AM05\SAS\PRG_Analysis\TAB.sas
Output: End of Text Tables Final 2017-07-21 Denosumab (XGEVA) Protocol 20101312 (X-TREME) (AM05).pdf (Date Generated: 20 February 2018)
Source: Annex 1, Table 15.3.3.1

Table 22. Persistence at 24 weeks – sensitivity analysis – reasons for non-persistence, full analysis set excluding patients with events before persistence assessment*

	Breast cancer (N=475)		Prostate cancer (N=279)		Lung cancer (N=106)		Kidney cancer (N=46)		Other cancer type (N=84)		Total (N=990)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Persistent	376	(79.2%)	213	(76.3%)	71	(67.0%)	34	(73.9%)	60	(71.4%)	754	(76.2%)
Reasons for non-persistence												
Prem. term. (adverse event)	4	(0.8%)	2	(0.7%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	6	(0.6%)
Prem. term. (patient refuses to take medication)	8	(1.7%)	5	(1.8%)	3	(2.8%)	1	(2.2%)	6	(7.1%)	23	(2.3%)
Prem. term. (physician`s decision)	5	(1.1%)	1	(0.4%)	4	(3.8%)	0	(0.0%)	1	(1.2%)	11	(1.1%)
Prem. term. (other)	4	(0.8%)	1	(0.4%)	2	(1.9%)	0	(0.0%)	2	(2.4%)	9	(0.9%)
Not enough injections	0	(0.0%)	1	(0.4%)	2	(1.9%)	0	(0.0%)	0	(0.0%)	3	(0.3%)
Violation of time windows	78	(16.4%)	56	(20.1%)	24	(22.6%)	11	(23.9%)	15	(17.9%)	184	(18.6%)
Number of time windows violated #												
1	72	(15.2%)	49	(17.6%)	22	(20.8%)	11	(23.9%)	13	(15.5%)	167	(16.9%)
2	5	(1.1%)	6	(2.2%)	2	(1.9%)	0	(0.0%)	2	(2.4%)	15	(1.5%)
3	1	(0.2%)	1	(0.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.2%)
More than 3	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)

*excluding subjects who died, withdrew consent or lost to follow-up **before** persistence assessment, patients who died, withdrew consent or who were lost to follow-up **after** being non-persistent were included.
Prem.term. = premature termination
# A time window of +/- 14 days was allowed for each injection relative to the previous injection and of + 4 weeks after 24 weeks endpoint.
Source: Annex 1, Table 15.3.3.1

Table 23. Persistence at 48 weeks by tumor type, full analysis set excluding patients with events before persistence assessment*

	Breast cancer (N=455)			Prostate cancer (N=267)			Lung cancer (N=88)		
	n	(%)	CI	n	(%)	CI	n	(%)	CI
No	257	(56.5%)	[51.8%-61.1%]	172	(64.4%)	[58.4%-70.2%]	62	(70.5%)	[59.8%-79.7%]
Yes	198	(43.5%)	[38.9%-48.2%]	95	(35.6%)	[29.8%-41.6%]	26	(29.5%)	[20.3%-40.2%]

	Kidney cancer (N=39)			Other cancer type (N=79)			Total (N=928)		
	n	(%)	CI	n	(%)	CI	n	(%)	CI
No	24	(61.5%)	[44.6%-76.6%]	63	(79.7%)	[69.2%-88.0%]	578	(62.3%)	[59.1%-65.4%]
Yes	15	(38.5%)	[23.4%-55.4%]	16	(20.3%)	[12.0%-30.8%]	350	(37.7%)	[34.6%-40.9%]

*excluding subjects who died, withdrew consent or lost to follow-up **before** persistence assessment, patients who died, withdrew consent or who were lost to follow-up **after** being non-persistent were included.
CI: exact 2-sided Clopper-Pearson 95%-confidence interval
Program: s:\Amgen\AM05\SAS\PRG_Analysis\TAB.sas
Output: End of Text Tables Final 2017-07-21 Denosumab (XGEVA) Protocol 20101312 (X-TREME) (AM05).pdf (Date Generated: 20 February 2018)
Source: Annex 1, Table 15.3.2.1

Table 24. Persistence at 48 weeks by tumor type – reasons for non-persistence full analysis set excluding patients with events before persistence assessment*

	Breast cancer (N=455)		Prostate cancer (N=267)		Lung cancer (N=88)		Kidney cancer (N=39)		Other cancer type (N=79)		Total (N=928)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Persistent	198	(43.5%)	95	(35.6%)	26	(29.5%)	15	(38.5%)	16	(20.3%)	350	(37.7%)
Reasons for non-persistence												
Prem. term. (adverse event)	4	(0.9%)	2	(0.7%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	6	(0.6%)
Prem. term. (patient refuses to take medication)	13	(2.9%)	11	(4.1%)	3	(3.4%)	2	(5.1%)	9	(11.4%)	38	(4.1%)
Prem. term. (physician`s decision)	6	(1.3%)	4	(1.5%)	2	(2.3%)	1	(2.6%)	1	(1.3%)	14	(1.5%)
Prem. term. (other)	6	(1.3%)	2	(0.7%)	2	(2.3%)	0	(0.0%)	4	(5.1%)	14	(1.5%)
Not enough injections	1	(0.2%)	3	(1.1%)	0	(0.0%)	0	(0.0%)	1	(1.3%)	5	(0.5%)
Violation of time windows	227	(49.9%)	150	(56.2%)	55	(62.5%)	21	(53.8%)	48	(60.8%)	501	(54.0%)
Number of time windows violated #												
1	141	(31.0%)	84	(31.5%)	39	(44.3%)	15	(38.5%)	29	(36.7%)	308	(33.2%)
2	58	(12.7%)	38	(14.2%)	12	(13.6%)	5	(12.8%)	11	(13.9%)	124	(13.4%)
3	15	(3.3%)	21	(7.9%)	3	(3.4%)	0	(0.0%)	5	(6.3%)	44	(4.7%)
More than 3	13	(2.9%)	7	(2.6%)	1	(1.1%)	1	(2.6%)	3	(3.8%)	25	(2.7%)

*excluding subjects who died, withdrew consent or lost to follow-up **before** persistence assessment, patients who died, withdrew consent or who were lost to follow-up **after** being non-persistent were included.
Prem.term. = premature termination
# A time window of **+/- 7 days** was allowed for each injection relative to the previous injection and of **+ 7 weeks** after 48 weeks endpoint.

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Output: End of Text Tables Final 2017-07-21 Denosumab (XGEVA) Protocol 20101312 (X-TREME) (AM05).pdf (Date Generated: 20 February 2018)
Source: Annex 1, Table 15.3.2.1

Table 25. Persistence at 48 weeks by tumor type – sensitivity analysis, full analysis set excluding patients with events before persistence assessment*

	Breast cancer (N=437)			Prostate cancer (N=260)			Lung cancer (N=72)		
	n	(%)	CI	n	(%)	CI	n	(%)	CI
No	172	(39.4%)	[34.7%-44.1%]	113	(43.5%)	[37.3%-49.7%]	39	(54.2%)	[42.0%-66.0%]
Yes	265	(60.6%)	[55.9%-65.3%]	147	(56.5%)	[50.3%-62.7%]	33	(45.8%)	[34.0%-58.0%]

	Kidney cancer (N=37)			Other cancer type (N=69)			Total (N=875)		
	n	(%)	CI	n	(%)	CI	n	(%)	CI
No	21	(56.8%)	[39.5%-72.9%]	42	(60.9%)	[48.4%-72.4%]	387	(44.2%)	[40.9%-47.6%]
Yes	16	(43.2%)	[27.1%-60.5%]	27	(39.1%)	[27.6%-51.6%]	488	(55.8%)	[52.4%-59.1%]

*excluding subjects who died, withdrew consent or lost to follow-up **before** persistence assessment, patients who died, withdrew consent or who were lost to follow-up **after** being non-persistent were included.
CI: exact 2-sided Clopper-Pearson 95%-confidence interval
Program: s:\Amgen\AM05\SAS\PRG_Analysis\TAB.sas
Output: End of Text Tables Final 2017-07-21 Denosumab (XGEVA) Protocol 20101312 (X-TREME) (AM05).pdf (Date Generated: 20 February 2018)
Source: Annex 1, Table 15.3.4.1

Table 26. Persistence at 48 weeks by tumor type – sensitivity analysis – reasons for non-persistence, full analysis set excluding patients with events before persistence assessment *

	Breast cancer (N=437)		Prostate cancer (N=260)		Lung cancer (N=72)		Kidney cancer (N=37)		Other cancer type (N=69)		Total (N=875)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Persistent	265	(60.6%)	147	(56.5%)	33	(45.8%)	16	(43.2%)	27	(39.1%)	488	(55.8%)
Reasons for non-persistence												
Prem. term. (adverse event)	4	(0.9%)	3	(1.2%)	1	(1.4%)	0	(0.0%)	0	(0.0%)	8	(0.9%)
Prem. term. (patient refuses to take medication)	15	(3.4%)	13	(5.0%)	3	(4.2%)	2	(5.4%)	10	(14.5%)	43	(4.9%)
Prem. term. (physician`s decision)	11	(2.5%)	5	(1.9%)	5	(6.9%)	1	(2.7%)	1	(1.4%)	23	(2.6%)
Prem. term. (other)	7	(1.6%)	2	(0.8%)	3	(4.2%)	0	(0.0%)	4	(5.8%)	16	(1.8%)
Not enough injections	2	(0.5%)	3	(1.2%)	0	(0.0%)	1	(2.7%)	1	(1.4%)	7	(0.8%)
Violation of time windows#	133	(30.4%)	87	(33.5%)	27	(37.5%)	17	(45.9%)	26	(37.7%)	290	(33.1%)
Number of time windows violated												
1	104	(23.8%)	66	(25.4%)	22	(30.6%)	12	(32.4%)	20	(29.0%)	224	(25.6%)
2	20	(4.6%)	15	(5.8%)	5	(6.9%)	5	(13.5%)	4	(5.8%)	49	(5.6%)
3	8	(1.8%)	5	(1.9%)	0	(0.0%)	0	(0.0%)	2	(2.9%)	15	(1.7%)
More than 3	1	(0.2%)	1	(0.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.2%)

*excluding subjects who died, withdrew consent or lost to follow-up **before** persistence assessment, patients who died, withdrew consent or who were lost to follow-up **after** being non-persistent were included.
# A time window of **+/- 14 days** was allowed for each injection relative to the previous injection and of **+ 10 weeks** after 48 weeks endpoint.
Prem.term. = premature termination
Program: s:\Amgen\AM05\SAS\PRG_Analysis\TAB.sas
Output: End of Text Tables Final 2017-07-21 Denosumab (XGEVA) Protocol 20101312 (X-TREME) (AM05).pdf (Date Generated: 20 February 2018)
Source: Annex 1, Table 15.3.4.1

Table 27. Time to non-persistence [weeks] – overall analysis Kaplan-Meier estimates

	Kaplan-Meier Quartiles [weeks]			
			95% CI	
	Quartile	Point Estimate	Lower Limit	Upper Limit
Overall (N=1128)	1st Quartile	13.00	12.14	16.14
	Median	33.29	31.71	37.14
	3rd Quartile	69.86	60.71	69.86

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Output: End of Text Tables Final 2017-07-21 Denosumab (XGEVA) Protocol 20101312 (X-TREME) (AM05).pdf (Date Generated: 20 February 2018)
Source: Annex 1, Table 15.3.5.1.2

Table 28. Time to non-persistence – analysis by tumor type Kaplan-Meier estimates

	Kaplan-Meier Quartiles [weeks]			
			95% CI	
	Quartile	Point Estimate	Lower Limit	Upper Limit
Breast cancer (N=509)	1st Quartile	15.86	12.29	17.00
	Median	37.29	33.14	44.14
	3rd Quartile	69.86	60.71	69.86
Kidney cancer (N=50)	1st Quartile	20.57	8.29	29.14
	Median	36.14	27.86	not estimable
	3rd Quartile	not estimable	48.29	not estimable
Lung cancer (N=159)	1st Quartile	11.86	8.14	13.29
	Median	33.29	20.57	51.43
	3rd Quartile	not estimable	53.29	not estimable
Other cancer type (N=116)	1st Quartile	12.86	8.14	16.14
	Median	24.14	19.86	36.14
	3rd Quartile	56.14	40.14	56.14
Prostate cancer (N=294)	1st Quartile	12.43	8.71	16.14
	Median	30.14	27.71	38.43
	3rd Quartile	57.29	53.29	not estimable

Program: s:\Amgen\AM05\SAS\PRG_Analysis\TAB.sas
Output: End of Text Tables Final 2017-07-21 Denosumab (XGEVA) Protocol 20101312 (X-TREME) (AM05).pdf (Date Generated: 20 February 2018)
Source: Annex 1, Table 15.3.5.2.2

Table 29. Probability of persistence at 24 weeks – estimated by Kaplan-Meier methods, full analysis set

Tumor type	Probability for persistence at 24 weeks, primary analysis[#]	Probability for persistence at 24 weeks, sensitivity analysis*
Overall (N=1128)	61.4 %	77.5 %
Breast cancer (N=509)	64.7 %	79.3 %
Prostate cancer (N=294)	60.8 %	75.3 %
Lung cancer (N=159)	54.1 %	74.3 %
Kidney cancer (N=50)	73.2 %	74.5 %
Other cancer type (N=116)	50.3 %	76.9 %

Time window between injections of +/- 7 days was allowed
* Time window between injections of +/- 14 days was allowed and patients who were lost to follow-up were censored
Program: s:\Amgen\AM05\SAS\PRG_Analysis\TAB.sas
Output: End of Text Tables Final 2017-07-21 Denosumab (XGEVA) Protocol 20101312 (X-TREME) (AM05).pdf (Date Generated: 20 February 2018)
Source: Annex 1, Tables 15.3.5.1.2, 15.3.5.2.2, 15.3.9.1.2, and 15.3.9.2.2

Table 30. Wald test and hazard ratio estimates for tested variables in proportional hazards model for time to non-persistence, primary analysis[#], full analysis set

Variable	p-value Wald test	Hazard Ratio	95% CI for Hazard Ratio
Age: Unit=1 y	0.2110	1.005	[0.997, 1.013]
Gender: Male vs Female	0.3981	1.137	[0.844, 1.532]
Tumor type	0.3539		
Tumor type: Breast cancer vs Other		0.766	[0.558, 1.050]
Tumor type: Kidney cancer vs Other		0.666	[0.422, 1.052]
Tumor type: Lung cancer vs Other		0.811	[0.584, 1.125]
Tumor type: Prostate cancer vs Other		0.881	[0.637, 1.219]
Visceral metastases: Yes vs No	0.0006	1.355	[1.138, 1.614]
Previous antineoplastic therapy: Yes vs No	0.9779	0.997	[0.821, 1.211]
SREs and/or tumor induced hypercalcemia: Yes vs No	0.1785	0.839	[0.650, 1.083]
ECOG status	0.0381		
ECOG status: 0 vs 2		0.716	[0.552, 0.929]
ECOG status: 1 vs 2		0.828	[0.653, 1.051]
Previous antiresorptive therapy: Yes vs No	0.2111	1.230	[0.889, 1.702]

Time window between injections of +/- 7 days was allowed
Program: s:\Amgen\AM05\SAS\PRG_Analysis\TAB.sas
Output: End of Text Tables Final 2017-07-21 Denosumab (XGEVA) Protocol 20101312 (X-TREME) (AM05).pdf (Date Generated: 20 February 2018)
Source: Annex 1, Table 15.3.6

Table 31. Wald test and hazard ratio estimates for tested variables in proportional hazards model for time to non-persistence, sensitivity analysis*, full analysis set

Variable	p-value Wald test	Hazard Ratio	95% CI for Hazard Ratio
Age: Unit=1 y	0.0011		
Gender: Male vs Female	0.7318	1.017	[1.007, 1.027]
Tumor type	0.5542	1.069	[0.731, 1.563]
Tumor type: Breast cancer vs Other		0.757	[0.509, 1.124]
Tumor type: Kidney cancer vs Other		0.910	[0.527, 1.572]
Tumor type: Lung cancer vs Other		0.744	[0.486, 1.138]
Tumor type: Prostate cancer vs Other		0.781	[0.519, 1.175]
Visceral metastases: Yes vs No	0.0230	1.286	[1.035, 1.597]
Previous antineoplastic therapy: Yes vs No	0.7883	1.034	[0.810, 1.321]
SREs and/or tumor induced hypercalcemia: Yes vs No	0.7143	0.944	[0.693, 1.285]
ECOG status	0.2320		
ECOG status: 0 vs 2		0.769	[0.558, 1.059]
ECOG status: 1 vs 2		0.790	[0.589, 1.059]
Previous antiresorptive therapy: Yes vs No	0.2513	1.258	[0.850, 1.863]

* Time window between injections of +/- 14 days was allowed and patients who were lost to follow-up were censored
Program: s:\Amgen\AM05\SAS\PRG_Analysis\TAB.sas
Output: End of Text Tables Final 2017-07-21 Denosumab (XGEVA) Protocol 20101312 (X-TREME) (AM05).pdf (Date Generated: 20 February 2018)
Source: Annex 1, Table 15.3.10

Table 32. Frequency of Vitamin D supplementation by visit, full analysis set

Visit	Missing	N Evaluable	Yes n (%)	No n (%)
Visit 1	4	1080	890 (82.4%)	190 (17.6%)
Visit 2	3	1040	869 (83.6%)	171 (16.4%)
Visit 3	3	999	847 (84.8%)	152 (15.2%)
Visit 4	8	942	799 (84.8%)	143 (15.2%)
Visit 5	3	904	766 (84.7%)	138 (15.3%)
Visit 6	1	850	729 (85.8%)	121 (14.2%)
Visit 7	2	817	698 (85.4%)	119 (14.6%)
Visit 8	1	775	663 (85.5%)	112 (14.5%)
Visit 9	2	737	629 (85.3%)	108 (14.7%)
Visit 10	1	697	598 (85.8%)	99 (14.2%)
Visit 11	5	635	547 (86.1%)	88 (13.9%)
Visit 12	3	546	483 (88.5%)	63 (11.5%)
Visit 13	4	370	327 (88.4%)	43 (11.6%)
Visit 14	1	100	87 (87.0%)	13 (13.0%)
Visit 15	0	22	20 (90.9%)	2 (9.1%)
Visit 16	0	10	10 (100.0%)	0 (0.0%)
Visit 17	0	5	5 (100.0%)	0 (0.0%)
Visit 18	0	3	3 (100.0%)	0 (0.0%)
Visit 19	0	3	3 (100.0%)	0 (0.0%)
Visit 20	0	3	3 (100.0%)	0 (0.0%)
Visit 21	0	1	1 (100.0%)	0 (0.0%)

Program: s:\Amgen\AM05\SAS\PRG_Analysis\TAB.sas
Output: End of Text Tables Final 2017-07-21 Denosumab (XGEVA) Protocol 20101312 (X-TREME) (AM05).pdf (Date Generated: 20 February 2018)
Source: Annex 1, Table 15.4.1.1

Table 33. Summary of daily dose of Vitamin D supplementation by visit (abridged table), full analysis set

Visit	Unit	N evaluable	Mean	SD	Min	Q1	Median	Q3	Max
Visit 1	IU	824	689.7	1653.0	13	400	400	800	41600
Visit 2	IU	795	628.7	780.0	126	400	400	800	20000
Visit 3	IU	780	615.8	376.5	143	400	400	800	2857
Visit 4	IU	731	623.6	423.5	120	400	400	800	5714
Visit 5	IU	699	625.4	436.3	33	400	400	800	5714
Visit 6	IU	664	632.7	450.8	143	400	400	800	5714
Visit 7	IU	637	630.8	444.5	40	400	400	800	5714
Visit 8	IU	603	638.2	468.2	13	400	400	800	5714
Visit 9	IU	574	650.1	515.4	29	400	400	800	5714
Visit 10	IU	545	643.4	520.9	143	400	400	800	5714
Visit 11	IU	498	662.1	648.5	143	400	400	800	8880
Visit 12	IU	438	639.6	503.7	143	400	400	800	5714
Visit 13	IU	301	677.3	572.0	200	400	400	800	5714
Visit 14	IU	81	600.2	372.7	400	400	400	800	2857
Visit 15	IU	18	705.4	578.5	400	400	400	800	2857

Visit	Unit	N evaluable	Mean	SD	Min	Q1	Median	Q3	Max
Visit 16	IU	10	773.7	759.5	400	400	400	800	2857
Visit 17	IU	5	576.0	242.7	400	400	400	800	880
Visit 18	IU	3	533.3	230.9	400	400	400	800	800
Visit 19	IU	3	533.3	230.9	400	400	400	800	800
Visit 20	IU	3	533.3	230.9	400	400	400	800	800
Visit 21	IU	1	400.0		400	400	400	400	400

Program: s:\Amgen\AM05\SAS\PRG_Analysis\TAB.sas
Output: End of Text Tables Final 2017-07-21 Denosumab (XGEVA) Protocol 20101312 (X-TREME) (AM05).pdf (Date Generated: 20 February 2018)
Source: Annex 1, Table 15.4.1.3

Table 34. Frequency of Calcium supplementation by visit, full analysis set

Visit	Missing	N Evaluable	Yes n (%)	No n (%)
Visit 1	3	1081	893 (82.6%)	188 (17.4%)
Visit 2	2	1041	878 (84.3%)	163 (15.7%)
Visit 3	3	999	857 (85.8%)	142 (14.2%)
Visit 4	6	944	806 (85.4%)	138 (14.6%)
Visit 5	3	904	777 (86.0%)	127 (14.0%)
Visit 6	1	850	736 (86.6%)	114 (13.4%)
Visit 7	2	817	704 (86.2%)	113 (13.8%)
Visit 8	1	775	668 (86.2%)	107 (13.8%)
Visit 9	2	737	635 (86.2%)	102 (13.8%)
Visit 10	1	697	601 (86.2%)	96 (13.8%)
Visit 11	4	636	550 (86.5%)	86 (13.5%)
Visit 12	3	546	483 (88.5%)	63 (11.5%)
Visit 13	4	370	328 (88.6%)	42 (11.4%)
Visit 14	1	100	89 (89.0%)	11 (11.0%)
Visit 15	0	22	20 (90.9%)	2 (9.1%)
Visit 16	0	10	9 (90.0%)	1 (10.0%)
Visit 17	0	5	5 (100.0%)	0 (0.0%)
Visit 18	0	3	3 (100.0%)	0 (0.0%)
Visit 19	0	3	3 (100.0%)	0 (0.0%)
Visit 20	0	3	3 (100.0%)	0 (0.0%)
Visit 21	0	1	1 (100.0%)	0 (0.0%)

Program: s:\Amgen\AM05\SAS\PRG_Analysis\TAB.sas
Output: End of Text Tables Final 2017-07-21 Denosumab (XGEVA) Protocol 20101312 (X-TREME) (AM05).pdf (Date Generated: 20 February 2018)
Source: Annex 1, Table 15.4.2.1

Table 35. Summary of daily dose of Calcium supplementation by visit (abridged table), full analysis set

Visit	Unit	N evaluable	Mean	SD	Min	Q1	Median	Q3	Max
Visit 1	mg	864	742.5	317.9	16	500	600	1000	3000
Visit 2	mg	843	744.2	337.2	31	500	600	1000	3600
Visit 3	mg	826	752.3	335.3	14	500	600	1000	3600
Visit 4	mg	773	745.8	321.5	31	500	600	1000	3000
Visit 5	mg	739	750.9	343.2	31	500	600	1000	3600
Visit 6	mg	702	753.0	337.8	34	500	600	1000	3600
Visit 7	mg	671	746.6	318.4	34	500	600	1000	3600
Visit 8	mg	636	748.2	326.7	34	500	600	1000	3600
Visit 9	mg	608	745.5	333.1	34	500	600	1000	3600
Visit 10	mg	574	753.1	346.5	34	500	600	1000	3600
Visit 11	mg	528	742.6	340.9	34	500	600	1000	3600
Visit 12	mg	462	745.5	355.6	34	500	600	1000	3600
Visit 13	mg	315	753.1	373.0	34	500	600	1000	3600
Visit 14	mg	81	701.0	331.0	34	500	600	1000	2400
Visit 15	mg	20	704.2	321.7	34	500	600	1000	1200
Visit 16	mg	9	700.0	229.1	500	500	600	1000	1000
Visit 17	mg	5	720.0	258.8	500	500	600	1000	1000
Visit 18	mg	3	700.0	264.6	500	500	600	1000	1000
Visit 19	mg	3	700.0	264.6	500	500	600	1000	1000
Visit 20	mg	3	700.0	264.6	500	500	600	1000	1000
Visit 21	mg	1	600.0		600	600	600	600	600

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Source: Annex 1, Table 15.4.2.3

Table 36. VAS pain score by tumor type and visit, full analysis set

Tumor type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Breast cancer	Visit 1	380	26.16	23.46	0.00	5.00	20.00	40.00	95.00
	Visit 2	335	25.24	22.53	0.00	5.00	23.00	40.00	95.00
	Visit 3	327	25.27	22.71	0.00	5.00	20.00	40.00	100.00
	Visit 4	318	25.27	22.65	0.00	5.00	20.00	40.00	100.00
	Visit 5	291	26.31	23.03	0.00	5.00	22.00	40.00	90.00
	Visit 6	272	25.24	21.69	0.00	5.00	20.00	40.00	95.00
	Visit 7	228	25.57	21.95	0.00	7.00	20.00	40.00	92.00
Prostate cancer	Visit 1	240	21.93	22.58	0.00	1.00	15.00	35.00	92.00
	Visit 2	211	18.89	20.36	0.00	2.00	10.00	30.00	100.00
	Visit 3	217	18.84	20.11	0.00	0.00	10.00	30.00	87.00
	Visit 4	205	22.44	22.68	0.00	5.00	15.00	37.00	100.00

Tumor type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
	Visit 5	187	20.56	21.27	0.00	4.00	10.00	30.00	85.00
	Visit 6	180	21.44	23.37	0.00	3.50	10.00	36.00	100.00
	Visit 7	127	21.36	23.25	0.00	0.00	10.00	40.00	94.00
Lung cancer	Visit 1	107	29.48	24.43	0.00	5.00	25.00	50.00	85.00
	Visit 2	88	30.76	25.05	0.00	8.50	30.00	50.00	90.00
	Visit 3	82	29.10	24.93	0.00	5.00	25.00	50.00	90.00
	Visit 4	67	32.99	27.12	0.00	7.00	30.00	58.00	85.00
	Visit 5	53	36.49	28.82	0.00	6.00	35.00	65.00	95.00
	Visit 6	42	25.55	23.09	0.00	5.00	23.50	35.00	80.00
	Visit 7	37	22.03	21.04	0.00	5.00	15.00	37.00	80.00
Kidney cancer	Visit 1	42	27.81	21.00	0.00	8.00	25.00	48.00	77.00
	Visit 2	35	25.86	24.62	0.00	4.00	20.00	45.00	85.00
	Visit 3	31	29.74	23.68	0.00	6.00	25.00	50.00	75.00
	Visit 4	29	27.10	19.82	0.00	15.00	25.00	40.00	75.00
	Visit 5	28	29.93	21.49	0.00	10.00	24.00	50.00	75.00
	Visit 6	19	34.05	22.67	0.00	12.00	35.00	50.00	70.00
	Visit 7	17	28.59	17.73	0.00	15.00	30.00	38.00	70.00
Other cancer type	Visit 1	83	30.34	22.12	0.00	10.00	30.00	45.00	85.00
	Visit 2	65	31.29	23.64	0.00	10.00	30.00	48.00	85.00
	Visit 3	57	30.35	24.45	0.00	10.00	25.00	50.00	85.00
	Visit 4	53	34.58	22.00	0.00	15.00	38.00	50.00	76.00
	Visit 5	46	31.70	21.16	0.00	11.00	32.50	45.00	85.00
	Visit 6	39	27.10	24.00	0.00	4.00	25.00	45.00	85.00
	Visit 7	31	26.39	20.45	0.00	8.00	25.00	40.00	75.00
Total	Visit 1	852	25.87	23.22	0.00	5.00	20.00	40.00	95.00
	Visit 2	734	24.64	22.79	0.00	5.00	20.00	40.00	100.00
	Visit 3	714	24.36	22.71	0.00	5.00	20.00	40.00	100.00
	Visit 4	672	25.99	23.24	0.00	5.00	20.00	40.00	100.00
	Visit 5	605	26.00	23.27	0.00	5.00	20.00	40.00	95.00
	Visit 6	552	24.46	22.63	0.00	5.00	20.00	40.00	100.00
	Visit 7	440	24.23	22.03	0.00	5.00	20.00	40.00	94.00

VAS = Visual analogue scale; recorded the patient's self-rated sensation of pain ranges from 0 (lowest pain) to 100 (highest pain).
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Source: Annex 1, Table 15.5.1

Table 37. EQ-5D item: mobility, by tumor type and visit, full analysis set

	Breast cancer			Prostate cancer			Lung cancer		
	N	n	%	N	n	%	N	n	%
Visit 1	363			224			107		
I have no problems in walking about		197	(54.3%)		129	(57.6%)		59	(55.1%)
I have some problems in walking about		162	(44.6%)		93	(41.5%)		47	(43.9%)
I am confined to bed		4	(1.1%)		2	(0.9%)		1	(0.9%)
Visit 4	285			193			61		
I have no problems in walking about		161	(56.5%)		110	(57.0%)		25	(41.0%)
I have some problems in walking about		119	(41.8%)		81	(42.0%)		35	(57.4%)
I am confined to bed		5	(1.8%)		2	(1.0%)		1	(1.6%)
Visit 7	248			166			35		
I have no problems in walking about		140	(56.5%)		86	(51.8%)		22	(62.9%)
I have some problems in walking about		104	(41.9%)		79	(47.6%)		12	(34.3%)
I am confined to bed		4	(1.6%)		1	(0.6%)		1	(2.9%)
Visit 10	218			148			22		
I have no problems in walking about		125	(57.3%)		84	(56.8%)		13	(59.1%)
I have some problems in walking about		92	(42.2%)		64	(43.2%)		9	(40.9%)
I am confined to bed		1	(0.5%)		0	(0.0%)		0	(0.0%)
Study end	144			92			9		
I have no problems in walking about		81	(56.3%)		52	(56.5%)		7	(77.8%)
I have some problems in walking about		63	(43.8%)		40	(43.5%)		2	(22.2%)
I am confined to bed		0	(0.0%)		0	(0.0%)		0	(0.0%)

	Kidney cancer			Other cancer type			Total		
	N	n	%	N	n	%	N	n	%
Visit 1	40			76			810		
I have no problems in walking about		20	(50.0%)		41	(53.9%)		446	(55.1%)
I have some problems in walking about		20	(50.0%)		32	(42.1%)		354	(43.7%)
I am confined to bed		0	(0.0%)		3	(3.9%)		10	(1.2%)
Visit 4	26			53			618		
I have no problems in walking about		11	(42.3%)		26	(49.1%)		333	(53.9%)
I have some problems in walking about		15	(57.7%)		25	(47.2%)		275	(44.5%)
I am confined to bed		0	(0.0%)		2	(3.8%)		10	(1.6%)
Visit 7	19			30			498		

	Kidney cancer			Other cancer type			Total		
	N	n	%	N	n	%	N	n	%
I have no problems in walking about		9	(47.4%)		12	(40.0%)		269	(54.0%)
I have some problems in walking about		10	(52.6%)		15	(50.0%)		220	(44.2%)
I am confined to bed		0	(0.0%)		3	(10.0%)		9	(1.8%)
Visit 10	12			22			422		
I have no problems in walking about		6	(50.0%)		8	(36.4%)		236	(55.9%)
I have some problems in walking about		6	(50.0%)		13	(59.1%)		184	(43.6%)
I am confined to bed		0	(0.0%)		1	(4.5%)		2	(0.5%)
Study end	11			16			272		
I have no problems in walking about		6	(54.5%)		10	(62.5%)		156	(57.4%)
I have some problems in walking about		5	(45.5%)		5	(31.3%)		115	(42.3%)
I am confined to bed		0	(0.0%)		1	(6.3%)		1	(0.4%)

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Source: Annex 1, Table 15.5.3

Table 38. EQ-5D item: self-care, by tumor type and visit, full analysis set

	Breast cancer			Prostate cancer			Lung cancer		
	N	n	%	N	n	%	N	n	%
Visit 1	364			223			107		
I have no problems with self-care		271	(74.5%)		166	(74.4%)		74	(69.2%)
I have some problem washing or dressing myself		80	(22.0%)		52	(23.3%)		27	(25.2%)
I am unable to wash or dress myself		13	(3.6%)		5	(2.2%)		6	(5.6%)
Visit 4	287			193			62		
I have no problems with self-care		222	(77.4%)		143	(74.1%)		36	(58.1%)
I have some problem washing or dressing myself		55	(19.2%)		44	(22.8%)		24	(38.7%)
I am unable to wash or dress myself		10	(3.5%)		6	(3.1%)		2	(3.2%)
Visit 7	248			164			35		
I have no problems with self-care		189	(76.2%)		116	(70.7%)		24	(68.6%)
I have some problem washing or dressing myself		51	(20.6%)		43	(26.2%)		11	(31.4%)
I am unable to wash or dress myself		8	(3.2%)		5	(3.0%)		0	(0.0%)
Visit 10	219			148			22		

	Breast cancer			Prostate cancer			Lung cancer		
	N	n	%	N	n	%	N	n	%
I have no problems with self-care		163	(74.4%)		106	(71.6%)		15	(68.2%)
I have some problem washing or dressing myself		48	(21.9%)		37	(25.0%)		5	(22.7%)
I am unable to wash or dress myself		8	(3.7%)		5	(3.4%)		2	(9.1%)
Study end	145			92			9		
I have no problems with self-care		105	(72.4%)		62	(67.4%)		8	(88.9%)
I have some problem washing or dressing myself		38	(26.2%)		27	(29.3%)		1	(11.1%)
I am unable to wash or dress myself		2	(1.4%)		3	(3.3%)		0	(0.0%)

	Kidney cancer			Other cancer type			Total		
	N	n	%	N	n	%	N	n	%
Visit 1	40			76			810		
I have no problems with self-care		30	(75.0%)		53	(69.7%)		594	(73.3%)
I have some problem washing or dressing myself		9	(22.5%)		19	(25.0%)		187	(23.1%)
I am unable to wash or dress myself		1	(2.5%)		4	(5.3%)		29	(3.6%)
Visit 4	25			53			620		
I have no problems with self-care		19	(76.0%)		37	(69.8%)		457	(73.7%)
I have some problem washing or dressing myself		5	(20.0%)		13	(24.5%)		141	(22.7%)
I am unable to wash or dress myself		1	(4.0%)		3	(5.7%)		22	(3.5%)
Visit 7	19			31			497		
I have no problems with self-care		14	(73.7%)		20	(64.5%)		363	(73.0%)
I have some problem washing or dressing myself		5	(26.3%)		9	(29.0%)		119	(23.9%)
I am unable to wash or dress myself		0	(0.0%)		2	(6.5%)		15	(3.0%)
Visit 10	12			22			423		
I have no problems with self-care		9	(75.0%)		14	(63.6%)		307	(72.6%)
I have some problem washing or dressing myself		2	(16.7%)		6	(27.3%)		98	(23.2%)
I am unable to wash or dress myself		1	(8.3%)		2	(9.1%)		18	(4.3%)
Study end	11			16			273		

	Kidney cancer			Other cancer type			Total		
	N	n	%	N	n	%	N	n	%
I have no problems with self-care		9	(81.8%)		10	(62.5%)		194	(71.1%)
I have some problem washing or dressing myself		1	(9.1%)		4	(25.0%)		71	(26.0%)
I am unable to wash or dress myself		1	(9.1%)		2	(12.5%)		8	(2.9%)

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Source: Annex 1, Table 15.5.4

Table 39. EQ-5D item: performing usual activity, by tumor type and visit, full analysis set

	Breast cancer			Prostate cancer			Lung cancer		
	N	n	%	N	n	%	N	n	%
Visit 1	364			224			107		
I have no problems with performing my usual activities		155	(42.6%)		126	(56.3%)		40	(37.4%)
I have some problems with performing my usual activities		178	(48.9%)		91	(40.6%)		48	(44.9%)
I am unable to perform my usual activities		31	(8.5%)		7	(3.1%)		19	(17.8%)
Visit 4	286			192			62		
I have no problems with performing my usual activities		135	(47.2%)		114	(59.4%)		16	(25.8%)
I have some problems with performing my usual activities		126	(44.1%)		69	(35.9%)		33	(53.2%)
I am unable to perform my usual activities		25	(8.7%)		9	(4.7%)		13	(21.0%)
Visit 7	247			164			35		
I have no problems with performing my usual activities		115	(46.6%)		94	(57.3%)		12	(34.3%)
I have some problems with performing my usual activities		115	(46.6%)		64	(39.0%)		20	(57.1%)
I am unable to perform my usual activities		17	(6.9%)		6	(3.7%)		3	(8.6%)
Visit 10	218			147			22		
I have no problems with performing my usual activities		110	(50.5%)		85	(57.8%)		9	(40.9%)
I have some problems with performing my usual activities		90	(41.3%)		54	(36.7%)		10	(45.5%)
I am unable to perform my usual activities		18	(8.3%)		8	(5.4%)		3	(13.6%)

	Breast cancer			Prostate cancer			Lung cancer		
	N	n	%	N	n	%	N	n	%
Study end	145			92			9		
I have no problems with performing my usual activities		70	(48.3%)		54	(58.7%)		5	(55.6%)
I have some problems with performing my usual activities		67	(46.2%)		34	(37.0%)		4	(44.4%)
I am unable to perform my usual activities		8	(5.5%)		4	(4.3%)		0	(0.0%)

	Kidney cancer			Other cancer type			Total		
	N	n	%	N	n	%	N	n	%
Visit 1	40			76			811		
I have no problems with performing my usual activities		16	(40.0%)		23	(30.3%)		360	(44.4%)
I have some problems with performing my usual activities		23	(57.5%)		44	(57.9%)		384	(47.3%)
I am unable to perform my usual activities		1	(2.5%)		9	(11.8%)		67	(8.3%)
Visit 4	26			52			618		
I have no problems with performing my usual activities		7	(26.9%)		14	(26.9%)		286	(46.3%)
I have some problems with performing my usual activities		16	(61.5%)		34	(65.4%)		278	(45.0%)
I am unable to perform my usual activities		3	(11.5%)		4	(7.7%)		54	(8.7%)
Visit 7	19			31			496		
I have no problems with performing my usual activities		5	(26.3%)		11	(35.5%)		237	(47.8%)
I have some problems with performing my usual activities		11	(57.9%)		16	(51.6%)		226	(45.6%)
I am unable to perform my usual activities		3	(15.8%)		4	(12.9%)		33	(6.7%)
Visit 10	40			76			811		
I have no problems with performing my usual activities		16	(40.0%)		23	(30.3%)		360	(44.4%)
I have some problems with performing my usual activities		23	(57.5%)		44	(57.9%)		384	(47.3%)
I am unable to perform my usual activities		1	(2.5%)		9	(11.8%)		67	(8.3%)
Study end	26			52			618		
I have no problems with performing my usual activities		7	(26.9%)		14	(26.9%)		286	(46.3%)

	Kidney cancer			Other cancer type			Total		
	N	n	%	N	n	%	N	n	%
I have some problems with performing my usual activities		16	(61.5%)		34	(65.4%)		278	(45.0%)
I am unable to perform my usual activities		3	(11.5%)		4	(7.7%)		54	(8.7%)

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Source: Annex 1, Table 15.5.5

Table 40. EQ-5D item: pain or discomfort, by tumor type and visit, full analysis set

	Breast cancer			Prostate cancer			Lung cancer		
	N	n	%	N	n	%	N	n	%
Visit 1	364			222			107		
I have no pain or discomfort		100	(27.5%)		94	(42.3%)		23	(21.5%)
I have moderate pain or discomfort		234	(64.3%)		119	(53.6%)		74	(69.2%)
I have extreme pain or discomfort		30	(8.2%)		9	(4.1%)		10	(9.3%)
Visit 4	285			191			62		
I have no pain or discomfort		91	(31.9%)		79	(41.4%)		9	(14.5%)
I have moderate pain or discomfort		184	(64.6%)		99	(51.8%)		43	(69.4%)
I have extreme pain or discomfort		10	(3.5%)		13	(6.8%)		10	(16.1%)
Visit 7	249			167			35		
I have no pain or discomfort		84	(33.7%)		59	(35.3%)		9	(25.7%)
I have moderate pain or discomfort		153	(61.4%)		103	(61.7%)		24	(68.6%)
I have extreme pain or discomfort		12	(4.8%)		5	(3.0%)		2	(5.7%)
Visit 10	219			148			22		
I have no pain or discomfort		67	(30.6%)		50	(33.8%)		7	(31.8%)
I have moderate pain or discomfort		137	(62.6%)		92	(62.2%)		15	(68.2%)
I have extreme pain or discomfort		15	(6.8%)		6	(4.1%)		0	(0.0%)
Study end	145			92			9		
I have no pain or discomfort		47	(32.4%)		32	(34.8%)		4	(44.4%)
I have moderate pain or discomfort		91	(62.8%)		57	(62.0%)		5	(55.6%)
I have extreme pain or discomfort		7	(4.8%)		3	(3.3%)		0	(0.0%)

	Kidney cancer			Other cancer type			Total		
	N	n	%	N	n	%	N	n	%
Visit 1	40			76			809		
I have no pain or discomfort		5	(12.5%)		13	(17.1%)		235	(29.0%)
I have moderate pain or discomfort		34	(85.0%)		59	(77.6%)		520	(64.3%)
I have extreme pain or discomfort		1	(2.5%)		4	(5.3%)		54	(6.7%)
Visit 4	26			53			617		
I have no pain or discomfort		3	(11.5%)		9	(17.0%)		191	(31.0%)
I have moderate pain or discomfort		22	(84.6%)		41	(77.4%)		389	(63.0%)
I have extreme pain or discomfort		1	(3.8%)		3	(5.7%)		37	(6.0%)
Visit 7	19			32			502		
I have no pain or discomfort		5	(26.3%)		9	(28.1%)		166	(33.1%)
I have moderate pain or discomfort		14	(73.7%)		23	(71.9%)		317	(63.1%)
I have extreme pain or discomfort		0	(0.0%)		0	(0.0%)		19	(3.8%)
Visit 10	12			22			423		
I have no pain or discomfort		2	(16.7%)		5	(22.7%)		131	(31.0%)
I have moderate pain or discomfort		8	(66.7%)		16	(72.7%)		268	(63.4%)
I have extreme pain or discomfort		2	(16.7%)		1	(4.5%)		24	(5.7%)
Study end	11			16			273		
I have no pain or discomfort		2	(18.2%)		6	(37.5%)		91	(33.3%)
I have moderate pain or discomfort		8	(72.7%)		9	(56.3%)		170	(62.3%)
I have extreme pain or discomfort		1	(9.1%)		1	(6.3%)		12	(4.4%)

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Source: Annex 1, Table 15.5.6

Table 41. EQ-5D item: anxiety or depression, by tumor type and visit, full analysis set

	Breast cancer			Prostate cancer			Lung cancer		
	N	n	%	N	n	%	N	n	%
Visit 1	363			222			104		
I am not anxious or depressed		188	(51.8%)		137	(61.7%)		70	(67.3%)
I am moderately anxious or depressed		160	(44.1%)		82	(36.9%)		33	(31.7%)
I am extremely anxious or depressed		15	(4.1%)		3	(1.4%)		1	(1.0%)
Visit 4	287			188			62		
I am not anxious or depressed		167	(58.2%)		124	(66.0%)		39	(62.9%)
I am moderately anxious or depressed		108	(37.6%)		59	(31.4%)		21	(33.9%)
I am extremely anxious or depressed		12	(4.2%)		5	(2.7%)		2	(3.2%)
Visit 7	245			165			35		
I am not anxious or depressed		138	(56.3%)		107	(64.8%)		25	(71.4%)
I am moderately anxious or depressed		99	(40.4%)		56	(33.9%)		9	(25.7%)
I am extremely anxious or depressed		8	(3.3%)		2	(1.2%)		1	(2.9%)
Visit 10	219			148			22		
I am not anxious or depressed		117	(53.4%)		89	(60.1%)		15	(68.2%)
I am moderately anxious or depressed		89	(40.6%)		55	(37.2%)		7	(31.8%)
I am extremely anxious or depressed		13	(5.9%)		4	(2.7%)		0	(0.0%)
Study end	143			91			9		
I am not anxious or depressed		90	(62.9%)		53	(58.2%)		8	(88.9%)
I am moderately anxious or depressed		48	(33.6%)		35	(38.5%)		1	(11.1%)
I am extremely anxious or depressed		5	(3.5%)		3	(3.3%)		0	(0.0%)

	Kidney cancer			Other cancer type			Total		
	N	n	%	N	n	%	N	n	%
Visit 1	40			76			805		
I am not anxious or depressed		24	(60.0%)		45	(59.2%)		464	(57.6%)
I am moderately anxious or depressed		15	(37.5%)		27	(35.5%)		317	(39.4%)
I am extremely anxious or depressed		1	(2.5%)		4	(5.3%)		24	(3.0%)
Visit 4	26			53			616		

	Kidney cancer			Other cancer type			Total		
	N	n	%	N	n	%	N	n	%
I am not anxious or depressed		9	(34.6%)		36	(67.9%)		375	(60.9%)
I am moderately anxious or depressed		16	(61.5%)		16	(30.2%)		220	(35.7%)
I am extremely anxious or depressed		1	(3.8%)		1	(1.9%)		21	(3.4%)
Visit 7	19			32			496		
I am not anxious or depressed		9	(47.4%)		18	(56.3%)		297	(59.9%)
I am moderately anxious or depressed		10	(52.6%)		12	(37.5%)		186	(37.5%)
I am extremely anxious or depressed		0	(0.0%)		2	(6.3%)		13	(2.6%)
Visit 10	12			22			423		
I am not anxious or depressed		5	(41.7%)		8	(36.4%)		234	(55.3%)
I am moderately anxious or depressed		6	(50.0%)		14	(63.6%)		171	(40.4%)
I am extremely anxious or depressed		1	(8.3%)		0	(0.0%)		18	(4.3%)
Study end	11			16			270		
I am not anxious or depressed		6	(54.5%)		10	(62.5%)		167	(61.9%)
I am moderately anxious or depressed		4	(36.4%)		6	(37.5%)		94	(34.8%)
I am extremely anxious or depressed		1	(9.1%)		0	(0.0%)		9	(3.3%)

Program: s:\Amgen\AM05\SAS\PRG_Analysis\TAB.sas
Output: End of Text Tables Final 2017-07-21 Denosumab (XGEVA) Protocol 20101312 (X-TREME) (AM05).pdf (Date Generated: 20 February 2018)
Source: Annex 1, Table 15.5.7

Table 42. EQ-5D item: VAS, by tumor type and visit, full analysis set

Tumor type	Visit	N evaluable	Mean	SD	Min	Q1	Median	Q3	Max
Breast cancer	Visit 1	359	64.71	21.19	0.00	50.00	70.00	80.00	100.00
	Visit 4	280	66.10	22.50	0.00	50.00	70.00	85.00	100.00
	Visit 7	245	65.22	22.31	0.00	50.00	70.00	80.00	100.00
	Visit 10	211	65.89	22.19	0.00	50.00	70.00	80.00	100.00
	Study end	143	67.16	20.85	0.00	50.00	70.00	85.00	100.00
Prostate cancer	Visit 1	223	66.58	21.37	0.00	50.00	70.00	80.00	100.00
	Visit 4	196	67.15	21.47	0.00	55.00	70.00	80.00	100.00
	Visit 7	167	68.08	22.04	0.00	50.00	74.00	85.00	100.00
	Visit 10	144	67.76	21.96	15.00	51.00	74.00	83.50	100.00
	Study end	90	69.31	21.74	4.00	60.00	73.00	85.00	100.00

Tumor type	Visit	N evaluable	Mean	SD	Min	Q1	Median	Q3	Max
Lung cancer	Visit 1	108	58.99	20.01	10.00	46.00	60.00	72.50	100.00
	Visit 4	61	58.89	23.08	0.00	40.00	60.00	75.00	100.00
	Visit 7	35	66.66	18.32	40.00	50.00	65.00	80.00	100.00
	Visit 10	20	70.00	20.87	20.00	57.50	75.00	90.00	98.00
	Study end	9	72.56	25.22	15.00	60.00	80.00	88.00	95.00
Kidney cancer	Visit 1	40	62.25	17.83	10.00	50.00	60.00	75.00	90.00
	Visit 4	26	64.27	20.29	25.00	50.00	70.00	75.00	95.00
	Visit 7	19	60.95	20.45	23.00	50.00	60.00	75.00	100.00
	Visit 10	12	65.42	18.88	25.00	55.00	70.00	79.00	90.00
	Study end	11	68.00	19.03	30.00	55.00	70.00	80.00	100.00
Other cancer type	Visit 1	74	59.97	20.44	10.00	48.00	65.00	75.00	100.00
	Visit 4	52	53.58	17.81	3.00	45.00	50.00	65.00	90.00
	Visit 7	32	56.88	21.92	5.00	44.00	57.50	70.00	100.00
	Visit 10	21	58.14	22.48	10.00	45.00	60.00	70.00	90.00
	Study end	15	65.13	23.60	15.00	50.00	70.00	80.00	95.00
Total	Visit 1	804	63.90	20.98	0.00	50.00	69.00	80.00	100.00
	Visit 4	615	64.58	22.10	0.00	50.00	68.00	80.00	100.00
	Visit 7	498	65.58	21.97	0.00	50.00	70.00	80.00	100.00
	Visit 10	408	66.34	21.99	0.00	50.00	70.00	82.00	100.00
	Study end	268	67.99	21.28	0.00	52.50	70.00	85.00	100.00

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Source: Annex 1, Table 15.5.8

Table 43. EQ-5D item: Absolute change from Visit 1 in VAS, by tumor type and visit, full analysis set

Tumor type	Visit	N evaluable	Mean	SD	Min	Q1	Median	Q3	Max
Breast cancer	Visit 4	229	-1.68	22.02	-100.00	-10.00	0.00	7.00	75.00
	Visit 7	210	0.98	20.85	-90.00	-10.00	0.00	10.00	85.00
	Visit 10	173	0.02	25.10	-95.00	-10.00	0.00	10.00	85.00
	Study end	116	1.16	25.67	-90.00	-10.00	0.00	15.00	83.00
Prostate cancer	Visit 4	169	0.52	23.00	-80.00	-7.00	0.00	10.00	96.00
	Visit 7	146	-0.85	22.90	-88.00	-10.00	0.00	10.00	81.00
	Visit 10	126	0.10	24.81	-70.00	-10.00	0.00	12.00	91.00
	Study end	76	-2.72	24.10	-86.00	-10.00	0.00	10.00	65.00
Lung cancer	Visit 4	54	-2.19	22.82	-70.00	-10.00	0.00	10.00	45.00
	Visit 7	33	7.94	19.56	-35.00	0.00	8.00	20.00	55.00
	Visit 10	19	8.16	19.28	-25.00	-5.00	8.00	20.00	50.00
	Study end	7	6.14	17.63	-25.00	-2.00	10.00	20.00	30.00
Kidney cancer	Visit 4	22	-3.14	24.13	-60.00	-20.00	-4.50	5.00	60.00
	Visit 7	16	-7.31	13.07	-30.00	-15.00	-5.00	0.00	20.00
	Visit 10	10	-4.50	11.97	-25.00	-10.00	-5.00	5.00	12.00
	Study end	9	5.89	15.24	-5.00	-5.00	-5.00	10.00	38.00
Other cancer type	Visit 4	43	-6.98	21.53	-48.00	-20.00	-5.00	5.00	50.00
	Visit 7	27	-4.78	26.28	-80.00	-18.00	-2.00	10.00	55.00
	Visit 10	17	-0.88	15.93	-25.00	-15.00	0.00	5.00	25.00
	Study end	12	-3.17	16.26	-25.00	-15.50	-3.50	7.50	30.00
Total	Visit 4	517	-1.51	22.48	-100.00	-10.00	0.00	9.00	96.00
	Visit 7	432	0.23	21.73	-90.00	-10.00	0.00	10.00	85.00
	Visit 10	345	0.32	24.04	-95.00	-10.00	0.00	10.00	91.00
	Study end	220	-0.06	24.11	-90.00	-10.00	0.00	10.00	83.00

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Output: End of Text Tables Final 2017-07-21 Denosumab (XGEVA) Protocol 20101312 (X-TREME) (AM05).pdf (Date Generated: 20 February 2018)
Source: Annex 1, Table 15.5.9

Table 44. Number of XGEVA® injections administered during study by tumor type, full analysis set

Tumor type	N evaluable	Mean	SD	Min	Q1	Median	Q3	Max
Breast cancer	509	11.8	3.9	1	10	13.0	14	21
Prostate cancer	294	11.5	3.6	1	10	13.0	14	22
Lung cancer	159	7.4	4.6	1	3	6.0	12	16
Kidney cancer	50	9.9	4.3	2	6	11.0	14	15
Other cancer type	116	7.8	4.5	1	4	7.0	13	15
Total	1128	10.6	4.4	1	7	13.0	14	22

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Output: End of Text Tables Final 2017-07-21 Denosumab (XGEVA) Protocol 20101312 (X-TREME) (AM05).pdf (Date Generated: 20 February 2018)
Source: Annex 1, Table 15.6.3

Table 45. Concomitant antineoplastic therapy by tumor type, full analysis set

	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Concomitant surgery												
No	490	(96.3%)	291	(99.0%)	156	(98.1%)	49	(98.0%)	112	(96.6%)	1098	(97.3%)
Yes	19	(3.7%)	3	(1.0%)	3	(1.9%)	1	(2.0%)	4	(3.4%)	30	(2.7%)
Concomitant radiotherapy												
No	362	(71.1%)	252	(85.7%)	119	(74.8%)	30	(60.0%)	80	(69.0%)	843	(74.7%)
Yes	147	(28.9%)	42	(14.3%)	40	(25.2%)	20	(40.0%)	36	(31.0%)	285	(25.3%)
Concomitant chemotherapy												
No	221	(43.4%)	171	(58.2%)	29	(18.2%)	6	(12.0%)	20	(17.2%)	447	(39.6%)
Yes	288	(56.6%)	123	(41.8%)	130	(81.8%)	44	(88.0%)	96	(82.8%)	681	(60.4%)
Concomitant antihormonal therapy												
No	187	(36.7%)	51	(17.3%)	159	(100.0%)	49	(98.0%)	110	(94.8%)	556	(49.3%)
Yes	322	(63.3%)	243	(82.7%)	0	(0.0%)	1	(2.0%)	6	(5.2%)	572	(50.7%)

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Output: End of Text Tables Final 2017-07-21 Denosumab (XGEVA) Protocol 20101312 (X-TREME) (AM05).pdf (Date Generated: 20 February 2018)
Source: Annex 1, Table 15.7.1

Table 46. Concomitant chemotherapy by preferred term - by tumor type (abridged table), full analysis set

	Breast cancer (N=288)		Prostate cancer (N=123)		Lung cancer (N=130)		Kidney cancer (N=44)		Other cancer type (N=96)		Total (N=681)	
Preferred term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Total	288	(100.0%)	123	(100.0%)	130	(100.0%)	44	(100.0%)	96	(100.0%)	681	(100.0%)
Docetaxel	39	(13.5%)	91	(74.0%)	17	(13.1%)	0	(0.0%)	5	(5.2%)	152	(22.3%)
Paclitaxel	96	(33.3%)	0	(0.0%)	30	(23.1%)	1	(2.3%)	18	(18.8%)	145	(21.3%)
Bevacizumab	87	(30.2%)	0	(0.0%)	24	(18.5%)	2	(4.5%)	15	(15.6%)	128	(18.8%)
Carboplatin	18	(6.3%)	3	(2.4%)	58	(44.6%)	0	(0.0%)	16	(16.7%)	95	(14.0%)
Trastuzumab	68	(23.6%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	4	(4.2%)	72	(10.6%)
Cisplatin	4	(1.4%)	1	(0.8%)	43	(33.1%)	1	(2.3%)	22	(22.9%)	71	(10.4%)
Capecitabine	52	(18.1%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	10	(10.4%)	62	(9.1%)
Vinorelbine	23	(8.0%)	0	(0.0%)	22	(16.9%)	0	(0.0%)	0	(0.0%)	45	(6.6%)
Gemcitabine	12	(4.2%)	2	(1.6%)	12	(9.2%)	2	(4.5%)	16	(16.7%)	44	(6.5%)
Everolimus	26	(9.0%)	0	(0.0%)	0	(0.0%)	12	(27.3%)	1	(1.0%)	39	(5.7%)

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Output: End of Text Tables Final 2017-07-21 Denosumab (XGEVA) Protocol 20101312 (X-TREME) (AM05).pdf (Date Generated: 20 February 2018)
Source: Annex 1, Table 15.7.3

Table 47. Concomitant antihormonal therapy (incl. antibodies and small molecules) by preferred term - by tumor type, full analysis set

	Breast cancer (N=322)		Prostate cancer (N=243)		Kidney cancer (N=1)		Other cancer type (N=6)		Total (N=572)	
Preferred term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Total	322	(100.0%)	243	(100.0%)	1	(100.0%)	6	(100.0%)	572	(100.0%)
Leuprorelin acetate	1	(0.3%)	137	(56.4%)	0	(0.0%)	1	(16.7%)	139	(24.3%)
Letrozole	118	(36.6%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	118	(20.6%)
Anastrozole	116	(36.0%)	0	(0.0%)	0	(0.0%)	1	(16.7%)	117	(20.5%)
Bicalutamide	0	(0.0%)	82	(33.7%)	0	(0.0%)	1	(16.7%)	83	(14.5%)
Exemestane	70	(21.7%)	0	(0.0%)	0	(0.0%)	2	(33.3%)	72	(12.6%)
Tamoxifen	57	(17.7%)	1	(0.4%)	0	(0.0%)	0	(0.0%)	58	(10.1%)
Abiraterone acetate	0	(0.0%)	37	(15.2%)	0	(0.0%)	0	(0.0%)	37	(6.5%)
Buserelin acetate	0	(0.0%)	34	(14.0%)	0	(0.0%)	0	(0.0%)	34	(5.9%)
Other antineoplastic agents	0	(0.0%)	24	(9.9%)	0	(0.0%)	0	(0.0%)	24	(4.2%)
Degarelix	0	(0.0%)	18	(7.4%)	0	(0.0%)	0	(0.0%)	18	(3.1%)

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Output: End of Text Tables Final 2017-07-21 Denosumab (XGEVA) Protocol 20101312 (X-TREME) (AM05).pdf (Date Generated: 20 February 2018)
Source: Annex 1, Table 15.7.4

Table 48. Consumption of analgesic drugs throughout the study, full analysis set

	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
Consumption of any analgesic drug?	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
No	271	(53.2%)	170	(57.8%)	59	(37.1%)	14	(28.0%)	30	(25.9%)	544	(48.2%)
Yes	238	(46.8%)	124	(42.2%)	100	(62.9%)	36	(72.0%)	86	(74.1%)	584	(51.8%)

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Output: End of Text Tables Final 2017-07-21 Denosumab (XGEVA) Protocol 20101312 (X-TREME) (AM05).pdf (Date Generated: 20 February 2018)
Source: Annex 1, Table 15.7.6

Table 49. Analgesic score (AQA) of pain medications given throughout the study, full analysis set

	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
Analgesic score (AQA)*	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
No analgesic	14	(2.8%)	7	(2.4%)	7	(4.4%)	4	(8.0%)	4	(3.4%)	36	(3.2%)
Non-opioid analgesics	193	(37.9%)	105	(35.7%)	78	(49.1%)	30	(60.0%)	70	(60.3%)	476	(42.2%)
Weak opioids	60	(11.8%)	33	(11.2%)	32	(20.1%)	8	(16.0%)	20	(17.2%)	153	(13.6%)
Strong opioids dose 1	84	(16.5%)	51	(17.3%)	63	(39.6%)	19	(38.0%)	55	(47.4%)	272	(24.1%)
Strong opioids dose 2	10	(2.0%)	5	(1.7%)	11	(6.9%)	5	(10.0%)	17	(14.7%)	48	(4.3%)
Strong opioids dose 3	6	(1.2%)	1	(0.3%)	5	(3.1%)	0	(0.0%)	11	(9.5%)	23	(2.0%)
Strong opioids dose 4	3	(0.6%)	0	(0.0%)	4	(2.5%)	0	(0.0%)	5	(4.3%)	12	(1.1%)
Strong opioids dose 5	0	(0.0%)	1	(0.3%)	1	(0.6%)	1	(2.0%)	0	(0.0%)	3	(0.3%)
Missing	5	(1.0%)	2	(0.7%)	0	(0.0%)	1	(2.0%)	3	(2.6%)	11	(1.0%)

* Number and percentages refer to patients who received at least one medication with the respective score. Some patients received more than one medication and are displayed in more than one AQA score category Program: s:\Amgen\AM05\SAS\PRG_Analysis\TAB.sas
Output: End of Text Tables Final 2017-07-21 Denosumab (XGEVA) Protocol 20101312 (X-TREME) (AM05).pdf (Date Generated: 20 February 2018)
Source: Annex 1, Table 15.7.7

Table 50. Worst analgesic score (AQA)* of pain medications given throughout the study as numeric variable by period, full analysis set

Time period	N evaluable	Mean	SD	Min	Q1	Median	Q3	Max
Period 1 (0 - 2 weeks)	344	3.08	1.11	1.00	2.00	3.00	4.00	8.00
Period 2 (2 - 6 weeks)	418	3.15	1.15	2.00	2.00	3.00	4.00	8.00
Period 3 (6 - 10 weeks)	445	3.16	1.17	2.00	2.00	3.00	4.00	8.00
Period 4 (10 - 14 weeks)	436	3.17	1.16	2.00	2.00	3.00	4.00	7.00
Period 5 (14 - 18 weeks)	419	3.21	1.18	2.00	2.00	3.00	4.00	7.00
Period 6 (18 - 22 weeks)	407	3.25	1.19	2.00	2.00	3.00	4.00	7.00
Period 7 (22 - 26 weeks)	386	3.23	1.18	2.00	2.00	3.00	4.00	8.00
Period 8 (26 - 30 weeks)	357	3.18	1.15	2.00	2.00	3.00	4.00	8.00
Period 9 (30 - 34 weeks)	343	3.14	1.16	1.00	2.00	3.00	4.00	8.00
Period 10 (34 - 38 weeks)	323	3.14	1.14	1.00	2.00	3.00	4.00	8.00
Period 11 (38 - 42 weeks)	310	3.15	1.11	1.00	2.00	3.00	4.00	8.00

Time period	N evaluable	Mean	SD	Min	Q1	Median	Q3	Max
Period 12 (42 - 46 weeks)	299	3.16	1.12	1.00	2.00	3.00	4.00	8.00
Period 13 (46 - 50 weeks)	284	3.17	1.13	1.00	2.00	3.00	4.00	8.00
Period 14 (50 - 54 weeks)	262	3.13	1.08	1.00	2.00	3.00	4.00	8.00
Period 15 (54 - 58 weeks)	182	3.15	1.05	2.00	2.00	3.00	4.00	7.00
Period 16 (58 - 62 weeks)	71	3.08	1.01	2.00	2.00	3.00	4.00	5.00
Period 17 (62 - 66 weeks)	28	3.00	1.09	2.00	2.00	3.00	4.00	5.00
Period 18 (66 - 70 weeks)	12	3.25	1.22	2.00	2.00	3.50	4.00	5.00
Period 19 (70 - 74 weeks)	6	2.83	0.98	2.00	2.00	2.50	4.00	4.00
Period 20 (74 - 78 weeks)	4	2.75	0.96	2.00	2.00	2.50	3.50	4.00
Period 21 (78 - 82 weeks)	3	2.67	1.15	2.00	2.00	2.00	4.00	4.00
Period 22 (82 - 86 weeks)	3	2.67	1.15	2.00	2.00	2.00	4.00	4.00
Period 23 (86 - 90 weeks)	3	2.67	1.15	2.00	2.00	2.00	4.00	4.00

* per patient within a period (each patient was only counted once in each period)
Program: s:\Amgen\AM05\SAS\PRG_Analysis\TAB.sas
Output: End of Text Tables Final 2017-07-21 Denosumab (XGEVA) Protocol 20101312 (X-TREME) (AM05).pdf (Date Generated: 20 February 2018)
Source: Annex 1, Table 15.7.11

Table 51. Best analgesic score (AQA)* of pain medications given throughout the study as numeric variable by period, full analysis set

Time period	N evaluable	Mean	SD	Min	Q1	Median	Q3	Max
Period 1 (0 - 2 weeks)	344	2.37	0.87	1.00	2.00	2.00	2.00	8.00
Period 2 (2 - 6 weeks)	418	2.35	0.87	1.00	2.00	2.00	2.00	8.00
Period 3 (6 - 10 weeks)	445	2.32	0.84	1.00	2.00	2.00	2.00	8.00
Period 4 (10 - 14 weeks)	436	2.28	0.78	1.00	2.00	2.00	2.00	6.00
Period 5 (14 - 18 weeks)	419	2.29	0.80	1.00	2.00	2.00	2.00	6.00
Period 6 (18 - 22 weeks)	407	2.31	0.83	1.00	2.00	2.00	2.00	7.00
Period 7 (22 - 26 weeks)	386	2.30	0.81	1.00	2.00	2.00	2.00	6.00
Period 8 (26 - 30 weeks)	357	2.29	0.78	1.00	2.00	2.00	2.00	5.00
Period 9 (30 - 34 weeks)	343	2.29	0.80	1.00	2.00	2.00	2.00	5.00
Period 10 (34 - 38 weeks)	323	2.30	0.80	1.00	2.00	2.00	2.00	5.00
Period 11 (38 - 42 weeks)	310	2.30	0.80	1.00	2.00	2.00	2.00	5.00
Period 12 (42 - 46 weeks)	299	2.31	0.82	1.00	2.00	2.00	2.00	5.00
Period 13 (46 - 50 weeks)	284	2.32	0.82	1.00	2.00	2.00	2.00	5.00
Period 14 (50 - 54 weeks)	262	2.33	0.84	1.00	2.00	2.00	2.00	5.00
Period 15 (54 - 58 weeks)	182	2.36	0.83	1.00	2.00	2.00	2.00	5.00
Period 16 (58 - 62 weeks)	71	2.34	0.81	1.00	2.00	2.00	2.00	5.00
Period 17 (62 - 66 weeks)	28	2.29	0.76	1.00	2.00	2.00	2.00	4.00
Period 18 (66 - 70 weeks)	12	2.33	0.89	1.00	2.00	2.00	2.50	4.00
Period 19 (70 - 74 weeks)	6	2.33	1.03	1.00	2.00	2.00	3.00	4.00
Period 20 (74 - 78 weeks)	4	2.00	0.82	1.00	1.50	2.00	2.50	3.00
Period 21 (78 - 82 weeks)	3	1.67	0.58	1.00	1.00	2.00	2.00	2.00
Period 22 (82 - 86 weeks)	3	1.67	0.58	1.00	1.00	2.00	2.00	2.00
Period 23 (86 - 90 weeks)	3	1.67	0.58	1.00	1.00	2.00	2.00	2.00

* per patient within a period (each patient was only counted once in each period)
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Source: Annex 1, Table 15.7.13

Table 52. Overall summary of reported ADRs

	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)		
	Events	**n**	**%**	**Events**	**n**	**%**	**Events**	**n**	**%**
All documented ADRs	43	33	(6.5%)	16	15	(5.1%)	22	14	(8.8%)
that are fatal	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)
leading to withdrawal of product	6	4	(0.8%)	4	4	(1.4%)	2	2	(1.3%)
related to XGEVA®	43	33	(6.5%)	16	15	(5.1%)	22	14	(8.8%)

	Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	Events	**n**	**%**	**Events**	**n**	**%**	**Events**	**n**	**%**
All documented ADRs	5	3	(6.0%)	9	7	(6.0%)	95	72	(6.4%)
that are fatal	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)
leading to withdrawal of product	0	0	(0.0%)	0	0	(0.0%)	12	10	(0.9%)
related to XGEVA®	5	3	(6.0%)	9	7	(6.0%)	95	72	(6.4%)

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Source: Annex 1, Table 15.9.1

Table 53. Summary of reported serious ADRs

MedDRA SOC Preferred Term	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)		
	Events	n	%	Events	n	%	Events	n	%
Total	2	2	(0.4%)	0	0	(0.0%)	2	2	(1.3%)
Metabolism and nutrition disorders									
Total	1	1	(0.2%)	0	0	(0.0%)	1	1	(0.6%)
Hypocalcaemia	1	1	(0.2%)	0	0	(0.0%)	1	1	(0.6%)
Blood and lymphatic system disorders									
Total	1	1	(0.2%)	0	0	(0.0%)	0	0	(0.0%)
Thrombocytopenia	1	1	(0.2%)	0	0	(0.0%)	0	0	(0.0%)
Infections and infestations									
Total	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.6%)
Respiratory tract infection	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.6%)

MedDRA SOC Preferred Term	Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	Events	n	%	Events	n	%	Events	n	%
Total	0	0	(0.0%)	0	0	(0.0%)	4	4	(0.4%)
Metabolism and nutrition disorders									
Total	0	0	(0.0%)	0	0	(0.0%)	2	2	(0.2%)
Hypocalcaemia	0	0	(0.0%)	0	0	(0.0%)	2	2	(0.2%)
Blood and lymphatic system disorders									
Total	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Thrombocytopenia	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Infections and infestations									
Total	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Respiratory tract infection	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)

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Source: Annex 1, Table 15.9.2

Table 54. Summary of reported ADRs (related to XGEVA®)

MedDRA SOC Preferred Term	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)		
	Events	n	%	Events	n	%	Events	n	%
Total	43	33	(6.5%)	16	15	(5.1%)	22	14	(8.8%)
Metabolism and nutrition disorders									
Total	27	19	(3.7%)	12	11	(3.7%)	10	9	(5.7%)
Hypocalcaemia	27	19	(3.7%)	11	10	(3.4%)	10	9	(5.7%)
Decreased appetite	0	0	(0.0%)	1	1	(0.3%)	0	0	(0.0%)
Musculoskeletal and connective tissue disorders									
Total	3	3	(0.6%)	2	2	(0.7%)	3	3	(1.9%)
Arthralgia	0	0	(0.0%)	2	2	(0.7%)	0	0	(0.0%)
Back pain	0	0	(0.0%)	0	0	(0.0%)	2	2	(1.3%)
Bone pain	1	1	(0.2%)	0	0	(0.0%)	1	1	(0.6%)
Musculoskeletal pain	1	1	(0.2%)	0	0	(0.0%)	0	0	(0.0%)
Myalgia	1	1	(0.2%)	0	0	(0.0%)	0	0	(0.0%)
Skin and subcutaneous tissue disorders									
Total	3	3	(0.6%)	0	0	(0.0%)	2	2	(1.3%)
Rash	2	2	(0.4%)	0	0	(0.0%)	1	1	(0.6%)
Hyperhidrosis	1	1	(0.2%)	0	0	(0.0%)	1	1	(0.6%)
General disorders and administration site conditions									
Total	3	3	(0.6%)	0	0	(0.0%)	0	0	(0.0%)
Fatigue	2	2	(0.4%)	0	0	(0.0%)	0	0	(0.0%)
General physical health deterioration	1	1	(0.2%)	0	0	(0.0%)	0	0	(0.0%)
Infections and infestations									
Total	0	0	(0.0%)	1	1	(0.3%)	2	2	(1.3%)
Bronchopneumonia	0	0	(0.0%)	1	1	(0.3%)	1	1	(0.6%)
Respiratory tract infection	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.6%)
Gastrointestinal disorders									
Total	1	1	(0.2%)	0	0	(0.0%)	2	1	(0.6%)
Diarrhoea	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.6%)
Nausea	1	1	(0.2%)	0	0	(0.0%)	0	0	(0.0%)
Vomiting	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.6%)
Investigations									
Total	2	2	(0.4%)	0	0	(0.0%)	0	0	(0.0%)
Blood calcium increased	1	1	(0.2%)	0	0	(0.0%)	0	0	(0.0%)
Blood potassium decreased	1	1	(0.2%)	0	0	(0.0%)	0	0	(0.0%)
Nervous system disorders									
Total	0	0	(0.0%)	1	1	(0.3%)	1	1	(0.6%)
Dizziness	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.6%)
Paraesthesia	0	0	(0.0%)	1	1	(0.3%)	0	0	(0.0%)
Vascular disorders									

MedDRA SOC Preferred Term	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)		
	Events	n	%	Events	n	%	Events	n	%
Total	2	2	(0.4%)	0	0	(0.0%)	0	0	(0.0%)
Circulatory collapse	1	1	(0.2%)	0	0	(0.0%)	0	0	(0.0%)
Vasculitis	1	1	(0.2%)	0	0	(0.0%)	0	0	(0.0%)
Blood and lymphatic system disorders									
Total	1	1	(0.2%)	0	0	(0.0%)	0	0	(0.0%)
Thrombocytopenia	1	1	(0.2%)	0	0	(0.0%)	0	0	(0.0%)
Immune system disorders									
Total	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.6%)
Reaction to drug excipients	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.6%)
Psychiatric disorders									
Total	1	1	(0.2%)	0	0	(0.0%)	0	0	(0.0%)
Depression	1	1	(0.2%)	0	0	(0.0%)	0	0	(0.0%)
Renal and urinary disorders									
Total	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.6%)
Dysuria	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.6%)

MedDRA SOC Preferred Term	Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	Events	n	%	Events	n	%	Events	n	%
Total	5	3	(6.0%)	9	7	(6.0%)	95	72	(6.4%)
Metabolism and nutrition disorders									
Total	5	3	(6.0%)	9	7	(6.0%)	63	49	(4.3%)
Hypocalcaemia	5	3	(6.0%)	9	7	(6.0%)	62	48	(4.3%)
Decreased appetite	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Musculoskeletal and connective tissue disorders									
Total	0	0	(0.0%)	0	0	(0.0%)	8	8	(0.7%)
Arthralgia	0	0	(0.0%)	0	0	(0.0%)	2	2	(0.2%)
Back pain	0	0	(0.0%)	0	0	(0.0%)	2	2	(0.2%)
Bone pain	0	0	(0.0%)	0	0	(0.0%)	2	2	(0.2%)
Musculoskeletal pain	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Myalgia	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Skin and subcutaneous tissue disorders									
Total	0	0	(0.0%)	0	0	(0.0%)	5	5	(0.4%)
Rash	0	0	(0.0%)	0	0	(0.0%)	3	3	(0.3%)
Hyperhidrosis	0	0	(0.0%)	0	0	(0.0%)	2	2	(0.2%)
General disorders and administration site conditions									
Total	0	0	(0.0%)	0	0	(0.0%)	3	3	(0.3%)
Fatigue	0	0	(0.0%)	0	0	(0.0%)	2	2	(0.2%)
General physical health deterioration	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Infections and infestations									
Total	0	0	(0.0%)	0	0	(0.0%)	3	3	(0.3%)
Bronchopneumonia	0	0	(0.0%)	0	0	(0.0%)	2	2	(0.2%)
Respiratory tract infection	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)

MedDRA SOC Preferred Term	Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	Events	n	%	Events	n	%	Events	n	%
Gastrointestinal disorders									
Total	0	0	(0.0%)	0	0	(0.0%)	3	2	(0.2%)
Diarrhoea	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Nausea	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Vomiting	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Investigations									
Total	0	0	(0.0%)	0	0	(0.0%)	2	2	(0.2%)
Blood calcium increased	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Blood potassium decreased	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Nervous system disorders									
Total	0	0	(0.0%)	0	0	(0.0%)	2	2	(0.2%)
Dizziness	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Paraesthesia	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Vascular disorders									
Total	0	0	(0.0%)	0	0	(0.0%)	2	2	(0.2%)
Circulatory collapse	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Vasculitis	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Blood and lymphatic system disorders									
Total	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Thrombocytopenia	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Immune system disorders									
Total	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Reaction to drug excipients	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Psychiatric disorders									
Total	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Depression	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Renal and urinary disorders									
Total	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Dysuria	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)

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Source: Annex 1, Table 15.9.3

16. ANNEXES

Annex 1. List of Stand-alone Documents

Number	Document Reference Number	Date	Title
1	List of investigators	26 February 2018	List of investigators
2	Statistical analysis plan	04 May 2017	Statistical Analysis Plan: 20101312
3	Patient data listings	20 February 2018	Patient Data Listings, Final v01, 20 February 2018
4	End of Text Tables	20 February 2018	End of Text Tables, Final v01, 20 February 2018

Annex 2. Observational Plan

Annex 1. Stand-alone Documents

Annex 1. List of Stand-alone Documents

Number	Document Reference Number	Date	Title
1	List of investigators	26 February 2018	List of investigators
2	Statistical analysis plan	04 May 2017	Statistical Analysis Plan: 20101312
3	End of Text Tables	20 February 2018	End of Text Tables, Final v01, 20 February 2018
4	Patient data listings	20 February 2018	Available on request

Investigator Name	Institution	Adress
[redacted]	Onkologie Westerfelde; Medizinische Studien Nord West GmbH	Kuhlenstraße 53, 26655 Westerstede
	OnkoLog Moers GbR	Xantener Straße 40, 47441 Moers
	Wissenschaftskontor Nord GmbH & Co KG	Trelleborger Straße 10 A, 18107 Rostock Lütten-Klein
	[redacted]	[redacted] 42551 Velbert
	Urologische Praxis [redacted]	[redacted] 21335 Lüneburg
	Diakoniekrankenhaus Rotenburg	Elise-Averdieck-Straße 17, 27356 Rotenburg
	Facharztpraxis f. Innere Medizin, Hämatologie	[redacted] 46236 Bottrop
	Praxis [redacted]	[redacted] 04416 Markkleeberg
	[redacted]	[redacted] 40822 Mettmann
	Urologische Praxis [redacted]	[redacted] 24103 Kiel
	pioh Studien- und Management GbR	Kölner Straße 9, 50226 Frechen
	Studienzentrum	Elisenstraße 26, 63739 Aschaffenburg
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	HILGARD Gesellschaft für medizinische Studien mbH	Hilgardstraße 30, 67346 Speyer
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	Lahn-Dill-Kliniken Wetzlar	Forsthausstr. 1-3,, 35578 Wetzlar
	[redacted]	[redacted] 96317 Kronach
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	[redacted]	[redacted] 59494 Soest-Paradiese
	[redacted] Gynäkologisches Zentrum - Schwerpunkt Gyn. C	Friedensplatz 16, 53111 Bonn
	HOPE München mbH	Winthirstrasse 7, 80698 München
	Onkologische Schwerpunktpraxis; [redacted]	Wönnichstraße 64, 10317 Berlin
	ÜBAG MVZ Mitte und MVZ Delitzsch GmbH	Johannisplatz 1, 04103 Leipzig
	[redacted] MVZ [redacted]	[redacted] 95028 Hof
	[redacted]	[redacted] 34119 Kassel
	[redacted]	[redacted] 04683 Naunhof

Investigator Name	Institution	Adress
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	CHOP GmbH	Tennelbachstraße 59, 65193 Wiesbaden
	[redacted]	[redacted] 26389 Wilhelmshaven
	Urologie am Malkasten	Jacobistrasse 7, 40211 Düsseldorf
	Hämatologie und Internistische Onkologie	Kurt-Schumacher-Platz 4, 44787 Bochum
	MVZ Die Gesundheitsunion GmbH	Hofaue 91 -93, 42103 Wuppertal
	[redacted]	[redacted] 04349 Leipzig
	Frauenärzte am Stadtpark	Am Stadtpark 2, 90409 Nürnberg
	OVZ Friedrichshain	Landsberger Allee 117, 10407 Berlin
	Rems-Murr-Kliniken GmbH	Am Jakobsweg 1, 71364 Winnenden
	G.SUND Onkologie GbR	Gr. Parower Straße 47-53, 18435 Stralsund
	Drittmittel Paracelsus-Klinik	Am Natruper Holz 69, 49076 Osnabrück
	[redacted]	[redacted] 14169 Berlin
	Klinikum Landkreis Tuttlingen Frauenklinik	Zeppelinstr. 21, 78534 Tuttlingen
	Gemeinschaftspraxis [redacted]	[redacted] 97080 Würzburg
	[redacted]	[redacted] 50677 Köln
	Uromedicum GmbH	Frankfurter Straße 35-39, 64720 Michelstadt
	Klinikum Augsburg	Postfach 101920, 86009 Augsburg
	Universitätsklinikum Essen	Hufelandstraße 55, 45147 Essen
	Onkonet-Marburg GmbH	Erlenring 9, 35037 Marburg
	[redacted]	[redacted] 10719 Berlin (Charlottenburg)
	[redacted]	[redacted] 88045 Friedrichshafen
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	[redacted]	[redacted] 91096 Möhrendorf
	eps GmbH	Hohes Gäßchen 8-10, 07381 Pößneck
	Spital 2 Medizinisches Institut GmbH	Spitalgasse 2, 90403 Nürnberg
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Investigator Name	Institution	Adress
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	onkomedic GbR	Niemeyerstraße 22, 06110 Halle (Saale)
	Luisenkrankenhaus GmbH	Luise-Rainer-Str. 6-10, 40235 Düsseldorf
	St. Elisabeth Krankenhaus - Brustzentrum	Werthmannstraße 1, 50935 Köln
	phase drei, Hämato-Onkologischer Studienkreis	Am Hasenkopf 1, 63739 Aschaffenburg
	MediOnko-Institut GbR	Möllendorffstraße 52, 10367 Berlin
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	[redacted] MOPS	Prielmayerstraße 1, 80335 München
	Universitätsklinikum Frankfurt	Theodor Stern Kai 7, 605090 Frankfurt am Main
	[redacted]	[redacted] 31275 Lehrte
	Clinical Research Stolberg GmbH	Steinfeldstraße 7, 52222 Stolberg
	Asklepios Paulinenklinik	Geisenheimerstr. 10, 65197 Wiesbaden
	Philipps Universität Marburg	Baldingerstraße, 35043 Marburg
	ICH Gesellschaft St. Vinzenz mbH [redacted]	Auf dem Schafsberg, 65549 Limburg
	[redacted]	[redacted] 04107 Leipzig
	Onkoplus, [redacted]	Clayallee 225 A, 14195 Berlin-Zehlendorf
	Frauenärzte Saarbrücken- West; [redacted]	[redacted] 66113 Saarbrücken
	DRK Krankenhaus Saarlouis	Vaubanstraße 25, 66740 Saarlouis
	AMEOS Klinikum Seepark Geestland GmbH	Langener Str. 66, 27607 Geestland
	Urologicum OF / Dietzenbach	Schmidtstraße 1, 63128 Dietzenbach
	St. Georg Klinikum Eisenach GmbH	Mühlhäuser Straße 94, 99817 Eisenach
	[redacted]	[redacted] 13055 Berlin
	[redacted]	[redacted] 14197 Berlin-Wilmersdorf
	Ambulantes Tumorzentrum Spandau	Klosterstr. 34/35, 13581 Berlin
	MVZ am Schlosssee GmbH	Zur Allerwelle 4, 38518 Gifhorn
	Klinik [redacted] GmbH	Harsefelder Straße 8, 21680 Stade
	Brustklinik Jerusalem-Krankenhaus Hamburg	Moorkamp 2-6, 20257 Hamburg
	Gesellschaft für Medizinische Studien Würselen	Mauerfeldchen 72, 52146 Würselen

Investigator Name	Institution	Adress
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[redacted]	[redacted]	[redacted] 86956 Schongau

STATISTICAL ANALYSIS PLAN FOR OBSERVATIONAL STUDIES

X-TREME

Prospective Observational Study to Evaluate Usage of XGEVA® 120 mg for Prevention of Skeletal Related Events (SRE´s) in Patients with Bone Metastases and Solid Tumors in Routine Clinical Practice

Protocol Number: 20101312

Version: Final 2.0

Date: 04 May 2017

Authors: [redacted]
Lead Statistician, Metronomia Clinical Research GmbH
05-May-2017 [redacted]
Date, Signature

[redacted]
Statistician, Metronomia Clinical Research GmbH
05 May 2017 [redacted]
Date, Signature

Approved by: [redacted]
Biostatistics Sr Mgr, Amgen
[redacted] 5 MAY 2017
Date, Signature

Table of Contents

Table of Abbreviations

Abbreviation	Definition
ADR	Adverse Drug Reaction
AQA	Analgesic Score (AQA)
CI	Confidence Interval
ECOG	Classification Eastern Cooperative Oncology Group
EQ-5D	EuroQol –5 Dimensions
eCRF	electronic Case Report Form
FAS	Full Analysis Set
NIS	Non Interventional Study
MPEP	Medical Practice Evaluation Program
ONJ	Osteonecrosis of the Jaw
SAP	Statistical Analysis Plan
SEV	Site Evaluation Visit
SRE	Skeletal Related Events
VAS	Visual Analogue Scale

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol for Denosumab (XGEVA®) Study 20101312 dated 10 October 2016. The scope of this plan includes the interim analysis and the final analysis that are planned and will be executed by Metronomia Clinical Research GmbH.

2. OBJECTIVES

This non-interventional Medical Practice Evaluation Program (MPEP) will collect patient related information about the use of XGEVA® in routine clinical practice. Moreover, this MPEP will collect data on demographics, disease characteristics, and concomitant anticancer therapy in solid tumor patients with bone metastases, and data on the medical history of these patients. Most of the data will be collected along clinical routine care and any collection of patient reported outcomes are kept at minimum and do not expose the patient to extensive burden.

2.1 Primary Objective

The primary objective of this study is to estimate the persistence at 24 weeks in patients with solid tumors and bone metastases treated with XGEVA® as per routine clinical practice.

2.2 Secondary Objectives

- Estimate the persistence to XGEVA® at 48 weeks as per routine clinical practice.
- Estimate time to non-persistence to XGEVA®.
- Describe the primary and secondary persistency outcomes by tumor type.
- Describe demographics, disease characteristics, concomitant anticancer therapy and medical history of patients treated with XGEVA® as per routine clinical practice.
- Describe dose and frequency of calcium and vitamin D supplementation of patients treated with XGEVA® as per routine clinical practice.

2.3 Exploratory Objectives

- Describe changes in individual pain scores between baseline and week 24 during use of XGEVA® as per routine clinical practice.
- Describe changes in individual pain medication between baseline and week 24 during use of XGEVA® as per routine clinical practice.
- Collect patient-reported outcomes describing problems with mobility, self-care, daily activities, pain/discomfort, and anxiety/depression (EQ-5D).
- Collect data on reportable adverse drug reactions to XGEVA®.

3. STUDY OVERVIEW

3.1 Study Design

This is a multi-center, prospective, observational, descriptive, non-interventional study in patients with solid tumors and bone metastases.

Patients will be recruited over a period of approximately 96 weeks. Patient data will be collected at baseline and every 4 weeks thereafter for a maximum of 48 weeks. The duration of the entire study is estimated to be approximately 144 weeks, i.e. from the first patient enrolled until all data has been abstracted for the last patient.

At the individual centers, consecutive patients fulfilling the inclusion and exclusion criteria will be included in the study. The decision to prescribe treatments must have been freely undertaken by the physician prior to consideration of including the patient into the study. An enrolment log file will be used to collect basic patient information (age, sex, tumor, planned chemotherapy, outcome of screening, and reasons for non-enrolment, if applicable) of all patients with bone metastases and solid tumors meeting the inclusion criteria at each site.

Patient data will be collected at enrolment and during oncologic treatment up to 30 days after the latest dose of XGEVA® or until the patient dies, is ‘lost to follow-up’ or withdraws informed consent, whichever occurs first.

Patients will be observed from enrolment until 30 days after the last dose of XGEVA® within the observational period of 48 weeks.

The study will end when the last patient remaining on the study either completes the observation period, dies, is ‘lost to follow-up’ or withdraws informed consent, whichever occurs first.

Upon independent ethic committee (IEC) recommendation of the project plan and patient consent, data for eligible patients will be collected during routinely scheduled hospital visits (both inpatient or outpatient). The study will collect prospective data for the defined observation period. All data will be collected using a web-based secured electronic data capture system.

This is a non-interventional study. No laboratory, diagnostic, or therapeutic procedures other than those currently performed as part of the patient's routine care will be required.

3.2 Data Source

All potentially participating sites will be selected by the medical team (TA/GCSM) following the existing Amgen quality standards for observational research. Selection is based on estimated number of patients, the type of site and their geographical location. The site selection should ensure a geographically balanced distribution of German sites. In all potential sites a site evaluation visit (SEV) is mandatory. A monitoring plan will be implemented.

Sites inactive for 6 months from site initiation will be considered to be closed. Details on all centers that were selected but did not participate will be recorded, including the primary reason for non-participation.

3.3 Sample Size

There will be no formal hypothesis testing. The aim is to provide statistical estimates of persistence at 24 weeks and 48 weeks (primary and secondary endpoints respectively) in solid tumor patients with bone metastases treated with XGEVA® as per routine clinical practice.

A total of approximately 1,400 patients will be enrolled across approximately 80 sites in Germany in order to minimize bias using centers representative of practice, not excluding difficult patients and to ensure the accuracy of estimate of the primary and secondary endpoints. It is anticipated that enrolment will take approximately 96 weeks and each patient will be followed for a maximum of 48 weeks.

The primary analyses will be descriptive in nature. The sample size therefore has not been assessed in terms of statistical power but rather the expected level of precision for the incidence of subjects persisting with XGEVA® at any time point and by tumor type. It is assumed that studied tumor types breast cancer, prostate cancer, lung cancer and other solid tumors will take respectively 35%, 35%, 20% and 10% of the enrolled

population. Different tumor type populations are expected to show different dropout rates on target time points (24 weeks and 48 weeks after initiation of the therapy)[1,2,3]. For breast cancer the proportions is assumed to be 15% for 24 weeks and 30% for 48 weeks, for prostate cancer 25% and 50%, for other lung cancer and other solid tumors 50% and 90%, respectively.

The planned sample size is based on the objective to estimate the 95% confidence interval (CI) around the proportion of persistence. The proportion of persistent patients is determined by not taking patients into account who dropped out of the study. A precision (half-width of the 95% CI) of 3.1% was deemed appropriate for the chosen primary endpoint in the overall patient population, which results in a sample size of approximately 1400 patients for an assumed proportion of 60% of patients persistent to XGEVA® after 24 weeks from start of treatment.

The sample size would allow for an estimate of precision for each of the covariates; prostate cancer, breast cancer, lung cancer and other solid tumors.

This sample size would also allow the estimation of the key secondary endpoint proportion of patients persistent to XGEVA® after 48 weeks from start of treatment: The assumed proportion of 30% of patients persistent to XGEVA® after 48 weeks could be estimated with a precision of 3.6% when an overall drop-out rate of 55% after 48 weeks is taken into account. The sample size would allow for an estimate of precision for each of the covariates; prostate cancer, breast cancer, lung cancer and other solid tumor.

4. STUDY ENDPOINTS/OUTCOMES

4.1 Primary Outcome

Persistence (yes/no) to XGEVA® at 24 weeks.

4.2 Secondary Outcome Measures

- Persistence (yes/no) to XGEVA® at 48 weeks.
- Time to non-persistence.
- Primary and secondary persistency outcomes by tumor type.
- Patient characteristics at baseline assessed for description of patients treated with XGEVA® as per clinical routine and their association with persistence / non-persistence.

- Dose and frequency of calcium and vitamin D supplementation at baseline and throughout treatment with XGEVA®.

4.3 Exploratory Outcome Measures

- Pain scores on a 10-item VAS at baseline and every 4 weeks for up to 24 weeks (or at end of study, whichever comes first).
- Pain medication and 8-point scale analgesics score (AQA) at baseline and every 4 weeks for up to 24 weeks (or at end of study, whichever comes first).
- EQ-5D at baseline and every 12 weeks for up to 48 weeks (or at end of study, whichever comes first).
- Reportable adverse drug reactions at baseline and 12 weeks for up to 48 weeks (or at end of study, whichever comes first).

5. HYPOTHESES OR ESTIMATION

No formal prospective hypotheses will be tested.

6. DEFINITIONS

6.1 Study day 1 and baseline

The date of the baseline assessment will serve as study baseline. The date of the first XGEVA® injection will serve as day 1.

6.2 Age

Age at baseline in days, months and years will be calculated using 1st of July of the birth year as a reference. For categorical analysis of age, the categories will be:

- 18-<25 years
- 25-<35 years
- 35-<45 years
- 45-<55 years
- 55-<65 years
- 65-<75 years
- >=75 years

In addition the two geriatric age groups (< 65 years, ≥ 65 years and < 75 years, ≥ 75 years) will be used.

6.3 Persistence (Primary Endpoint)

Persistence will be calculated based on the full analysis set (FAS), excluding those who died, withdrew informed consent or who are lost to follow-up before the persistence assessment. Therefore, the denominator for the proportion of persistent patients will include all persistent patients plus patients who refused further XGEVA® treatment, whose physician stopped treatment, for whom treatment was stopped because of a reportable ADR or who showed lack of compliance to planned treatment visits based on the permissible gap defined below. The summary of non-persistance due to violation of time windows will include the following information:

- Violation of 1 time window
- Violation of 2 time windows
- Violation of 3 time windows
- Violation of more than 3 time windows

Persistence (yes/no) to XGEVA® at 24 weeks – a patient will be considered persistent with XGEVA® at 24 weeks if the patient received at least 6 XGEVA® injections no more than 4 weeks plus 7 days (= 35 days) apart. A time window of +2 weeks will be allowed after the 24 weeks endpoint. A time window of ± 7 days will be allowed for each injection relative to the previous injection. Therefore, patients who finished at least 6 XGEVA® injections until week 26 (= up to 182 days) and who are respecting the permissible time window for each single injection will be defined as persistent at 24 weeks. Persistence after 48 weeks is defined equivalently with a minimum of 12 injections with not more than 4 weeks (+7 days) between each injection. A time window of +7 weeks will be allowed after the 48 weeks endpoint. A time window of ± 7 days will be allowed for each injection relative to the previous injections. Therefore, patients who finished at least 12 XGEVA® injections until week 55 (= up to 385 days) and who are respecting the permissible time window for each single injection will be defined as persistent at 48 weeks.

6.3.1 Persistence (Primary Endpoint) – Sensitivity Analysis

Additionally to the analysis of persistence a sensitivity analysis of persistence will be included. For the sensitivity analysis the same definition as for persistence analysis is valid (see section 6.3) with the following exceptions:

- a time window of ± 14 days (instead of ± 7 days) will be allowed for each injection relative to the previous injection for persistence (yes/no) to XGEVA® at 24 weeks and after 48 weeks.
- a time window of +4 weeks (instead of +2 weeks) will be allowed after the 24 weeks endpoint.
- a time window of +10 weeks (instead of +7 weeks) will be allowed after the 48 weeks endpoint.

6.4 Time to Non-Persistence (Secondary Endpoint)

Time to non-persistence will be calculated as the time in days between the date of the first injection and the date of the last injection received during the period where the patient is still classified as persistent plus 4 weeks (28 days) for patients who are non-persistent at any time during the study as defined below.

Patients will be defined as non-persistent if:

- they refuse to receive further XGEVA® treatment.
- the physician decided to stop treatment.
- treatment was stopped because of a reportable ADR
- they showed lack of compliance (as previously defined in section 6.3) with the scheduled treatment visits.
- they are lost to follow-up.

Patients will be regarded as censored if:

- they died (censoring date will be equal to date of death).
- finished treatment per protocol after 52 weeks (censoring date will be equal to date of last injection).
- withdrew informed consent (censoring date will be equal to date of withdrawal of consent).

Patients will only be censored if censoring day is before time to non-persistence.

6.4.1 Time to Non-Persistence (Secondary Endpoint) – Sensitivity Analyses

6.4.1.1 Time to Non-Persistence (Secondary Endpoint) – Sensitivity Analysis – Censoring Lost to Follow-Up Subjects

Additionally to the analysis of time to non-persistence a sensitivity analysis of time to non-persistence will be included. For the sensitivity analysis the same definition as for time to non-persistence analysis is valid (see section 6.4) but with one exception: Also lost to follow-up subjects will be censored at time of last XGEVA injection.

6.4.1.2 Time to Non-Persistence (Secondary Endpoint) – Sensitivity Analysis – Time Window of ± 14 Days Between Injections and Censoring Lost to Follow-Up Subjects

For the sensitivity analysis of 'time to non-persistence – time window of ± 14 days between injections and censoring lost to follow-up subjects' the same definition as in section 6.4.1.1 is valid with one exception: For 'patient is still classified as persistent' the definition of 'persistence (primary endpoint) – sensitivity analysis'(see section 6.3.1) has to be used.

6.5 Previous and Concomitant Therapies

A therapy is defined as previous if a tick box for previous therapy is available in the eCRF and if it is ticked with 'Yes' or if the start date of the therapy is prior to day 1 (before very first application) or if the start date of the therapy is missing and the end date of the therapy is before day 1 (before very first application) or missing.

A therapy is defined as concomitant if the stop date of the therapy is on or after day 1 or if the stop date of the therapy is missing.

Incomplete start and stop dates will be estimated as described in chapter 9.3.

6.6 Calculation of Duration in Months and Years

Duration in months will be calculated as duration [days] / 30.4375.

Duration in years will be calculated as duration [days] / 365.25.

7. ANALYSIS SUBSETS

7.1 Primary Analysis Set

The primary analysis set will be the Full Analysis Set (FAS), which is defined as the set of all patients who are documented in the e-CRF and who received at least one injection of XGEVA®. Patients who violated inclusion/exclusion criteria or who had no valid date of informed consent will be excluded from the FAS.

The statistical analyses will be based in general on the Full Analysis Set (FAS). For the evaluation of the primary and the first secondary outcome measure the basis of analysis will the FAS as well, but excluding patients who died, withdrew informed consent or who are lost to follow-up before the respective persistence assessment.

7.2 Interim Analyses Set

At least one interim analysis is planned during the conduct of the study after at least 25% of the targeted number of patients have completed enrolment and 24 weeks of the study. Patients will be eligible for the interim analysis if their data is complete and all queries have been solved. The corresponding definition for the analysis set as described above restricted to patients eligible for the interim analysis will be applied.

7.3 Planned Subsets

All summary tables will be calculated stratified by tumor type and overall (depending on the type of summary statistics either shown in columns or rows):

- Patients with prostate cancer
- Patients with breast cancer
- Patients with lung cancer
- Patients with kidney cancer
- Patients with other solid tumors
- Overall

The following subgroup analyses will be performed for all persistence outcomes:

Analysis by previous antiresorptive treatment (alendronic acid, ibandronic acid, pamidronic acid, risedronic acid, zoledronic acid or Denosumab (Prolia®)) (see section 6.5 for definition of previous therapy):

- Patients with previous antiresorptive treatment
- Patients with no previous antiresorptive treatment

Analyses by previous systemic antineoplastic therapy (see section 6.5 for definition of previous therapy):

- Patients who underwent surgery (Yes vs No)
- Patients who underwent chemotherapy (Yes vs No)
- Patients who underwent radiotherapy (Yes vs No)
- Patients who underwent antihormonal therapy (Yes vs No)

8. INTERIM ANALYSIS

At least one interim analysis is planned during the conduct of the study after at least 25% of the targeted number of patients have completed 24 weeks of the study. Additional interim analyses may be performed if more data is required to support reimbursement negotiations ahead of the final analysis. The first interim analysis will provide results about persistence to XGEVA® supporting reimbursement negotiations ahead of the final analysis as well. Any interim analysis will be performed only after full data cleaning activities have been performed on those patient data that are intended to be included in the interim analysis. However as data collected for reportable ADRs due to the setup of the e-CRF cannot be cleaned before the patient has completed the end of study visit those data might not be included into the interim analysis. The results of an interim analysis may be used for publication ahead of the final analysis to support reimbursement negotiations. The study design and conduct will not be affected by the interim analysis results.

It is not planned to install a Data Monitoring Committee (DMC) or Data Review Team (DRT) for this study.

9. DATA SCREENING AND ACCEPTANCE

9.1 General Principles

The objective of the data screening is to assess the quantity, quality and statistical characteristics of the data relative to the requirements of the planned analyses. Data screening will be performed according to the data handling manual.

9.2 Data Handling and Electronic Transfer of Data

The data to be used in the planned analyses will come from the e-CRF database ”clincase” (by Quadratec Data Solutions Ltd., www.clincase.com). Data dumps will be provided for all planned analyses.

9.3 Handling of Missing and Incomplete Data

In general, missing or incomplete data will not be replaced or imputed.

For all summary tables the number of patients with missing information will also be tabulated. For incomplete dates the 15th of the respective month will be imputed. If the month is also missing, the 1st of July of the respective year will be assumed. However, the start date of an adverse reaction will be not be imputed to be before the first injection. If the imputed date is before the first injection then the date of first injection will be used as start date of the adverse reaction instead.

9.4 Outliers

No continuous outcomes are studied as primary or secondary outcomes in this study. Therefore, no outlier detection will be performed. Laboratory values will be checked for plausibility against their clinical plausible ranges.

9.5 Distributional Characteristics

No statistical methodology is being used that relies on assumption regarding distribution or specific variability of data.

9.6 Validation of Statistical Analyses

SAS programming will be performed according to Metronomia standards as defined in BM-08-SOP “Statistical Analysis and Programming” and related work instructions. Special attention will be paid to planning and performance of quality control measures as documented in the QC plan for the analysis of this study (see BM-08-WIN03 “How to Plan and Document QC for Statistical Analysis”). Tables, figures and listings will be produced with validated standard macro programs where standard macros can produce the specified outputs.

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software, specifically the SAS system in version 9.3 or higher. Data will be stored in SAS data sets. Results will be stored as Word and PDF files. Both data and results will be transferred to Amgen by secure file transfer.

10. STATISTICAL METHODS OF ANALYSIS

10.1 General Principles

The principal aim of this prospective observational study is to demonstrate the persistence to with XGEVA® according to SmPC in routine clinical practice in Germany in different therapeutic indications. Therefore, the statistical analyses performed for the study will be descriptive in nature. No formal prospective hypotheses will be tested.

Continuous outcomes will be summarized by number of non-missing values, mean, median, standard deviation (SD), lower and upper 25th quartiles and minimum and maximum. For categorical outcomes, the number and percentage of patients in each category will be presented.

10.2 Subject Accountability

The number of subjects included in the study and the number of subjects that completed the baseline visit and each treatment visit will be summarized.

For study termination the following categories will be defined: Study termination prior to 24 weeks, between 24 weeks and 26 weeks, more than 26 weeks and prior 48 weeks and at least 48 weeks.

The number of patients who discontinued the study will be summarized including the reason for discontinuation. The reason for study termination will be summarized by category for study termination.

Additionally the patients who are still on-treatment at 24 weeks and at 48 weeks will be summarized. A time window of -7 days is allowed, i.e. patients are counted as ‘still on treatment at 24 weeks’ if they have at least one injection at or after day 161 (week 23) and at or after day 329 (week 47) respectively. The study duration in weeks will be summarized.

The physician’s special qualification will be summarized.

10.3 Demographic and Baseline Characteristics

Age will be summarized as a continuous outcome as well as in categories. Sex will be summarized.

Patients will be characterized regarding tumor type (breast / prostate / lung / kidney / other) and TNM status at initial diagnosis. Other tumor type will be coded using MedDRA version 15.1.

Duration since initial tumor diagnosis in years and in months will be summarized. For patients with breast cancer, hormone receptor status, Her-2/neu-status and triple-negative status (estrogen receptor-negative, progesterone receptor-negative and HER2-negative) at the time of first diagnosis of metastases will be summarized. For patients with lung cancer, histology (NSCLC, SCLC) at the time of first diagnosis of metastases will be summarized. For patients with SCLC, type of disease (Extended / Limited disease) will be summarized.

Duration since initial diagnosis of metastases in years and in months will be summarized.

Visceral metastases (yes / no), localization of visceral metastases (lung / liver / brain / skin / other) and specification of other metastases localizations will be summarized. Specification of other metastases localizations will be coded using MedDRA version 15.1.

Duration since initial diagnosis of bone metastases in years and in months will be summarized.

Bone metastases (yes / no), localization of bone metastases (cranium, humerus, scapula, ribs, cervical spine, thoracic spine, lumbar spine, sacrum, pelvis, femoral, other), specification of other bone metastases localizations, sum of bone metastases localizations, distribution pattern and type of diagnosis of bone metastases (Imaging (asymptomatic) / based on symptoms) will be summarized. Specification of other bone metastases localizations will be coded using MedDRA version 15.1.

Skeletal related events (SREs) that occurred before the study, number of prior SREs, occurrence of bone pain and hypercalcaemia, type of SRE (spinal cord compression / pathologic fracture / bone surgery / radiotherapy) and type of SRE therapy (radionuclides / bisphosphonates) by tumor type will be summarized.

Duration since diagnosis of previous SRE in years and in months will be summarized.

Previous antineoplastic therapy will be summarized by type (surgery / chemotherapy / radiotherapy / antihormonal treatment) (see section 6.5 for definition of previous therapy).

Previous surgeries, previous chemotherapy and previous antihormonal therapy will be summarized. Surgeries will be coded using MedDRA version 15.1. Chemotherapies and antihormonal therapies will be coded using WHO Drug Dictionary version 2012 June.

ECOG status before treatment start will be summarized in categories (0 / 1 / 2).

The number of patients with concomitant medical conditions will be summarized by type of condition (Cardiac Infarction / Congestive Heart Failure / Peripheral Artery Occlusive Disease / Cerebrovascular Disease / Dementia / Chronic Lung Disease / Connective Tissue Disease / Ulcer Disease / Mild Liver Disease / Diabetes / Hemiplegia / Moderate up to Severe Kidney Disease / Diabetes with end organ damages / Tumor / Leukemia / Lymphoma / Moderate up to Severe Liver Disease / Aids).

10.4 Persistence Analyses

10.4.1 Analyses of Persistence

Persistence will be analyzed as a binary outcome (yes/no) for the 24 weeks outcome as well as the 48 weeks outcome. For the proportion of persistent patients an exact two-sided 95% confidence interval will be calculated. Analyses of persistence will be repeated separately by tumor type.

10.4.2 Analyses of Time to Non-Persistence

Time to non-persistence will be analyzed using Kaplan-Meier methods. Median time to non-persistence with 95% confidence interval, 1st quartile and 3rd quartile will be shown. Confidence intervals for quartiles of the times to non-persistence will be calculated based on the log-log transformation (SAS PROC LIFETEST option CONFTYPE=LOGLOG). Based on the Kaplan-Meier method an estimate of proportion of patients who are still persistent at 24 weeks and 48 weeks will be derived and compared to the binary analysis as described in 10.4.1.

A Kaplan-Meier curve will be plotted.

Analyses of time to non-persistence will be repeated separately by tumor type.

In order to describe the association between demographic/baseline characteristics and the time to non-persistence, a Cox proportional hazards model will be calculated with time to non-persistence as an outcome variable and the following explanatory variables:

- Age (continuous)
- Sex (in categories: “male” versus “female”)
- Tumor type (in categories: “breast” / “prostate” / “lung” versus “other”)
- Visceral metastases (in categories: “yes” versus “no”)

- Bone metastases (in categories: symptomatic"" versus "asymptomatic (imaging)", exclude 'unknown')
- Previous antineoplastic therapy (in categories: "chemotherapy" / "radiotherapy" versus "antihormonal treatment") (see section 6.5 for definition of previous therapy)
- Skeletal related events occurring before study (in categories: "yes" versus "no")
- ECOG status before treatment start (in categories: "0" / "1" versus "2")
- Previous bisphosphonate therapy (in categories: "yes" versus "no") (see section 6.5 for definition of previous therapy)

10.4.3 Analyses of Dose and Frequency of Calcium and Vitamin D Supplementation

Calcium and vitamin D supplementation will be analyzed as a binary outcome (yes/no) respectively by treatment visit. Calcium and vitamin D supplementation will also be analyzed by average daily dose in mg and by treatment visit.

10.4.4 Analyses of Exploratory Endpoints

- Pain scores on a 10-item VAS will be tabulated by tumor type and visit. Additionally the absolute changes from visit 1 in VAS pain score will be tabulated by tumor type and visit. Only planned visits according to protocol will be included in the analyses. Data of visits that were not planned will only be listed. Pain medication and 8-point scale analgesics score (AQA) will be tabulated overall and by period. For analysis of scale analgesics score by period the following periods will be used:

  period 1: 0 weeks to 2 weeks (Day 1 (date of the first XGEVA® injection) to day 14)
  period 2: 2 weeks to 6 weeks (Day 15 to Day 42)
  period 3: 6 weeks to 10 weeks (Day 43 to Day 70)
  period 4: 10 weeks to 14 weeks (Day 71 to Day 98)
  period 5: 14 weeks to 18 weeks (Day 99 to Day 126)
  period 6: 18 weeks to 22 weeks (Day 127 to Day 154)

  Two tables will be presented for analysis by period. In the first table the worst score per patient within a period will be used. In the second table the best score per patient within a period will be used. A footnote with the respective definition will be included in the tables.

Additionally the analgesics score will be summarized as continous variable by period. Also the absolute changes from baseline will be summarized by period. For this analysis the baseline value is defined as the analgesics score between day -15 and day 5. If more than one value are available in this period the value nearest to day 1 will be used. These summaries will also be done for the worst and the best score per patient within a period.

- EQ-5D will be tabulated by tumor type and visit. Additionally the absolute changes from visit 1 in EQ-5D will be tabulated by tumor type and visit. Only planned visits according to protocol will be included in the analysis. Data of visits that were not planned will only be listed.

10.5 Safety Analyses

10.5.1 Reportable Adverse Drug Reactions

The Medical Dictionary for Regulatory Activities (MedDRA) version 15.1 will be used to code all adverse reactions, other safety events and suspected ONJ cases not related (i.e. reportable adverse drug reactions) to a system organ class and a preferred term. All reportable ADRs will be summarized by type of tumor and overall. Treatment-emergent adverse events are events with an onset after the administration of the first dose of XGEVA®.

The subject incidence of reportable adverse drug reactions will be summarized for all events, fatal events, events related to XGEVA as well as those leading to withdrawal of product. Events will be tabulated by system organ class and preferred term in descending order of frequency. Cases of osteonecrosis of the jaw (ONJ) will be listed separately and summarized by number of injections received. In addition the time from XGEVA initiation to ONJ event will be analyzed using Kaplan-Meier methods. Median time from XGEVA initiation to ONJ event with 95% confidence interval, 1st quartile and 3rd quartile will be shown. Confidence intervals for quartiles of the time to ONJ event will be calculated based on the log-log transformation (SAS PROC LIFETEST option CONFTYPE=LOGLOG). A Kaplan-Meier curve will be plotted. Analyses of time to ONJ event will be repeated separately by tumor type. Data on hypocalcemia serious adverse drug reaction will be listed. The hypocalcemia SADR will be classified into a visit. If the subject was on Ca/VitD supplementation at that visit, then the assumption that the subject was on calcium/vitamin D supplementation at the time of the SADR will be used, and a footnote will be added to the listing to point to this assumption.

10.5.2 Exposure to Product

Descriptive statistics will be produced to describe the exposure to XGEVA®. Number of injections will be summarized as well as the number and percentage of subjects with dose modifications.

10.5.3 Exposure to Concomitant Medication (Antineoplastic Treatments)

The number of patients with concomitant antineoplastic treatments will be summarized by type (chemotherapy / radiotherapy / antihormone therapy) (see section 6.5 for definition of concomitant therapy). The number and proportion of subjects receiving concomitant antineoplastic treatments (chemotherapy and antihormone therapy) will be summarized by preferred term (INN name) as coded by the World Health Organization Drug (WHODRUG) dictionary.

10.5.4 Laboratory Parameters

Laboratory parameters will be summarized by parameter (serum calcium / serum creatinine / creatinine clearance) and treatment visit and by tumor type and overall. In order to harmonize laboratory results by using the same units, laboratory results will be converted into SI units.

10.5.5 Previous Antiresorptive Therapies

The number of patients with previous antiresorptive therapies, preparation (Alendronic acid / Etidronic acid / Ibandronic acid / Pamidronic acid / Risedronic acid / Zoledronic acid / Denosumab), route of application and application frequency of previous antiresorptive therapy will be summarized by tumor type and overall (please see section 6.5 for definition of previous therapy).

11. CHANGES FROM RPP SPECIFIED ANALYSES

There are no changes to the pre-specified analyses.

12. LIST OF PLANNED TABLES, FIGURES, AND LISTINGS

12.1 Planned Tables

Category	Data/Endpoint	Description

Category	Data/Endpoint	Description
1. Disposition	Subject Disposition - All Subjects	Reasons for individual patient exclusions will be tabulated by tumor type and overall. Patients who are still on-treatment at 24 weeks and at 48 weeks, patient still in study and reason for study termination by tumor type and overall. Study duration in weeks by tumor type and overall. Physician's special qualification by tumor type and overall.
2. Demographic and Baseline Characteristics	Baseline Demographics	Summarize the demographic data (sex, age, age in categories) for all subjects by tumor type and overall.
	Summary of Tumor Type and TNM Status at initial diagnosis	Summarize tumor type and TNM status by tumor type and overall. Summarize specification of other tumor type by MedDRA system organ class and preferred term and by tumor type and overall.
	Duration Since Initial Tumor Diagnosis	Duration since initial tumor diagnosis (years in categories) will be tabulated by tumor type and overall.
	Summary of Hormone Receptor Status and Her-2/neu-Status for Patients with Breast Cancer	Summarize hormone receptor status, Her-2/neu-status and triple-negative status for patients with breast cancer by tumor type and overall.
	Summary of Histology for Patients with Lung Cancer	Summarize histology for patients with lung cancer by tumor type and overall. For patients with SCLC, summarize by type of disease
	Duration Since Initial Diagnosis of Metastases (years)	Duration since initial diagnosis of metastases (years in categories) will be tabulated by tumor type and overall.
	Duration Since Initial Diagnosis of Metastases (months)	Summarize duration since initial diagnosis of metastases by tumor type and overall.

Category	Data/Endpoint	Description
	Summary of Visceral Metastases, localization of Visceral Metastases and Specification of Other Metastases Localizations	Summarize visceral metastases and localization of visceral metastases by tumor type and overall. Summarize specification of other metastases localizations by MedDRA system organ class and preferred term and by tumor type and overall.
	Duration Since Initial Diagnosis of Bone Metastases (years)	Duration since initial diagnosis of bone metastases (years in categories) will be tabulated by tumor type and overall.
	Duration Since Initial Diagnosis of Bone Metastases (months)	Summarize duration since initial diagnosis of bone metastases by tumor type and overall.
	Summary of Bone Metastases, Location of Bone Metastases, Specification of Other Bone Metastases Localizations, Sum of Bone Metastases Localizations, Distribution Pattern and Type of Diagnosis of Bone Metastases.	Summarize bone metastases, location of bone metastases, sum of bone metastases localizations, distribution pattern and type of diagnosis of bone metastases by tumor type and overall. Summarize specification of other bone metastases localizations by MedDRA system organ class and preferred term and by tumor type and overall.
	Summary of Skeletal Related Events (SREs), Type of SRE and Type of SRE Therapy.	Summarize skeletal related events (SREs), number of prior SREs, bone pain and tumor induced hypercalcemia associated with previous SRE, type of previous SRE, further therapeutic interventions for previous SRE and specification of other Bisphosphonate for therapy of previous SRE by tumor type and overall.
	Duration Since Diagnosis of Previous SRE (years)	Duration since diagnosis of previous SRE (years in categories) will be tabulated by tumor type and overall.
	Duration Since Initial Diagnosis of Previous SRE (months)	Summarize duration since diagnosis of previous SRE by tumor type and overall.
	Summary of Previous Antineoplastic Therapy	Summarize previous antineoplastic therapy by tumor type and overall.
	Summary of Previous Surgeries	Summarize previous surgeries by tumor type and overall.

Category	Data/Endpoint	Description
	Summary of Previous Chemotherapy	Summarize previous chemotherapy by tumor type and overall.
	Summary of Previous Antihormonal Therapy	Summarize previous antihormonal therapy by tumor type and overall.
	Summary of ECOG Status and Presence of Concomitant Diseases	Summarize ECOG status before treatment start and presence of concomitant diseases by tumor type and overall.
	Summary of Concomitant Diseases	Summarize patients with concomitant diseases by tumor type and overall.
3. Persistence	Summary of Persistence at 24 Weeks	Summarize persistence at 24 weeks by tumor type and overall. Including sensitivity analysis.
	Summary of Persistence at 48 Weeks	Summarize persistence at 48 weeks by tumor type and overall. Including sensitivity analysis.
	Summary of Time to Non-Persistence	Summarize time to non-persistence using Kaplan-Meier methods by tumor type and overall. Including sensitivity analyses.
	Proportional Hazards Analysis of Time to Non-Persistence	Summarize results of Cox Proportional Hazards Model with time to non-persistence as outcome variable. Including sensitivity analyses.
4. Dose and Frequency of Calcium and Vitamin D supplementation	Summary of Dose and Frequency of Calcium and Vitamin D supplementation	Summarize dose of calcium and vitamin D supplementation by treatment visit by tumor type and overall.
	Summary of Frequency of Calcium and Vitamin D supplementation	Summarize frequency of calcium and vitamin D supplementation by treatment visit and overall. Including a graphic for the proportion with supplementation by visit.
5. Changes in Pain Score and Medication	Summary of Pain Score by Treatment Visit	Summarize pain score on VAS and change from visit 1 by treatment visit and by tumor type and overall..
	Summary of Pain Medication by Treatment Visit	Summarize pain medication and analgesic score (AQA) of pain medications by tumor type and overall and by tumor type and period.

Category	Data/Endpoint	Description
6. Quality of Life	Summary of EQ5D Results	Summarize EQ5D and change from visit 1 by treatment visit and item by tumor type and overall.
7. Extent of Exposure	Exposure to XGEVA®	Summarize the number of subjects exposed to XGEVA®, duration of exposure to XGEVA® and number of doses received, and dose by tumor type and overall.
8. Concomitant Medication	Summary of Concomitant Antineoplastic Medications	Summarize medications, concomitant antineoplastic chemotherapy medications, concomitant antineoplastic antihormone medications (incl. antibodies and small molecules) by tumor type and overall.
9. Previous Antiresorptive Therapies	Summary of Previous Antiresorptive Therapies	Summarize previous antiresorptive therapies, preparation, route of application, and application frequency of previous antiresorptive therapy by tumor type and overall. Summarize cycle shift and permanent discontinuation of bisphosphonate therapy by tumor type and overall for patients with previous antiresorptive therapy.
10. Laboratory Results	Summary of Creatinine Clearance	Summarize creatinine clearance by treatment visit and by tumor type and overall.
	Summary of Serum Calcium	Summarize serum calcium by treatment visit and by tumor type and overall.
	Summary of Serum Creatinine	Summarize serum creatinine by treatment visit and by tumor type and overall.
11. Reportable Adverse Drug Reactions	Overall Summary of Reportable Adverse Drug Reactions Related to XGEVA®	Tabulation of subjects experiencing the following types of reportable adverse drug reactions: all, fatal, those leading to withdrawal of product, serious by tumor type and overall.
	Summary of Reportable Adverse Drug Reactions Related to XGEVA®	Tabulation of subjects experiencing any reportable adverse drug reactions related to XGEVA® by MedDRA system organ class and preferred term in descending order of frequency by tumor type and overall.

Category	Data/Endpoint	Description
	Summary of Fatal Adverse Drug Reactions Related to XGEVA®	Tabulation of subjects experiencing fatal adverse drug reactions related to XGEVA® by MedDRA system organ class and preferred term in descending order of frequency by tumor type and overall.
	Summary of Adverse Drug Reactions Related to XGEVA® Leading to Withdrawal of Product	Tabulation of subjects experiencing adverse drug reactions related to XGEVA® leading to withdrawal of product by MedDRA system organ class and preferred term and in descending order of frequency by tumor type and overall.
	Summary of Serious Reportable Adverse Drug Reactions	Tabulation of subjects experiencing serious adverse drug reactions by MedDRA system organ class and preferred term in descending order of frequency by tumor type and overall.
	Summary of Serious Reportable Adverse Drug Reactions Related to XGEVA®	Tabulation of subjects experiencing serious adverse drug reactions related to XGEVA® by MedDRA system organ class and preferred term in descending order of frequency by tumor type and overall.
	Summary of osteonecrosis of the jaw (ONJ) events	Tabulation of subjects experiencing adverse events that are classified as osteonecrosis of the jaw (according to preferred term) by number of XGEVA injections received and overall. Time from XGEVA initiation to ONJ event using Kaplan-Meier methods by tumor type and overall.

12.2 Planned Listings

All CRF data will be listed.

12.3 Planned Figures

Data/Endpoint	Description
Time to non-persistence	Kaplan-Meier curve of time to non-persistence

13. LITERATURE CITATIONS / REFERENCES

1. Stopeck AT, Lipton A, Body JJ, et al: Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: A randomized, double-blind study. J Clin Oncol 28:5132-5139, 2010.

2. Fizazi K. et al: Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. The Lancet, Vol. 377 No. 9768 pp 813-822

3. Henry DH, Costa L, Goldwasser F, et al: Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. J Clin Oncol 29:1125-1132, 2011

Study title

Prospective Observational Study to Evaluate Usage of XGEVA® (denosumab) 120 mg for Prevention of Skeletal Related Events (SREs) in Patients with Bone Metastases and Solid Tumors in Routine Clinical Practice X-TREME

Study code

Protocol 20101312 (X-TREME) (AM05)

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15.1.1 Patient overview - All patients

	Missing cancer type (N=144)		Breast cancer (N=511)		Prostate cancer (N=296)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1276)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Documented in eCRF	144	(100.0%)	511	(100.0%)	296	(100.0%)	159	(100.0%)	50	(100.0%)	116	(100.0%)	1276	(100.0%)
Not included in FAS*#	144	(100.0%)	2	(0.4%)	2	(0.7%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	148	(11.6%)
Included in FAS*	0	(0.0%)	509	(99.6%)	294	(99.3%)	159	(100.0%)	50	(100.0%)	116	(100.0%)	1128	(88.4%)

* FAS: Full Analysis Set. Patients who violated inclusion/exclusion criteria, were screening failues, had not received any XGEVA injection, or had no valid date of informed consent are excluded from the FAS.
# 144 screening failures and 4 violations of exclusion criteria EC3

15.1.2 Patient disposition by cancer type - FAS

	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients who are still on-treatment[a] at 24 weeks												
No	68	(13.4%)	35	(11.9%)	80	(50.3%)	12	(24.0%)	49	(42.2%)	244	(21.6%)
Yes	441	(86.6%)	259	(88.1%)	79	(49.7%)	38	(76.0%)	67	(57.8%)	884	(78.4%)
Patients who are still on-treatment[a] at 48 weeks												
No	145	(28.5%)	89	(30.3%)	123	(77.4%)	25	(50.0%)	81	(69.8%)	463	(41.0%)
Yes	364	(71.5%)	205	(69.7%)	36	(22.6%)	25	(50.0%)	35	(30.2%)	665	(59.0%)
Study termination												
Observation completed	347	(68.2%)	187	(63.6%)	28	(17.6%)	23	(46.0%)	31	(26.7%)	616	(54.6%)
Observation not completed	162	(31.8%)	107	(36.4%)	131	(82.4%)	27	(54.0%)	85	(73.3%)	512	(45.4%)
Prior to 24 weeks[b]	59	(11.6%)	32	(10.9%)	70	(44.0%)	9	(18.0%)	44	(37.9%)	214	(19.0%)
Between 24 weeks and 26 weeks[b]	6	(1.2%)	2	(0.7%)	5	(3.1%)	1	(2.0%)	4	(3.4%)	18	(1.6%)
More than 26 weeks and prior to 48 weeks[b]	65	(12.8%)	40	(13.6%)	39	(24.5%)	13	(26.0%)	29	(25.0%)	186	(16.5%)
At least 48 weeks[b]	32	(6.3%)	33	(11.2%)	17	(10.7%)	4	(8.0%)	8	(6.9%)	94	(8.3%)
Reason for study termination												
Reported event	5	(1.0%)	6	(2.0%)	1	(0.6%)	3	(6.0%)	0	(0.0%)	15	(1.3%)
Death	76	(14.9%)	43	(14.6%)	98	(61.6%)	14	(28.0%)	51	(44.0%)	282	(25.0%)
Patient did not show up any more	28	(5.5%)	18	(6.1%)	16	(10.1%)	5	(10.0%)	11	(9.5%)	78	(6.9%)
Patient's wish	22	(4.3%)	20	(6.8%)	5	(3.1%)	3	(6.0%)	13	(11.2%)	63	(5.6%)
Withdrawal of informed consent	2	(0.4%)	1	(0.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	3	(0.3%)

[a]Still on treatment: A time window of -7 days is allowed, i.e. patients are counted as 'still on treatment at 24 weeks and at 48 weeks' if they have at least one injection at or after day 161 (week 23) and at or after day 329 (week 47) respectively.
[b]For allocation into these classes the exact day was used ('prior to 24 weeks': prior to day 168, 'between 24 weeks and 26 weeks': between day 168 and 182, 'more than 26 weeks and prior to 48 weeks': between day 183 and 335, 'At least 48 weeks': after day 335).
Due to different definitions of 'still on treatment at 24 weeks' and 'termination prior to 24 weeks' number of patients in the two categories differs.

15.1.2 Patient disposition by cancer type - FAS

	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Investigator's decision	18	(3.5%)	12	(4.1%)	7	(4.4%)	2	(4.0%)	3	(2.6%)	42	(3.7%)
Other	11	(2.2%)	7	(2.4%)	4	(2.5%)	0	(0.0%)	7	(6.0%)	29	(2.6%)
Reason for study termination prior to 24 weeks												
Reported event	3	(0.6%)	3	(1.0%)	0	(0.0%)	1	(2.0%)	0	(0.0%)	7	(0.6%)
Death	25	(4.9%)	13	(4.4%)	48	(30.2%)	6	(12.0%)	28	(24.1%)	120	(10.6%)
Patient did not show up any more	9	(1.8%)	5	(1.7%)	13	(8.2%)	1	(2.0%)	6	(5.2%)	34	(3.0%)
Patient's wish	8	(1.6%)	9	(3.1%)	3	(1.9%)	1	(2.0%)	8	(6.9%)	29	(2.6%)
Withdrawal of informed consent	2	(0.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.2%)
Investigator's decision	5	(1.0%)	1	(0.3%)	4	(2.5%)	0	(0.0%)	0	(0.0%)	10	(0.9%)
Other	7	(1.4%)	1	(0.3%)	2	(1.3%)	0	(0.0%)	2	(1.7%)	12	(1.1%)
Reason for study termination between 24 weeks and 26 weeks												
Reported event	1	(0.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Death	4	(0.8%)	1	(0.3%)	5	(3.1%)	1	(2.0%)	4	(3.4%)	15	(1.3%)
Patient did not show up any more	0	(0.0%)	1	(0.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Patient's wish	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Withdrawal of informed consent	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Investigator's decision	1	(0.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Other	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Reason for study termination more than 26 weeks and prior 48 weeks												

[a]Still on treatment: A time window of -7 days is allowed, i.e. patients are counted as 'still on treatment at 24 weeks and at 48 weeks' if they have at least one injection at or after day 161 (week 23) and at or after day 329 (week 47) respectively.
[b]For allocation into these classes the exact day was used ('prior to 24 weeks': prior to day 168, 'between 24 weeks and 26 weeks': between day 168 and 182, 'more than 26 weeks and prior to 48 weeks': between day 183 and 335, 'At least 48 weeks': after day 335).
Due to different definitions of 'still on treatment at 24 weeks' and 'termination prior to 24 weeks' number of patients in the two categories differs.

15.1.2 Patient disposition by cancer type - FAS

	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Reported event	0	(0.0%)	2	(0.7%)	1	(0.6%)	2	(4.0%)	0	(0.0%)	5	(0.4%)
Death	33	(6.5%)	17	(5.8%)	30	(18.9%)	5	(10.0%)	14	(12.1%)	99	(8.8%)
Patient did not show up any more	13	(2.6%)	6	(2.0%)	2	(1.3%)	2	(4.0%)	5	(4.3%)	28	(2.5%)
Patient's wish	10	(2.0%)	8	(2.7%)	2	(1.3%)	2	(4.0%)	3	(2.6%)	25	(2.2%)
Withdrawal of informed consent	0	(0.0%)	1	(0.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Investigator's decision	7	(1.4%)	3	(1.0%)	2	(1.3%)	2	(4.0%)	3	(2.6%)	17	(1.5%)
Other	2	(0.4%)	3	(1.0%)	2	(1.3%)	0	(0.0%)	4	(3.4%)	11	(1.0%)
Reason for study termination at least 48 weeks												
Reported event	1	(0.2%)	1	(0.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.2%)
Death	14	(2.8%)	12	(4.1%)	15	(9.4%)	2	(4.0%)	5	(4.3%)	48	(4.3%)
Patient did not show up any more	6	(1.2%)	6	(2.0%)	1	(0.6%)	2	(4.0%)	0	(0.0%)	15	(1.3%)
Patient's wish	4	(0.8%)	3	(1.0%)	0	(0.0%)	0	(0.0%)	2	(1.7%)	9	(0.8%)
Withdrawal of informed consent	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Investigator's decision	5	(1.0%)	8	(2.7%)	1	(0.6%)	0	(0.0%)	0	(0.0%)	14	(1.2%)
Other	2	(0.4%)	3	(1.0%)	0	(0.0%)	0	(0.0%)	1	(0.9%)	6	(0.5%)

[a]Still on treatment: A time window of -7 days is allowed, i.e. patients are counted as 'still on treatment at 24 weeks and at 48 weeks' if they have at least one injection at or after day 161 (week 23) and at or after day 329 (week 47) respectively.
[b]For allocation into these classes the exact day was used ('prior to 24 weeks': prior to day 168, 'between 24 weeks and 26 weeks': between day 168 and 182, 'more than 26 weeks and prior to 48 weeks': between day 183 and 335, 'At least 48 weeks': after day 335).
Due to different definitions of 'still on treatment at 24 weeks' and 'termination prior to 24 weeks' number of patients in the two categories differs.

15.1.2 Patient disposition by cancer type - FAS

Number of subjects that completed baseline visit and each treatment visit	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
	n	%	n	%	n	%	n	%	n	%	n	%
Baseline	509	(100.0%)	294	(100.0%)	159	(100.0%)	50	(100.0%)	116	(100.0%)	1128	(100.0%)
Visit 1	491	(96.5%)	290	(98.6%)	147	(92.5%)	48	(96.0%)	108	(93.1%)	1084	(96.1%)
Visit 2	486	(95.5%)	284	(96.6%)	128	(80.5%)	47	(94.0%)	98	(84.5%)	1043	(92.5%)
Visit 3	474	(93.1%)	277	(94.2%)	117	(73.6%)	45	(90.0%)	89	(76.7%)	1002	(88.8%)
Visit 4	460	(90.4%)	267	(90.8%)	101	(63.5%)	42	(84.0%)	80	(69.0%)	950	(84.2%)
Visit 5	449	(88.2%)	262	(89.1%)	86	(54.1%)	40	(80.0%)	70	(60.3%)	907	(80.4%)
Visit 6	430	(84.5%)	254	(86.4%)	70	(44.0%)	35	(70.0%)	62	(53.4%)	851	(75.4%)
Visit 7	418	(82.1%)	248	(84.4%)	66	(41.5%)	33	(66.0%)	54	(46.6%)	819	(72.6%)
Visit 8	401	(78.8%)	234	(79.6%)	61	(38.4%)	29	(58.0%)	51	(44.0%)	776	(68.8%)
Visit 9	392	(77.0%)	223	(75.9%)	53	(33.3%)	27	(54.0%)	44	(37.9%)	739	(65.5%)
Visit 10	372	(73.1%)	213	(72.4%)	50	(31.4%)	26	(52.0%)	37	(31.9%)	698	(61.9%)
Visit 11	353	(69.4%)	192	(65.3%)	39	(24.5%)	24	(48.0%)	32	(27.6%)	640	(56.7%)
Visit 12	305	(59.9%)	163	(55.4%)	31	(19.5%)	22	(44.0%)	28	(24.1%)	549	(48.7%)
Visit 13	221	(43.4%)	99	(33.7%)	22	(13.8%)	15	(30.0%)	17	(14.7%)	374	(33.2%)
Visit 14	65	(12.8%)	22	(7.5%)	6	(3.8%)	5	(10.0%)	3	(2.6%)	101	(9.0%)
Visit 15	17	(3.3%)	4	(1.4%)	1	(0.6%)	0	(0.0%)	0	(0.0%)	22	(2.0%)
Visit 16	7	(1.4%)	3	(1.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	10	(0.9%)
Visit 17	3	(0.6%)	2	(0.7%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	5	(0.4%)
Visit 18	2	(0.4%)	1	(0.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	3	(0.3%)
Visit 19	2	(0.4%)	1	(0.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	3	(0.3%)

Number of subjects who performed respective visit
Baseline is defined as anamnesis visit before first XGEVA application. Visits are planned at each XGEVA application (every 4 weeks).

15.1.2 Patient disposition by cancer type - FAS

Number of subjects that completed baseline visit and each treatment visit	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
	n	%	n	%	n	%	n	%	n	%	n	%
Visit 20	2	(0.4%)	1	(0.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	3	(0.3%)
Visit 21	1	(0.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)

Number of subjects who performed respective visit
Baseline is defined as anamnesis visit before first XGEVA application. Visits are planned at each XGEVA application (every 4 weeks).

15.1.3 Study duration (weeks) by cancer type - FAS

Cancer type	N	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Breast cancer	509	49.2	15.5	1	47	54	58	89
Prostate cancer	294	49.5	15.7	1	48	54	57	141
Lung cancer	159	31.6	18.5	1	16	29	50	64
Kidney cancer	50	43.7	17.1	8	30	52	58	66
Other cancer type	116	33.3	18.7	0	17	30	53	67
Total	1128	44.9	17.9	0	32	53	57	141

Study duration was calculated from the first study treatment application ('day 1') to study termination.

15.1.4 Physician`s special qualification, by tumortype - FAS

	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
Special qualification	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Gynaecologist with focus on gynaecologic oncology	207	(40.7%)	1	(0.3%)	0	(0.0%)	0	(0.0%)	7	(6.0%)	215	(19.1%)
Internist with additional competence in hematology and oncology	302	(59.3%)	110	(37.4%)	159	(100.0%)	38	(76.0%)	99	(85.3%)	708	(62.8%)
Urologist with additional competence in tumor drug treatment	0	(0.0%)	183	(62.2%)	0	(0.0%)	12	(24.0%)	10	(8.6%)	205	(18.2%)

15.2.1.1 Demographics - sex and age in categories by cancer type - FAS

	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Sex												
Male	5	(1.0%)	294	(100.0%)	106	(66.7%)	33	(66.0%)	63	(54.3%)	501	(44.4%)
Female	504	(99.0%)	0	(0.0%)	53	(33.3%)	17	(34.0%)	53	(45.7%)	627	(55.6%)
Age in categories												
18-<25 y	1	(0.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
25-<35 y	1	(0.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.9%)	2	(0.2%)
35-<45 y	23	(4.5%)	0	(0.0%)	4	(2.5%)	1	(2.0%)	5	(4.3%)	33	(2.9%)
45-<55 y	89	(17.5%)	3	(1.0%)	17	(10.7%)	5	(10.0%)	12	(10.3%)	126	(11.2%)
55-<65 y	149	(29.3%)	39	(13.3%)	53	(33.3%)	15	(30.0%)	33	(28.4%)	289	(25.6%)
65-<75 y	147	(28.9%)	103	(35.0%)	59	(37.1%)	20	(40.0%)	39	(33.6%)	368	(32.6%)
75-<85 y	89	(17.5%)	122	(41.5%)	26	(16.4%)	9	(18.0%)	25	(21.6%)	271	(24.0%)
>=85 y	10	(2.0%)	27	(9.2%)	0	(0.0%)	0	(0.0%)	1	(0.9%)	38	(3.4%)
Geriatric age group 1												
< 65 y	263	(51.7%)	42	(14.3%)	74	(46.5%)	21	(42.0%)	51	(44.0%)	451	(40.0%)
>= 65 y	246	(48.3%)	252	(85.7%)	85	(53.5%)	29	(58.0%)	65	(56.0%)	677	(60.0%)
Geriatric age group 2												
< 75 y	410	(80.6%)	145	(49.3%)	133	(83.6%)	41	(82.0%)	90	(77.6%)	819	(72.6%)
>= 75 y	99	(19.4%)	149	(50.7%)	26	(16.4%)	9	(18.0%)	26	(22.4%)	309	(27.4%)

15.2.1.2 Demographics - age by cancer type - FAS

Cancer type	N	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Breast cancer	509	63.8	11.5	24	56	64	73	87
Prostate cancer	294	73.8	8.0	50	69	75	79	93
Lung cancer	159	65.1	9.6	37	58	66	73	84
Kidney cancer	50	66.4	9.2	43	62	69	73	83
Other cancer type	116	65.2	11.1	27	58	68	73	87
Total	1128	66.8	11.1	24	59	68	75	93

15.2.2.1 Type of tumor - FAS

	Total (N=1128)	
	n	(%)
Type of tumor		
Breast cancer	509	(45.1%)
Prostate cancer	294	(26.1%)
Lung cancer	159	(14.1%)
Kidney cancer	50	(4.4%)
Other cancer type	116	(10.3%)

15.2.2.2 Specification of other cancer type by MedDRA system organ class and preferred term - FAS

MedDRA System Organ Class Preferred Term	Other cancer type (N=116) n	 (%)
Total	116	(100.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Total	116	(100.0%)
Colon cancer	16	(13.8%)
Gastric cancer	7	(6.0%)
Rectal cancer	7	(6.0%)
Bile duct cancer	6	(5.2%)
Endometrial cancer	6	(5.2%)
Metastatic neoplasm	6	(5.2%)
Pancreatic carcinoma	6	(5.2%)
Bladder cancer	5	(4.3%)
Cervix carcinoma	5	(4.3%)
Oesophageal carcinoma	5	(4.3%)
Transitional cell carcinoma	5	(4.3%)
Bladder transitional cell carcinoma	4	(3.4%)
Gallbladder cancer	3	(2.6%)
Hepatic neoplasm malignant	3	(2.6%)
Salivary gland cancer	3	(2.6%)
Thyroid cancer	3	(2.6%)
Neuroendocrine carcinoma	2	(1.7%)

Subjects can have more than one other cancer type. Therefore, subject incidence for individual cancer types may not sum up to the total for a given category.
The patient with breast cancer (patient 26088-004) documented 'other: Zökumkarzinom / Mammakarzinom 1991' as primary cancer type. Because the patient had beast cancer in 1991 and colon cancer in 2010, 'colon cancer' was the primary tumor for this study and the patient has to be classified as 'other'.

15.2.2.2 Specification of other cancer type by MedDRA system organ class and preferred term - FAS

MedDRA System Organ Class Preferred Term	Other cancer type (N=116) n	 (%)
Oesophageal adenocarcinoma	2	(1.7%)
Oropharyngeal cancer stage unspecified	2	(1.7%)
Ovarian cancer	2	(1.7%)
Uterine cancer	2	(1.7%)
Adenocarcinoma	1	(0.9%)
Bladder cancer stage 0, with cancer in situ	1	(0.9%)
Bone neoplasm malignant	1	(0.9%)
Breast cancer	1	(0.9%)
Choroid melanoma	1	(0.9%)
Laryngeal cancer	1	(0.9%)
Leiomyosarcoma	1	(0.9%)
Malignant melanoma	1	(0.9%)
Malignant neoplasm of ampulla of Vater	1	(0.9%)
Malignant peritoneal neoplasm	1	(0.9%)
Metastases to bone	1	(0.9%)
Neuroendocrine tumour	1	(0.9%)
Ovarian cancer metastatic	1	(0.9%)
Pancoast's tumour	1	(0.9%)
Pancreatic neuroendocrine tumour	1	(0.9%)
Penis carcinoma	1	(0.9%)

Subjects can have more than one other cancer type. Therefore, subject incidence for individual cancer types may not sum up to the total for a given category.
The patient with breast cancer (patient 26088-004) documented 'other: Zökumkarzinom / Mammakarzinom 1991' as primary cancer type. Because the patient had beast cancer in 1991 and colon cancer in 2010, 'colon cancer' was the primary tumor for this study and the patient has to be classified as 'other'.

15.2.2.2 Specification of other cancer type by MedDRA system organ class and preferred term - FAS

MedDRA System Organ Class Preferred Term	Other cancer type (N=116) n	 (%)
Pharyngeal cancer stage unspecified	1	(0.9%)
Sarcoma	1	(0.9%)
Tongue neoplasm malignant stage unspecified	1	(0.9%)
Urethral cancer	1	(0.9%)

Subjects can have more than one other cancer type. Therefore, subject incidence for individual cancer types may not sum up to the total for a given category.
The patient with breast cancer (patient 26088-004) documented 'other: Zökumkarzinom / Mammakarzinom 1991' as primary cancer type. Because the patient had beast cancer in 1991 and colon cancer in 2010, 'colon cancer' was the primary tumor for this study and the patient has to be classified as 'other'.

15.2.2.3 Duration since initial tumor diagnosis to first XGEVA application (years in categories) by cancer type - FAS

	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Duration since initial tumor diagnosis to first XGEVA application (years)												
during study	0	(0.0%)	3	(1.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	3	(0.3%)
<1 y	155	(30.5%)	120	(41.0%)	139	(87.4%)	19	(38.0%)	51	(44.0%)	484	(42.9%)
1-<2 y	38	(7.5%)	33	(11.3%)	10	(6.3%)	6	(12.0%)	16	(13.8%)	103	(9.1%)
2-<5 y	91	(17.9%)	51	(17.4%)	9	(5.7%)	14	(28.0%)	31	(26.7%)	196	(17.4%)
5-<10 y	120	(23.6%)	52	(17.7%)	1	(0.6%)	5	(10.0%)	11	(9.5%)	189	(16.8%)
10-<20 y	86	(16.9%)	31	(10.6%)	0	(0.0%)	4	(8.0%)	5	(4.3%)	126	(11.2%)
>=20 y	19	(3.7%)	3	(1.0%)	0	(0.0%)	2	(4.0%)	2	(1.7%)	26	(2.3%)
Missing	0		1		0		0		0		1	

Incomplete dates of diagnosis were imputed as specified in the SAP.
Percentages do not include subjects with missing information on the duration since initial tumor diagnosis to first XGEVA application.

15.2.2.4 Duration since initial tumor diagnosis to first XGEVA application (months) by cancer type - FAS

Cancer type	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Breast cancer	509	69.1	75.3	0.1	6.0	48.0	104.4	422.8
Prostate cancer	293	44.6	55.9	0.0	1.8	17.9	74.9	291.2
Lung cancer	159	6.8	11.7	0.1	1.1	3.1	8.1	109.5
Kidney cancer	50	51.6	72.3	1.0	6.7	23.4	54.7	319.7
Other cancer type	116	35.7	54.4	0.3	3.2	15.5	39.0	310.1
Total	1127	49.7	66.1	0.0	2.4	20.1	74.9	422.8

Incomplete dates of diagnosis were imputed as specified in the SAP.
Negative durations (diagnosis during study) were set to zero.
Not all patients were evaluable due to missing diagnosis date.

15.2.2.5 Hormone receptor status and Her2/neu status for breast cancer - patients with breast cancer FAS

	Breast cancer (N=509)	
	n	(%)
Hormone receptor status		
ER positive	73	(14.5%)
PR Positive	45	(8.9%)
ER/PR positive	313	(62.2%)
ER/PR negative	55	(10.9%)
Not determined	17	(3.4%)
Missing	6	
Her2/neu status		
Positive	96	(19.0%)
Negative	356	(70.5%)
Not determined	53	(10.5%)
Missing	4	
Triple-negative status		
No	453	(93.4%)
Yes	32	(6.6%)
Missing	24	

Triple-negative status: 'yes' if ER, PR and Her2/neu status negative, 'no' if at least one status positive, else missing
Percentages do not include subjects with missing information on the respective status.

15.2.2.6 Histology of lung cancer - patients with lung cancer in FAS

	Lung cancer (N=159)	
	n	(%)
Histology		
Non-small-cell lung carcinoma	122	(77.7%)
Small-cell lung carcinoma (SCLC)	35	(22.3%)
Missing	2	

Percentages do not include subjects with missing histology of lung cancer.

15.2.2.7 Type of disease for lung cancer with SCLC - patients with lung cancer with SCLC in FAS

	Small cell lung cancer (N=35)	
	n	(%)
Type of disease		
Extended disease (ED)	25	(83.3%)
Limited disease (LD)	5	(16.7%)
Missing	5	

Percentages are based on the number of patients with lung cancer with SCLC. The column header 'N' denotes the number of patients with lung cancer with SCLC.
Percentages do not include subjects with missing information on the type of the disease.

15.2.2.8 TNM classification at initial tumor diagnosis by cancer type - FAS

	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Size or direct extent of initial tumor (T)												
T1	124	(24.4%)	47	(16.2%)	14	(8.9%)	11	(22.0%)	11	(9.7%)	207	(18.5%)
T2	213	(41.9%)	39	(13.4%)	35	(22.3%)	9	(18.0%)	17	(15.0%)	313	(28.0%)
T3	57	(11.2%)	80	(27.5%)	29	(18.5%)	24	(48.0%)	34	(30.1%)	224	(20.0%)
T4	46	(9.1%)	30	(10.3%)	43	(27.4%)	2	(4.0%)	9	(8.0%)	130	(11.6%)
T4a	4	(0.8%)	1	(0.3%)	0	(0.0%)	0	(0.0%)	4	(3.5%)	9	(0.8%)
T4b	23	(4.5%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	3	(2.7%)	26	(2.3%)
Unknown	41	(8.1%)	94	(32.3%)	36	(22.9%)	4	(8.0%)	35	(31.0%)	210	(18.8%)
Missing	1		3		2		0		3		9	
Degree of spread to regional lymph nodes (N)												
NX	31	(6.1%)	65	(22.3%)	11	(7.0%)	19	(38.0%)	15	(13.0%)	141	(12.6%)
N0	130	(25.6%)	72	(24.7%)	25	(15.8%)	17	(34.0%)	25	(21.7%)	269	(24.0%)
N1	170	(33.5%)	56	(19.2%)	15	(9.5%)	6	(12.0%)	24	(20.9%)	271	(24.2%)
N2	75	(14.8%)	7	(2.4%)	45	(28.5%)	1	(2.0%)	21	(18.3%)	149	(13.3%)
N3	66	(13.0%)	2	(0.7%)	40	(25.3%)	0	(0.0%)	4	(3.5%)	112	(0.0%)
Unknown	36	(7.1%)	89	(30.6%)	22	(13.9%)	7	(14.0%)	26	(22.6%)	180	(16.0%)
Missing	1		3		1		0		1		6	
Presence of distant metastasis (M)												
MX	36	(7.1%)	29	(9.9%)	5	(3.2%)	7	(14.0%)	6	(5.2%)	83	(7.4%)
M0	296	(58.3%)	80	(27.4%)	25	(15.8%)	14	(28.0%)	37	(31.9%)	452	(40.2%)
M1	139	(27.4%)	127	(43.5%)	121	(76.6%)	22	(44.0%)	55	(47.4%)	464	(41.3%)

Percentages do not include subjects with missing information on the respective classification.

15.2.2.8 TNM classification at initial tumor diagnosis by cancer type - FAS

	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Unknown	37	(7.3%)	56	(19.2%)	7	(4.4%)	7	(14.0%)	18	(15.5%)	125	(11.1%)
Missing	1		2		1		0		0		4	

Percentages do not include subjects with missing information on the respective classification.

15.2.3.1 Duration since initial diagnosis of metastases to first XGEVA application (years in categories) by cancer type - FAS

	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Duration since initial diagnosis to first XGEVA application of metastases (years)												
during study	9	(1.8%)	7	(2.4%)	1	(0.6%)	0	(0.0%)	1	(0.9%)	18	(1.6%)
<1 y	438	(86.1%)	227	(77.7%)	147	(92.5%)	30	(60.0%)	87	(75.0%)	929	(82.5%)
1-<2 y	19	(3.7%)	27	(9.2%)	7	(4.4%)	4	(8.0%)	13	(11.2%)	70	(6.2%)
2-<5 y	23	(4.5%)	19	(6.5%)	3	(1.9%)	14	(28.0%)	10	(8.6%)	69	(6.1%)
5-<10 y	16	(3.1%)	10	(3.4%)	1	(0.6%)	2	(4.0%)	4	(3.4%)	33	(2.9%)
10-<20 y	4	(0.8%)	2	(0.7%)	0	(0.0%)	0	(0.0%)	1	(0.9%)	7	(0.6%)
Missing	0		2		0		0		0		2	

Incomplete dates of diagnosis were imputed as specified in the SAP.
Percentages do not include subjects with missing information on the duration since initial diagnosis of metastases to first XGEVA application.

15.2.3.2 Duration since initial diagnosis of metastases to first XGEVA application (months) by cancer type - FAS

Cancer type	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Breast cancer	509	8.0	20.3	0.0	0.7	1.6	4.0	147.4
Prostate cancer	292	10.3	23.7	0.0	0.5	1.5	6.9	156.3
Lung cancer	159	4.4	8.6	0.0	0.8	1.7	5.4	87.5
Kidney cancer	50	18.2	23.5	0.2	1.9	7.2	31.8	119.2
Other cancer type	116	12.2	23.1	0.0	1.0	4.2	11.4	143.1
Total	1126	9.0	20.7	0.0	0.7	1.8	5.9	156.3

Incomplete dates of diagnosis were imputed as specified in the SAP.
Negative durations (diagnosis during study) were partially based on imputed dates and were set to zero.
Some patients were not evaluable due to missing diagnosis date.

15.2.3.3 Visceral metastases by cancer type - FAS

	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Visceral metastases												
No	213	(41.8%)	221	(75.2%)	39	(24.5%)	13	(26.0%)	26	(22.4%)	512	(45.4%)
Yes	296	(58.2%)	73	(24.8%)	120	(75.5%)	37	(74.0%)	90	(77.6%)	616	(54.6%)

15.2.3.4 Localization of visceral metastases by cancer type - FAS

	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Lung												
No	377	(74.1%)	283	(96.3%)	115	(72.3%)	20	(40.0%)	75	(64.7%)	870	(77.1%)
Yes	132	(25.9%)	11	(3.7%)	44	(27.7%)	30	(60.0%)	41	(35.3%)	258	(22.9%)
Liver												
No	385	(75.6%)	283	(96.3%)	123	(77.4%)	41	(82.0%)	69	(59.5%)	901	(79.9%)
Yes	124	(24.4%)	11	(3.7%)	36	(22.6%)	9	(18.0%)	47	(40.5%)	227	(20.1%)
Brain												
No	499	(98.0%)	294	(100.0%)	144	(90.6%)	48	(96.0%)	111	(95.7%)	1096	(97.2%)
Yes	10	(2.0%)	0	(0.0%)	15	(9.4%)	2	(4.0%)	5	(4.3%)	32	(2.8%)
Skin												
No	483	(94.9%)	294	(100.0%)	156	(98.1%)	50	(100.0%)	111	(95.7%)	1094	(97.0%)
Yes	26	(5.1%)	0	(0.0%)	3	(1.9%)	0	(0.0%)	5	(4.3%)	34	(3.0%)
Other												
No	379	(74.5%)	234	(79.6%)	80	(50.3%)	34	(68.0%)	70	(60.3%)	797	(70.7%)
Yes	130	(25.5%)	60	(20.4%)	79	(49.7%)	16	(32.0%)	46	(39.7%)	331	(29.3%)

15.2.3.5 Specification of other metastases localizations by MedDRA system organ class and preferred term and by cancer type and overall - FAS

MedDRA System Organ Class Preferred Term	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Total	130	(25.5%)	60	(20.4%)	79	(49.7%)	16	(32.0%)	46	(39.7%)	331	(29.3%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)												
Total	129	(25.3%)	59	(20.1%)	79	(49.7%)	16	(32.0%)	46	(39.7%)	329	(29.2%)
Metastases to lymph nodes	64	(12.6%)	54	(18.4%)	44	(27.7%)	9	(18.0%)	24	(20.7%)	195	(17.3%)
Metastases to pleura	30	(5.9%)	0	(0.0%)	11	(6.9%)	0	(0.0%)	3	(2.6%)	44	(3.9%)
Metastases to adrenals	5	(1.0%)	0	(0.0%)	19	(11.9%)	3	(6.0%)	3	(2.6%)	30	(2.7%)
Metastases to peritoneum	13	(2.6%)	0	(0.0%)	0	(0.0%)	1	(2.0%)	5	(4.3%)	19	(1.7%)
Metastases to the mediastinum	3	(0.6%)	1	(0.3%)	5	(3.1%)	2	(4.0%)	3	(2.6%)	14	(1.2%)
Metastases to soft tissue	2	(0.4%)	0	(0.0%)	3	(1.9%)	0	(0.0%)	3	(2.6%)	8	(0.7%)
Metastases to large intestine	3	(0.6%)	1	(0.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	4	(0.4%)
Metastases to ovary	2	(0.4%)	0	(0.0%)	1	(0.6%)	0	(0.0%)	1	(0.9%)	4	(0.4%)
Metastases to stomach	4	(0.8%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	4	(0.4%)
Lymphangiosis carcinomatosa	2	(0.4%)	0	(0.0%)	1	(0.6%)	0	(0.0%)	0	(0.0%)	3	(0.3%)
Metastases to chest wall	2	(0.4%)	0	(0.0%)	1	(0.6%)	0	(0.0%)	0	(0.0%)	3	(0.3%)
Metastases to kidney	2	(0.4%)	0	(0.0%)	1	(0.6%)	0	(0.0%)	0	(0.0%)	3	(0.3%)
Metastases to reproductive organ	2	(0.4%)	1	(0.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	3	(0.3%)
Metastases to spleen	1	(0.2%)	0	(0.0%)	1	(0.6%)	0	(0.0%)	1	(0.9%)	3	(0.3%)
Tumour invasion	1	(0.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(1.7%)	3	(0.3%)
Choroid neoplasm	1	(0.2%)	0	(0.0%)	1	(0.6%)	0	(0.0%)	0	(0.0%)	2	(0.2%)
Malignant pleural effusion	2	(0.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.2%)
Metastases to abdominal cavity	1	(0.2%)	1	(0.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.2%)

Subjects can have more than one metastases localizations. Therefore, subject incidence for individual metastases localizations may not sum up to the total for a given category.

15.2.3.5 Specification of other metastases localizations by MedDRA system organ class and preferred term and by cancer type and overall - FAS

MedDRA System Organ Class Preferred Term	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Metastases to abdominal wall	1	(0.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.9%)	2	(0.2%)
Metastases to bone	0	(0.0%)	0	(0.0%)	2	(1.3%)	0	(0.0%)	0	(0.0%)	2	(0.2%)
Metastases to bone marrow	2	(0.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.2%)
Metastases to heart	2	(0.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.2%)
Metastases to pancreas	1	(0.2%)	0	(0.0%)	1	(0.6%)	0	(0.0%)	0	(0.0%)	2	(0.2%)
Breast cancer recurrent	1	(0.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Cervix carcinoma	1	(0.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Endometrial cancer	1	(0.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Lymphoma	0	(0.0%)	1	(0.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Malignant neoplasm of seminal vesicle	0	(0.0%)	1	(0.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Mesenteric neoplasm	1	(0.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Metastases to bladder	1	(0.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Metastases to diaphragm	0	(0.0%)	0	(0.0%)	1	(0.6%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Metastases to eye	1	(0.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Metastases to gallbladder	1	(0.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Metastases to gastrointestinal tract	0	(0.0%)	1	(0.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Metastases to pelvis	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.9%)	1	(0.1%)
Metastases to penis	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.9%)	1	(0.1%)
Metastases to peripheral nervous system	1	(0.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Metastases to rectum	0	(0.0%)	1	(0.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Metastases to retroperitoneum	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.9%)	1	(0.1%)
Metastases to salivary gland	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(2.0%)	0	(0.0%)	1	(0.1%)

Subjects can have more than one metastases localizations. Therefore, subject incidence for individual metastases localizations may not sum up to the total for a given category.

15.2.3.5 Specification of other metastases localizations by MedDRA system organ class and preferred term and by cancer type and overall - FAS

MedDRA System Organ Class Preferred Term	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Metastases to spine	1	(0.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Metastasis	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.9%)	1	(0.1%)
Renal cell carcinoma	1	(0.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Thyroid cancer	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(2.0%)	0	(0.0%)	1	(0.1%)
Uterine cancer	1	(0.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Vaginal cancer recurrent	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.9%)	1	(0.1%)
Respiratory, thoracic and mediastinal disorders												
Total	1	(0.2%)	0	(0.0%)	1	(0.6%)	0	(0.0%)	0	(0.0%)	2	(0.2%)
Pleural effusion	1	(0.2%)	0	(0.0%)	1	(0.6%)	0	(0.0%)	0	(0.0%)	2	(0.2%)
Gastrointestinal disorders												
Total	0	(0.0%)	1	(0.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Abdominal mass	0	(0.0%)	1	(0.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Surgical and medical procedures												
Total	1	(0.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Mastectomy	1	(0.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)

Subjects can have more than one metastases localizations. Therefore, subject incidence for individual metastases localizations may not sum up to the total for a given category.

15.2.3.6 Duration since initial diagnosis of bone metastases to first XGEVA application (years in categories) by cancer type - FAS

	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Duration since initial diagnosis of bone metastases to first XGEVA application (years)												
during study	16	(3.1%)	7	(2.4%)	6	(3.8%)	1	(2.0%)	5	(4.3%)	35	(3.1%)
<1 y	476	(93.5%)	242	(82.6%)	152	(95.6%)	42	(84.0%)	103	(88.8%)	1015	(90.1%)
1-<2 y	5	(1.0%)	24	(8.2%)	1	(0.6%)	3	(6.0%)	4	(3.4%)	37	(3.3%)
2-<5 y	8	(1.6%)	10	(3.4%)	0	(0.0%)	4	(8.0%)	4	(3.4%)	26	(2.3%)
5-<10 y	3	(0.6%)	9	(3.1%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	12	(1.1%)
10-<20 y	1	(0.2%)	1	(0.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.2%)
Missing	0		1		0		0		0		1	

Incomplete dates of diagnosis were imputed as specified in the SAP.
Percentages do not include subjects with missing information on the duration since initial diagnosis of bone metastases to first XGEVA application.

15.2.3.7 Duration since initial diagnosis of bone metastases to first XGEVA application (months) by cancer type - FAS

Cancer type	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Breast cancer	509	3.1	9.7	0.0	0.6	1.2	2.3	132.6
Prostate cancer	293	8.1	21.3	0.0	0.5	1.3	4.0	156.3
Lung cancer	159	2.1	2.7	0.0	0.6	1.1	2.9	21.2
Kidney cancer	50	6.2	11.1	0.0	0.7	1.6	4.3	47.1
Other cancer type	116	3.7	7.3	0.0	0.5	1.1	3.2	49.7
Total	1127	4.5	13.3	0.0	0.6	1.2	2.8	156.3

Incomplete dates of diagnosis were imputed as specified in the SAP.
Negative durations (diagnosis during study) were partially based on imputed dates and were set to zero.

15.2.3.8 Distribution pattern and type of diagnosis of bone metastases by cancer type - FAS

	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Distribution pattern												
Singular / region	179	(35.2%)	100	(34.0%)	76	(47.8%)	30	(60.0%)	61	(52.6%)	446	(39.5%)
Oligometastatic (>3) / region	317	(62.3%)	188	(63.9%)	74	(46.5%)	18	(36.0%)	49	(42.2%)	646	(57.3%)
Not determined	13	(2.6%)	6	(2.0%)	9	(5.7%)	2	(4.0%)	6	(5.2%)	36	(3.2%)
Type of diagnosis												
Symptoms	61	(12.0%)	28	(9.6%)	13	(8.2%)	12	(24.0%)	19	(16.4%)	133	(11.8%)
Imaging (asymptomatic)	439	(86.2%)	258	(88.1%)	142	(89.3%)	38	(76.0%)	91	(78.4%)	968	(85.9%)
Unknown	9	(1.8%)	7	(2.4%)	4	(2.5%)	0	(0.0%)	6	(5.2%)	26	(2.3%)
Missing	0		1		0		0		0		1	

Percentages do not include subjects with missing information on the type of diagnosis.

15.2.3.9 Bone metastases by cancer type - FAS

	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Bone metastases												
Yes	509	(100.0%)	294	(100.0%)	159	(100.0%)	50	(100.0%)	116	(100.0%)	1128	(100.0%)

15.2.3.10 Localization of bone metastases by cancer type - FAS

	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Cranium												
No	402	(81.0%)	244	(84.7%)	138	(92.0%)	44	(91.7%)	96	(87.3%)	924	(84.6%)
Yes	94	(19.0%)	44	(15.3%)	12	(8.0%)	4	(8.3%)	14	(12.7%)	168	(15.4%)
Missing	13		6		9		2		6		36	
Humerus												
No	459	(92.5%)	247	(85.8%)	138	(92.0%)	46	(95.8%)	103	(93.6%)	993	(90.9%)
Yes	37	(7.5%)	41	(14.2%)	12	(8.0%)	2	(4.2%)	7	(6.4%)	99	(9.1%)
Missing	13		6		9		2		6		36	
Scapula												
No	440	(88.7%)	236	(81.9%)	133	(88.7%)	42	(87.5%)	98	(89.1%)	949	(86.9%)
Yes	56	(11.3%)	52	(18.1%)	17	(11.3%)	6	(12.5%)	12	(10.9%)	143	(13.1%)
Missing	13		6		9		2		6		36	
Ribs												
No	258	(52.0%)	127	(44.1%)	87	(58.0%)	25	(52.1%)	70	(63.6%)	567	(51.9%)
Yes	238	(48.0%)	161	(55.9%)	63	(42.0%)	23	(47.9%)	40	(36.4%)	525	(48.1%)
Missing	13		6		9		2		6		36	
Cervicalspine												
No	394	(79.4%)	224	(77.8%)	133	(88.7%)	42	(87.5%)	93	(84.5%)	886	(81.1%)
Yes	102	(20.6%)	64	(22.2%)	17	(11.3%)	6	(12.5%)	17	(15.5%)	206	(18.9%)
Missing	13		6		9		2		6		36	
Thoracicspine												
No	202	(40.7%)	128	(44.4%)	81	(54.0%)	31	(64.6%)	63	(57.3%)	505	(46.2%)

Percentages do not include subjects with missing information on the respective localization.

15.2.3.10 Localization of bone metastases by cancer type - FAS

	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Yes	294	(59.3%)	160	(55.6%)	69	(46.0%)	17	(35.4%)	47	(42.7%)	587	(53.8%)
Missing	13		6		9		2		6		36	
Lumbarspine												
No	247	(49.8%)	134	(46.5%)	95	(63.3%)	33	(68.8%)	60	(54.5%)	569	(52.1%)
Yes	249	(50.2%)	154	(53.5%)	55	(36.7%)	15	(31.3%)	50	(45.5%)	523	(47.9%)
Missing	13		6		9		2		6		36	
Sacrum												
No	379	(76.4%)	206	(71.5%)	130	(86.7%)	38	(79.2%)	88	(80.0%)	841	(77.0%)
Yes	117	(23.6%)	82	(28.5%)	20	(13.3%)	10	(20.8%)	22	(20.0%)	251	(23.0%)
Missing	13		6		9		2		6		36	
Pelvis												
No	312	(62.9%)	104	(36.1%)	95	(63.3%)	34	(70.8%)	75	(68.2%)	620	(56.8%)
Yes	184	(37.1%)	184	(63.9%)	55	(36.7%)	14	(29.2%)	35	(31.8%)	472	(43.2%)
Missing	13		6		9		2		6		36	
Femoral												
No	393	(79.2%)	209	(72.6%)	130	(86.7%)	37	(77.1%)	92	(83.6%)	861	(78.8%)
Yes	103	(20.8%)	79	(27.4%)	20	(13.3%)	11	(22.9%)	18	(16.4%)	231	(21.2%)
Missing	13		6		9		2		6		36	
Other												
No	439	(88.5%)	248	(86.1%)	134	(89.3%)	38	(79.2%)	86	(78.2%)	945	(86.5%)
Yes	57	(11.5%)	40	(13.9%)	16	(10.7%)	10	(20.8%)	24	(21.8%)	147	(13.5%)
Missing	13		6		9		2		6		36	

Percentages do not include subjects with missing information on the respective localization.

15.2.3.11 Specification of other bone metastases localizations by MedDRA system organ class and preferred term and by cancer type and overall - FAS

MedDRA System Organ Class Preferred Term	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Total	57	(11.2%)	40	(13.6%)	16	(10.1%)	10	(20.0%)	24	(20.7%)	147	(13.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)												
Total	57	(11.2%)	40	(13.6%)	16	(10.1%)	10	(20.0%)	24	(20.7%)	147	(13.0%)
Metastases to bone	53	(10.4%)	38	(12.9%)	16	(10.1%)	9	(18.0%)	22	(19.0%)	138	(12.2%)
Metastases to lymph nodes	1	(0.2%)	1	(0.3%)	0	(0.0%)	1	(2.0%)	0	(0.0%)	3	(0.3%)
Metastases to spine	2	(0.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.9%)	3	(0.3%)
Metastases to abdominal cavity	0	(0.0%)	1	(0.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Metastases to bone marrow	0	(0.0%)	1	(0.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Metastases to eye	1	(0.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Metastases to the mediastinum	0	(0.0%)	1	(0.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Metastasis	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.9%)	1	(0.1%)

15.2.3.12 Sum of bone metastases localizations by cancer type - FAS

Cancer type	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Breast cancer	496	3.1	2.2	1	1	3	4	10
Prostate cancer	288	3.7	2.4	1	2	3	5	10
Lung cancer	150	2.4	1.8	0	1	2	3	10
Kidney cancer	48	2.5	2.1	1	1	2	3	9
Other cancer type	110	2.6	2.1	1	1	2	3	10
Total	1092	3.1	2.2	0	1	2	4	10

Some patients were not evaluable due to missing sum of bone metastases localizations.

15.2.4.1 Frequency of previous SREs and/or tumor induced hypercalcemias by cancer type - FAS

	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Previous tumor-induced hypercalcemia only	3	(0.6%)	1	(0.3%)	1	(0.6%)	1	(2.0%)	0	(0.0%)	6	(0.5%)
Previous SRE (excluding tumor-induced hypercalcemia) only	53	(10.4%)	14	(4.8%)	19	(11.9%)	11	(22.0%)	8	(6.9%)	105	(9.3%)
Previous skeletal compression	7	(1.4%)	1	(0.3%)	1	(0.6%)	2	(4.0%)	0	(0.0%)	11	(1.0%)
Previous pathologic fracture	38	(7.5%)	11	(3.7%)	11	(6.9%)	6	(12.0%)	6	(5.2%)	72	(6.4%)
Previous surgery to bone	20	(3.9%)	5	(1.7%)	9	(5.7%)	5	(10.0%)	3	(2.6%)	42	(3.7%)
Previous radiation therapy to bone	27	(5.3%)	8	(2.7%)	13	(8.2%)	7	(14.0%)	3	(2.6%)	58	(5.1%)
Previous SRE and tumor-induced hypercalcemia	2	(0.4%)	2	(0.7%)	0	(0.0%)	1	(2.0%)	1	(0.9%)	6	(0.5%)

Definition of 'previous': all documented SREs and/or tumor induced hypercalcemias were used because only previous 'SREs and/or tumor induced hypercalcemias' were requested.
One patient could have more than one reported event.

15.2.4.2 Duration since diagnosis of previous SRE and/or tumor induced hypercalcemias (years in categories) by cancer type - patients with previous SRE and/or tumor induced hypercalcemias in FAS

	Breast cancer (N=58)			Prostate cancer (N=17)			Lung cancer (N=20)			Kidney cancer (N=13)			Other cancer type (N=9)			Total (N=117)		
	N*	n	(%)	N*	n	(%)	N*	n	(%)	N*	n	(%)	N*	n	(%)	N*	n	(%)
Duration since diagnosis of previous tumor-induced hypercalcemia only (years)	3			1			1			1			0			6		
<1 y		3	(100.0%)		1	(100.0%)		1	(100.0%)		1	(100.0%)		0	(0.0%)		6	(100.0%)
Duration since diagnosis of previous SRE (excluding tumor-induced hypercalcemia) only (years)	53			14			19			11			8			105		
during study		5	(9.6%)		2	(14.3%)		1	(5.3%)		1	(9.1%)		0	(0.0%)		9	(8.7%)
<1 y		45	(86.5%)		10	(71.4%)		18	(94.7%)		10	(90.9%)		6	(85.7%)		89	(86.4%)
1-<2 y		1	(1.9%)		1	(7.1%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		2	(1.9%)
2-<5 y		1	(1.9%)		1	(7.1%)		0	(0.0%)		0	(0.0%)		1	(14.3%)		3	(2.9%)
Missing		1			0			0			0			1			2	
Duration since diagnosis of previous SRE and tumor-induced hypercalcemia (years)	2			2			0			1			1			6		
<1 y		2	(100.0%)		2	(100.0%)		0	(0.0%)		1	(100.0%)		1	(100.0%)		6	(100.0%)

If a patient had more than one event the maximum duration of all events was used.
Percentages are based on the number of subjects with previous tumor-indueced hypercalcemia, previous SRE (excluding tumor-induced hypercalcemia) or previous SRE and tumor-induced hypercalcemias respectively for each cancer type. In each column header 'N' denotes the number of subjects with previous SRE and/or tumor induced hypercalcemias. 'N*' denotes the number of subjects in the respective subgroup.
Percentages do not include subjects with missing information on the respective duration.
Definition of 'previous': all documented SREs and/or tumor induced hypercalcemias were used because only previous 'SREs and/or tumor induced hypercalcemias' were requested.

15.2.4.3 Duration since diagnosis of previous SRE and/or tumor induced hypercalcemias (months) by cancer type - patients with previous SRE and/or tumor induced hypercalcemias in FAS

Category Cancer type	N	N missing	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Duration since previous tumor-induced hypercalcemia only (months)	6	0	6	1.2	1.9	0.0	0.2	0.5	0.9	5.0
Breast cancer	3	0	3	0.3	0.2	0.0	0.0	0.2	0.5	0.5
Prostate cancer	1	0	1	5.0		5.0	5.0	5.0	5.0	5.0
Lung cancer	1	0	1	0.9		0.9	0.9	0.9	0.9	0.9
Kidney cancer	1	0	1	0.4		0.4	0.4	0.4	0.4	0.4
Duration since diagnosis of previous SRE (excluding tumor-induced hypercalcemia) only (months)	105	2	103	3.5	6.4	-1.4	0.7	1.4	3.1	34.9
Breast cancer	53	1	52	3.1	5.9	-1.4	0.6	1.4	2.6	34.9
Prostate cancer	14	0	14	5.6	9.1	-0.2	1.2	2.1	5.6	32.9
Lung cancer	19	0	19	2.1	3.0	-0.2	0.4	1.0	2.3	11.0
Kidney cancer	11	0	11	3.3	3.1	-0.1	0.9	1.2	7.3	7.8
Other cancer type	8	1	7	6.0	12.1	0.2	0.9	1.4	3.1	33.4
Duration since diagnosis of previous SRE and tumor-induced hypercalcemia (months)	6	0	6	1.5	1.2	0.2	0.4	1.3	2.6	2.9
Breast cancer	2	0	2	2.4	0.7	2.0	2.0	2.4	2.9	2.9
Prostate cancer	2	0	2	0.5	0.3	0.2	0.2	0.5	0.7	0.7
Kidney cancer	1	0	1	2.6		2.6	2.6	2.6	2.6	2.6
Other cancer type	1	0	1	0.4		0.4	0.4	0.4	0.4	0.4

If a patient had more than one event the maximum duration of all events was used.
Definition of 'previous': all documented SREs and/or tumor induced hypercalcemias were used because only previous 'SREs and/or tumor induced hypercalcemias' were requested.

15.2.4.4 Bone pain and tumor induced hypercalcemia associated with previous SRE and/or tumor induced hypercalcemias by cancer type - FAS

	Breast cancer (N=58)		Prostate cancer (N=17)		Lung cancer (N=20)		Kidney cancer (N=13)		Other cancer type (N=9)		Total (N=117)	
Patient with reported:	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Bone pain	43	(74.1%)	15	(88.2%)	15	(75.0%)	11	(84.6%)	8	(88.9%)	92	(78.6%)
Tumor induced hypercalcemia	5	(8.6%)	3	(17.6%)	1	(5.0%)	2	(15.4%)	1	(11.1%)	12	(10.3%)

Patients with documented bone pain but having no SREs and/or tumor induced hypercalcemias were not included in this table.
Definition of 'previous': all documented SREs and/or tumor induced hypercalcemias were used because only previous 'SREs and/or tumor induced hypercalcemias' were requested.

15.2.4.5 Type of previous SRE by cancer type - patients with previous SRE - FAS

	Breast cancer (N=55)		Prostate cancer (N=16)		Lung cancer (N=19)		Kidney cancer (N=12)		Other cancer type (N=9)		Total (N=111)	
Patient with reported:	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Spinal cord compression	7	(12.7%)	1	(6.3%)	1	(5.3%)	2	(16.7%)	0	(0.0%)	11	(9.9%)
Pathologic fracture	40	(72.7%)	13	(81.3%)	11	(57.9%)	6	(50.0%)	7	(77.8%)	77	(69.4%)
Bone surgery	21	(38.2%)	6	(37.5%)	9	(47.4%)	5	(41.7%)	3	(33.3%)	44	(39.6%)
Bone radiation	27	(49.1%)	10	(62.5%)	13	(68.4%)	8	(66.7%)	3	(33.3%)	61	(55.0%)

Patients can have more than one previous SRE. A SRE can have more than one types.
Definition of 'previous': all documented SREs were used because only previous 'SREs' were requested.

15.2.4.6 Further therapeutic interventions for previous SRE and/or tumor induced hypercalcemias by cancer type - patients with previous SRE and/or tumor induced hypercalcemias in FAS

	Breast cancer (N=58)		Prostate cancer (N=17)		Lung cancer (N=20)		Kidney cancer (N=13)		Other cancer type (N=9)		Total (N=117)	
Patient with reported:	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Bisphosphonates	9	(15.5%)	3	(17.6%)	1	(5.0%)	2	(15.4%)	0	(0.0%)	15	(12.8%)
Alendronic acid	1	(1.7%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.9%)
Ibandronic acid	1	(1.7%)	0	(0.0%)	0	(0.0%)	1	(7.7%)	0	(0.0%)	2	(1.7%)
Pamidronic acid	2	(3.4%)	1	(5.9%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	3	(2.6%)
Zoledronic acid	5	(8.6%)	2	(11.8%)	1	(5.0%)	1	(7.7%)	0	(0.0%)	9	(7.7%)
Radionuclide therapy	1	(1.7%)	0	(0.0%)	1	(5.0%)	0	(0.0%)	0	(0.0%)	2	(1.7%)

Patients with documented bone pain but having no SREs and/or tumor induced hypercalcemias were not included in this table.
Definition of 'previous': all documented SREs and/or tumor induced hypercalcemias were used because only previous 'SREs and/or tumor induced hypercalcemias' were requested.

15.2.4.7 Specification of other Bisphosphonate for therapy of previous SREs and/or tumor induced hypercalcemias - patients with previous SRE and/or tumor induced hypercalcemias in FAS

No data available

15.2.5.1 Previous antiresorptive therapy by cancer type - FAS

	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
Previous antiresorptive therapy	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
No	469	(92.1%)	280	(95.2%)	151	(95.0%)	45	(90.0%)	111	(95.7%)	1056	(93.6%)
Yes	40	(7.9%)	14	(4.8%)	8	(5.0%)	5	(10.0%)	5	(4.3%)	72	(6.4%)

Antiresorptive therapies are counted as previous antiresorptive therapies if the start date of the therapy is prior to day 1 or if the start date is missing and the end date is before day 1 or missing.

15.2.5.2 Preparation, route of application, and application frequency of previous antiresorptive therapy by cancer type for patients with previous antiresorptive therapy - FAS

	Breast cancer (N=40)		Prostate cancer (N=14)		Lung cancer (N=8)		Kidney cancer (N=5)		Other cancer type (N=5)		Total (N=72)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Preparation												
Alendronic acid	2	(5.0%)	3	(21.4%)	3	(37.5%)	0	(0.0%)	0	(0.0%)	8	(11.1%)
Ibandronic acid	6	(15.0%)	1	(7.1%)	0	(0.0%)	1	(20.0%)	0	(0.0%)	8	(11.1%)
Pamidronic acid	5	(12.5%)	1	(7.1%)	1	(12.5%)	0	(0.0%)	1	(20.0%)	8	(11.1%)
Zoledronic acid	25	(62.5%)	8	(57.1%)	4	(50.0%)	4	(80.0%)	5	(100.0%)	46	(63.9%)
Denosumab (Prolia®)	3	(7.5%)	1	(7.1%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	4	(5.6%)
Route of application												
Intravenous	37	(92.5%)	11	(78.6%)	6	(75.0%)	5	(100.0%)	4	(80.0%)	63	(87.5%)
Oral	2	(5.0%)	2	(14.3%)	1	(12.5%)	0	(0.0%)	0	(0.0%)	5	(6.9%)
Subcutaneous	2	(5.0%)	1	(7.1%)	1	(12.5%)	0	(0.0%)	1	(20.0%)	5	(6.9%)
Application frequency												
Q3W	9	(22.5%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	9	(12.5%)
Q4W	26	(65.0%)	7	(50.0%)	6	(75.0%)	4	(80.0%)	5	(100.0%)	48	(66.7%)
Q6M	1	(2.5%)	1	(7.1%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(2.8%)
QD	0	(0.0%)	0	(0.0%)	1	(12.5%)	0	(0.0%)	0	(0.0%)	1	(1.4%)
Other	5	(12.5%)	5	(35.7%)	1	(12.5%)	0	(0.0%)	0	(0.0%)	11	(15.3%)
Missing	0	(0.0%)	1	(7.1%)	0	(0.0%)	1	(20.0%)	0	(0.0%)	2	(2.8%)

Percentages are based on the number of patients with previous antiresorptive therapy. The column header 'N' denotes the number of patients with previous antiresorptive therapy.
Antiresorptive therapies are counted as previous antiresorptive therapies if the start date of the therapy is prior to day 1 or if the start date is missing and the end date is before day 1 or missing.
QD: daily, Q3W: every 3 weeks, Q4W: every 4 weeks, Q6M: every 6 months
Patients may have documented more than one previous therapy therefore a patient may have different routes and frequencies.

15.2.5.3 At least one cycle shift and permanent discontinuation of antiresorptive therapy by cancer type for patients with previous antiresorptive therapy - FAS

	Breast cancer (N=40)		Prostate cancer (N=14)		Lung cancer (N=8)		Kidney cancer (N=5)		Other cancer type (N=5)		Total (N=72)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
At least one cycle shift												
No	39	(97.5%)	12	(85.7%)	7	(87.5%)	4	(80.0%)	5	(100.0%)	67	(93.1%)
Yes	1	(2.5%)	0	(0.0%)	1	(12.5%)	0	(0.0%)	0	(0.0%)	2	(2.8%)
Missing	0	(0.0%)	2	(14.3%)	0	(0.0%)	1	(20.0%)	0	(0.0%)	3	(4.2%)
Reason for permanent discontinuation of antiresorptive therapy												
Patient's refusal	2	(5.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(2.8%)
Renal insufficiency	2	(5.0%)	4	(28.6%)	2	(25.0%)	2	(40.0%)	0	(0.0%)	10	(13.9%)
Medical decision	32	(80.0%)	7	(50.0%)	3	(37.5%)	3	(60.0%)	2	(40.0%)	47	(65.3%)
Other reason	3	(7.5%)	2	(14.3%)	3	(37.5%)	0	(0.0%)	3	(60.0%)	11	(15.3%)
Missing	2	(5.0%)	1	(7.1%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	3	(4.2%)

Percentages are based on the number of patients with previous antiresorptive therapy. The column header 'N' denotes the number of patients with previous antiresorptive therapy.
Antiresorptive therapies are counted as previous antiresorptive therapies if the start date of the therapy is prior to day 1 or if the start date is missing and the end date is before day 1 or missing.
Patients may have documented more than one discontinuation of antiresorptive therapy.

15.2.6.1 Performance status (ECOG) before start of therapy and presence of concomitant diseases by cancer type - FAS

	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
ECOG performance status before start of therapy												
0	193	(38.4%)	82	(29.5%)	37	(23.3%)	5	(10.4%)	30	(26.1%)	347	(31.5%)
1	244	(48.5%)	160	(57.6%)	95	(59.7%)	38	(79.2%)	67	(58.3%)	604	(54.8%)
2	66	(13.1%)	36	(12.9%)	27	(17.0%)	5	(10.4%)	18	(15.7%)	152	(13.8%)
Missing	6		16		0		2		1		25	
Any concomitant diseases (except tumor)?												
No	377	(74.1%)	165	(56.1%)	63	(39.6%)	27	(54.0%)	59	(50.9%)	691	(61.3%)
Yes	132	(25.9%)	129	(43.9%)	96	(60.4%)	23	(46.0%)	57	(49.1%)	437	(38.7%)

ECOG Status:
0 - Fully active, able to carry on all pre-disease performance without restriction
1 - Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5 - Dead
Percentages do not include subjects with missing information on the ECOG performance status.

15.2.6.2 Concomitant diseases by cancer type - FAS

	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
Concomitant disease	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Cardiac infarction												
No	505	(99.4%)	272	(92.8%)	148	(93.1%)	48	(96.0%)	113	(97.4%)	1086	(96.4%)
Yes	3	(0.6%)	21	(7.2%)	11	(6.9%)	2	(4.0%)	3	(2.6%)	40	(3.6%)
Missing	1		1		0		0		0		2	
Congestive heart failure												
No	500	(98.4%)	273	(93.2%)	152	(95.6%)	50	(100.0%)	109	(94.0%)	1084	(96.3%)
Yes	8	(1.6%)	20	(6.8%)	7	(4.4%)	0	(0.0%)	7	(6.0%)	42	(3.7%)
Missing	1		1		0		0		0		2	
Peripheral artery occlusive disease												
No	500	(98.4%)	273	(93.2%)	142	(89.3%)	47	(94.0%)	105	(90.5%)	1067	(94.8%)
Yes	8	(1.6%)	20	(6.8%)	17	(10.7%)	3	(6.0%)	11	(9.5%)	59	(5.2%)
Missing	1		1		0		0		0		2	
Cerebrovascular disease												
No	499	(98.2%)	284	(96.9%)	153	(96.2%)	50	(100.0%)	113	(97.4%)	1099	(97.6%)
Yes	9	(1.8%)	9	(3.1%)	6	(3.8%)	0	(0.0%)	3	(2.6%)	27	(2.4%)
Missing	1		1		0		0		0		2	
Dementia												
No	508	(99.8%)	291	(99.0%)	159	(100.0%)	49	(98.0%)	116	(100.0%)	1123	(99.6%)
Yes	1	(0.2%)	3	(1.0%)	0	(0.0%)	1	(2.0%)	0	(0.0%)	5	(0.4%)
Chronic lung disease												
No	492	(96.7%)	273	(93.2%)	108	(67.9%)	47	(94.0%)	105	(90.5%)	1025	(90.9%)
Yes	17	(3.3%)	20	(6.8%)	51	(32.1%)	3	(6.0%)	11	(9.5%)	102	(9.1%)

Percentages do not include subjects with missing information on the respective disease.

15.2.6.2 Concomitant diseases by cancer type - FAS

	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
Concomitant disease	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Missing	0		1		0		0		0		1	
Connective tissue disease												
No	507	(99.6%)	292	(100.0%)	159	(100.0%)	50	(100.0%)	116	(100.0%)	1124	(99.8%)
Yes	2	(0.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.2%)
Missing	0		2		0		0		0		2	
Ulcer disease												
No	506	(99.4%)	292	(100.0%)	154	(96.9%)	50	(100.0%)	114	(98.3%)	1116	(99.1%)
Yes	3	(0.6%)	0	(0.0%)	5	(3.1%)	0	(0.0%)	2	(1.7%)	10	(0.9%)
Missing	0		2		0		0		0		2	
Mild liver disease												
No	501	(98.4%)	287	(97.6%)	153	(96.2%)	49	(98.0%)	108	(93.1%)	1098	(97.3%)
Yes	8	(1.6%)	7	(2.4%)	6	(3.8%)	1	(2.0%)	8	(6.9%)	30	(2.7%)
Diabetes												
No	435	(85.5%)	238	(81.2%)	127	(79.9%)	46	(92.0%)	90	(77.6%)	936	(83.1%)
Yes	74	(14.5%)	55	(18.8%)	32	(20.1%)	4	(8.0%)	26	(22.4%)	191	(16.9%)
Missing	0		1		0		0		0		1	
Hemiplegia												
No	507	(99.8%)	293	(100.0%)	158	(99.4%)	50	(100.0%)	116	(100.0%)	1124	(99.8%)
Yes	1	(0.2%)	0	(0.0%)	1	(0.6%)	0	(0.0%)	0	(0.0%)	2	(0.2%)
Missing	1		1		0		0		0		2	
Moderate to severe kidney disease												
No	476	(93.5%)	260	(88.4%)	144	(90.6%)	32	(64.0%)	104	(89.7%)	1016	(90.1%)
Yes	33	(6.5%)	34	(11.6%)	15	(9.4%)	18	(36.0%)	12	(10.3%)	112	(9.9%)

Percentages do not include subjects with missing information on the respective disease.

15.2.6.2 Concomitant diseases by cancer type - FAS

	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
Concomitant disease	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Diabetes with end organ damages												
No	500	(98.2%)	293	(100.0%)	156	(98.1%)	49	(98.0%)	113	(97.4%)	1111	(98.6%)
Yes	9	(1.8%)	0	(0.0%)	3	(1.9%)	1	(2.0%)	3	(2.6%)	16	(1.4%)
Missing	0		1		0		0		0		1	
Tumor												
Yes	509	(100.0%)	294	(100.0%)	159	(100.0%)	50	(100.0%)	116	(100.0%)	1128	(100.0%)
Leukemia												
No	508	(99.8%)	294	(100.0%)	158	(99.4%)	47	(94.0%)	116	(100.0%)	1123	(99.6%)
Yes	1	(0.2%)	0	(0.0%)	1	(0.6%)	3	(6.0%)	0	(0.0%)	5	(0.4%)
Lymphoma												
No	508	(99.8%)	286	(97.3%)	158	(99.4%)	47	(94.0%)	116	(100.0%)	1115	(98.8%)
Yes	1	(0.2%)	8	(2.7%)	1	(0.6%)	3	(6.0%)	0	(0.0%)	13	(1.2%)
Moderate to severe liver disease												
No	500	(98.2%)	290	(98.6%)	155	(97.5%)	50	(100.0%)	113	(97.4%)	1108	(98.2%)
Yes	9	(1.8%)	4	(1.4%)	4	(2.5%)	0	(0.0%)	3	(2.6%)	20	(1.8%)
Aids												
No	509	(100.0%)	293	(100.0%)	159	(100.0%)	50	(100.0%)	115	(99.1%)	1126	(99.9%)
Yes	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.9%)	1	(0.1%)
Missing	0		1		0		0		0		1	

Percentages do not include subjects with missing information on the respective disease.

15.2.6.3 Previous antineoplastic therapy by cancer type - FAS

	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Previous surgery												
No	425	(83.5%)	271	(92.2%)	134	(84.3%)	29	(58.0%)	81	(69.8%)	940	(83.3%)
Yes	84	(16.5%)	23	(7.8%)	25	(15.7%)	21	(42.0%)	35	(30.2%)	188	(16.7%)
Previous radiotherapy												
No	367	(72.1%)	257	(87.4%)	105	(66.0%)	31	(62.0%)	76	(65.5%)	836	(74.1%)
Yes	142	(27.9%)	37	(12.6%)	54	(34.0%)	19	(38.0%)	40	(34.5%)	292	(25.9%)
Previous chemotherapy												
No	322	(63.3%)	230	(78.2%)	46	(28.9%)	16	(32.0%)	48	(41.4%)	662	(58.7%)
Yes	187	(36.7%)	64	(21.8%)	113	(71.1%)	34	(68.0%)	68	(58.6%)	466	(41.3%)
Previous antihormonal therapy												
No	291	(57.2%)	102	(34.7%)	158	(99.4%)	49	(98.0%)	111	(95.7%)	711	(63.0%)
Yes	218	(42.8%)	192	(65.3%)	1	(0.6%)	1	(2.0%)	5	(4.3%)	417	(37.0%)

Surgeries are counted as previous surgeries if the tick box for previous surgery in the eCRF is ticked with 'Yes' or if the start date of the surgery is prior to day 1.
Therapies are counted as previous therapies if the tick box for previous therapy in the eCRF is ticked with 'Yes' or if the start date of the therapy is prior to day 1 or if the start date is missing and the end date is before day 1 or missing.

15.2.6.4 Previous surgeries by MedDRA system organ class and preferred term and by cancer type and overall - FAS

MedDRA System Organ Class Preferred Term	Breast cancer (N=84)		Prostate cancer (N=23)		Lung cancer (N=25)		Kidney cancer (N=21)		Other cancer type (N=35)		Total (N=188)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Total	84	(100.0%)	23	(100.0%)	25	(100.0%)	21	(100.0%)	35	(100.0%)	188	(100.0%)
Surgical and medical procedures												
Total	77	(91.7%)	19	(82.6%)	20	(80.0%)	20	(95.2%)	33	(94.3%)	169	(89.9%)
Lymphadenectomy	25	(29.8%)	2	(8.7%)	2	(8.0%)	4	(19.0%)	4	(11.4%)	37	(19.7%)
Mastectomy	27	(32.1%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	27	(14.4%)
Tumour excision	11	(13.1%)	1	(4.3%)	1	(4.0%)	0	(0.0%)	4	(11.4%)	17	(9.0%)
Malignant tumour excision	6	(7.1%)	1	(4.3%)	0	(0.0%)	1	(4.8%)	6	(17.1%)	14	(7.4%)
Nephrectomy	0	(0.0%)	0	(0.0%)	0	(0.0%)	13	(61.9%)	0	(0.0%)	13	(6.9%)
Partial lung resection	2	(2.4%)	0	(0.0%)	5	(20.0%)	2	(9.5%)	3	(8.6%)	12	(6.4%)
Internal fixation of spine	5	(6.0%)	0	(0.0%)	2	(8.0%)	1	(4.8%)	1	(2.9%)	9	(4.8%)
Malignant breast lump removal	9	(10.7%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	9	(4.8%)
Transurethral prostatectomy	0	(0.0%)	8	(34.8%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	8	(4.3%)
Pleurectomy	3	(3.6%)	0	(0.0%)	4	(16.0%)	0	(0.0%)	0	(0.0%)	7	(3.7%)
Thoracotomy	1	(1.2%)	0	(0.0%)	2	(8.0%)	1	(4.8%)	2	(5.7%)	6	(3.2%)
Hysterectomy	1	(1.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	4	(11.4%)	5	(2.7%)
Spinal decompression	2	(2.4%)	0	(0.0%)	1	(4.0%)	0	(0.0%)	2	(5.7%)	5	(2.7%)
Vertebroplasty	2	(2.4%)	1	(4.3%)	0	(0.0%)	0	(0.0%)	2	(5.7%)	5	(2.7%)
Central venous catheterisation	1	(1.2%)	0	(0.0%)	2	(8.0%)	0	(0.0%)	1	(2.9%)	4	(2.1%)
Colectomy	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	4	(11.4%)	4	(2.1%)
Hepatectomy	1	(1.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	3	(8.6%)	4	(2.1%)
Osteosynthesis	0	(0.0%)	0	(0.0%)	2	(8.0%)	1	(4.8%)	1	(2.9%)	4	(2.1%)

Surgeries are counted as previous surgeries if the tick box for previous surgery in the eCRF is ticked with 'Yes' or if the start date of the surgery is prior to day 1.
MedDRA version 15.1.

15.2.6.4 Previous surgeries by MedDRA system organ class and preferred term and by cancer type and overall - FAS

MedDRA System Organ Class Preferred Term	Breast cancer (N=84)		Prostate cancer (N=23)		Lung cancer (N=25)		Kidney cancer (N=21)		Other cancer type (N=35)		Total (N=188)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Salpingo-oophorectomy	1	(1.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	3	(8.6%)	4	(2.1%)
Spinal laminectomy	2	(2.4%)	0	(0.0%)	2	(8.0%)	0	(0.0%)	0	(0.0%)	4	(2.1%)
Lung lobectomy	1	(1.2%)	0	(0.0%)	1	(4.0%)	0	(0.0%)	1	(2.9%)	3	(1.6%)
Modified radical mastectomy	3	(3.6%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	3	(1.6%)
Pleurodesis	2	(2.4%)	0	(0.0%)	1	(4.0%)	0	(0.0%)	0	(0.0%)	3	(1.6%)
Prostatectomy	0	(0.0%)	3	(13.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	3	(1.6%)
Spinal corpectomy	1	(1.2%)	1	(4.3%)	0	(0.0%)	0	(0.0%)	1	(2.9%)	3	(1.6%)
Bone lesion excision	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(9.5%)	0	(0.0%)	2	(1.1%)
Breast reconstruction	2	(2.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(1.1%)
Colostomy	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(5.7%)	2	(1.1%)
High frequency ablation	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(4.8%)	1	(2.9%)	2	(1.1%)
Laparoscopic surgery	0	(0.0%)	1	(4.3%)	0	(0.0%)	0	(0.0%)	1	(2.9%)	2	(1.1%)
Laparotomy	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(5.7%)	2	(1.1%)
Muscle lesion excision	2	(2.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(1.1%)
Muscle operation	2	(2.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(1.1%)
Omentectomy	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(5.7%)	2	(1.1%)
Orchidectomy	0	(0.0%)	2	(8.7%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(1.1%)
Pericardial excision	1	(1.2%)	0	(0.0%)	1	(4.0%)	0	(0.0%)	0	(0.0%)	2	(1.1%)
Prosthesis implantation	0	(0.0%)	1	(4.3%)	0	(0.0%)	1	(4.8%)	0	(0.0%)	2	(1.1%)
Radical cystectomy	0	(0.0%)	1	(4.3%)	0	(0.0%)	0	(0.0%)	1	(2.9%)	2	(1.1%)
Radical mastectomy	2	(2.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(1.1%)

Surgeries are counted as previous surgeries if the tick box for previous surgery in the eCRF is ticked with 'Yes' or if the start date of the surgery is prior to day 1.
MedDRA version 15.1.

15.2.6.4 Previous surgeries by MedDRA system organ class and preferred term and by cancer type and overall - FAS

MedDRA System Organ Class Preferred Term	Breast cancer (N=84)		Prostate cancer (N=23)		Lung cancer (N=25)		Kidney cancer (N=21)		Other cancer type (N=35)		Total (N=188)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Thoracic operation	1	(1.2%)	0	(0.0%)	1	(4.0%)	0	(0.0%)	0	(0.0%)	2	(1.1%)
Adhesiolysis	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(2.9%)	1	(0.5%)
Adrenalectomy	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(4.8%)	0	(0.0%)	1	(0.5%)
Amputation of penis	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(2.9%)	1	(0.5%)
Brain tumour operation	1	(1.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.5%)
Breast prosthesis removal	1	(1.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.5%)
Chest wall operation	1	(1.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.5%)
Craniectomy	1	(1.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.5%)
Cranioplasty	1	(1.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.5%)
Cytoreductive surgery	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(4.8%)	0	(0.0%)	1	(0.5%)
Explorative laparotomy	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(2.9%)	1	(0.5%)
Gastrectomy	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(2.9%)	1	(0.5%)
Hip arthroplasty	1	(1.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.5%)
Ileostomy	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(2.9%)	1	(0.5%)
Jejunectomy	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(2.9%)	1	(0.5%)
Leg amputation	1	(1.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.5%)
Mass excision	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(2.9%)	1	(0.5%)
Open reduction of fracture	0	(0.0%)	1	(4.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.5%)
Osteotomy	1	(1.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.5%)
Pleural operation	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(4.8%)	0	(0.0%)	1	(0.5%)
Radical neck dissection	1	(1.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.5%)

Surgeries are counted as previous surgeries if the tick box for previous surgery in the eCRF is ticked with 'Yes' or if the start date of the surgery is prior to day 1.
MedDRA version 15.1.

15.2.6.4 Previous surgeries by MedDRA system organ class and preferred term and by cancer type and overall - FAS

MedDRA System Organ Class Preferred Term	Breast cancer (N=84)		Prostate cancer (N=23)		Lung cancer (N=25)		Kidney cancer (N=21)		Other cancer type (N=35)		Total (N=188)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Radical prostatectomy	0	(0.0%)	1	(4.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.5%)
Renal tumour excision	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(2.9%)	1	(0.5%)
Resection of rectum	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(2.9%)	1	(0.5%)
Rib excision	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(4.8%)	0	(0.0%)	1	(0.5%)
Salpingo-oophorectomy bilateral	1	(1.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.5%)
Sigmoidectomy	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(2.9%)	1	(0.5%)
Skin neoplasm excision	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(2.9%)	1	(0.5%)
Spinal deformity correction	1	(1.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.5%)
Spinal fusion surgery	1	(1.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.5%)
Thoracic cavity drainage	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(2.9%)	1	(0.5%)
Transurethral bladder resection	0	(0.0%)	1	(4.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.5%)
Investigations												
Total	6	(7.1%)	4	(17.4%)	7	(28.0%)	1	(4.8%)	6	(17.1%)	24	(12.8%)
Mediastinoscopy	1	(1.2%)	0	(0.0%)	2	(8.0%)	1	(4.8%)	1	(2.9%)	5	(2.7%)
Biopsy bone	2	(2.4%)	1	(4.3%)	1	(4.0%)	0	(0.0%)	0	(0.0%)	4	(2.1%)
Biopsy liver	3	(3.6%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	3	(1.6%)
Biopsy prostate	0	(0.0%)	3	(13.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	3	(1.6%)
Biopsy spinal cord	0	(0.0%)	0	(0.0%)	1	(4.0%)	0	(0.0%)	2	(5.7%)	3	(1.6%)
Biopsy pleura	0	(0.0%)	0	(0.0%)	2	(8.0%)	0	(0.0%)	0	(0.0%)	2	(1.1%)
Bronchoscopy	0	(0.0%)	0	(0.0%)	2	(8.0%)	0	(0.0%)	0	(0.0%)	2	(1.1%)
Laparoscopy	1	(1.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(2.9%)	2	(1.1%)

Surgeries are counted as previous surgeries if the tick box for previous surgery in the eCRF is ticked with 'Yes' or if the start date of the surgery is prior to day 1.
MedDRA version 15.1.

15.2.6.4 Previous surgeries by MedDRA system organ class and preferred term and by cancer type and overall - FAS

MedDRA System Organ Class Preferred Term	Breast cancer (N=84)		Prostate cancer (N=23)		Lung cancer (N=25)		Kidney cancer (N=21)		Other cancer type (N=35)		Total (N=188)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Biopsy bronchus	0	(0.0%)	0	(0.0%)	1	(4.0%)	0	(0.0%)	0	(0.0%)	1	(0.5%)
Biopsy lung	0	(0.0%)	0	(0.0%)	1	(4.0%)	0	(0.0%)	0	(0.0%)	1	(0.5%)
Biopsy lymph gland	1	(1.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.5%)
Biopsy peritoneum	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(2.9%)	1	(0.5%)
Hysteroscopy	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(2.9%)	1	(0.5%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)												
Total	5	(6.0%)	0	(0.0%)	0	(0.0%)	1	(4.8%)	2	(5.7%)	8	(4.3%)
Metastases to skin	1	(1.2%)	0	(0.0%)	0	(0.0%)	1	(4.8%)	0	(0.0%)	2	(1.1%)
Endometrial cancer	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(2.9%)	1	(0.5%)
Inflammatory carcinoma of the breast	1	(1.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.5%)
Metastases to central nervous system	1	(1.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.5%)
Metastases to chest wall	1	(1.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.5%)
Metastases to lymph nodes	1	(1.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.5%)
Metastases to peritoneum	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(2.9%)	1	(0.5%)
Tumour invasion	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(2.9%)	1	(0.5%)
Musculoskeletal and connective tissue disorders												
Total	3	(3.6%)	1	(4.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	4	(2.1%)
Osteolysis	1	(1.2%)	1	(4.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(1.1%)
Pathological fracture	1	(1.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.5%)
Spinal column stenosis	1	(1.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.5%)

Surgeries are counted as previous surgeries if the tick box for previous surgery in the eCRF is ticked with 'Yes' or if the start date of the surgery is prior to day 1.
MedDRA version 15.1.

15.2.6.4 Previous surgeries by MedDRA system organ class and preferred term and by cancer type and overall - FAS

MedDRA System Organ Class Preferred Term	Breast cancer (N=84)		Prostate cancer (N=23)		Lung cancer (N=25)		Kidney cancer (N=21)		Other cancer type (N=35)		Total (N=188)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Respiratory, thoracic and mediastinal disorders												
Total	0	(0.0%)	0	(0.0%)	1	(4.0%)	0	(0.0%)	0	(0.0%)	1	(0.5%)
Haemothorax	0	(0.0%)	0	(0.0%)	1	(4.0%)	0	(0.0%)	0	(0.0%)	1	(0.5%)
Social circumstances												
Total	1	(1.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.5%)
Limb prosthesis user	1	(1.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.5%)

Surgeries are counted as previous surgeries if the tick box for previous surgery in the eCRF is ticked with 'Yes' or if the start date of the surgery is prior to day 1.
MedDRA version 15.1.

15.2.6.5 Previous chemotherapy by preferred term - by cancer type - FAS

	Breast cancer (N=187)		Prostate cancer (N=64)		Lung cancer (N=113)		Kidney cancer (N=34)		Other cancer type (N=68)		Total (N=466)	
Preferred term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Total	187	(100.0%)	64	(100.0%)	113	(100.0%)	34	(100.0%)	68	(100.0%)	466	(100.0%)
Docetaxel	36	(19.3%)	51	(79.7%)	4	(3.5%)	0	(0.0%)	3	(4.4%)	94	(20.2%)
Paclitaxel	62	(33.2%)	0	(0.0%)	21	(18.6%)	1	(2.9%)	10	(14.7%)	94	(20.2%)
Bevacizumab	52	(27.8%)	0	(0.0%)	15	(13.3%)	2	(5.9%)	11	(16.2%)	80	(17.2%)
Carboplatin	9	(4.8%)	1	(1.6%)	52	(46.0%)	0	(0.0%)	12	(17.6%)	74	(15.9%)
Cisplatin	2	(1.1%)	1	(1.6%)	44	(38.9%)	2	(5.9%)	20	(29.4%)	69	(14.8%)
Trastuzumab	47	(25.1%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	3	(4.4%)	50	(10.7%)
Capecitabine	33	(17.6%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	7	(10.3%)	40	(8.6%)
Cyclophosphamide	28	(15.0%)	1	(1.6%)	3	(2.7%)	0	(0.0%)	1	(1.5%)	33	(7.1%)
Vinorelbine	17	(9.1%)	0	(0.0%)	10	(8.8%)	0	(0.0%)	2	(2.9%)	29	(6.2%)
Gemcitabine	4	(2.1%)	1	(1.6%)	7	(6.2%)	1	(2.9%)	12	(17.6%)	25	(5.4%)
Doxorubicin	16	(8.6%)	1	(1.6%)	1	(0.9%)	0	(0.0%)	3	(4.4%)	21	(4.5%)
Etoposide	0	(0.0%)	0	(0.0%)	19	(16.8%)	0	(0.0%)	1	(1.5%)	20	(4.3%)
Pemetrexed	0	(0.0%)	0	(0.0%)	19	(16.8%)	0	(0.0%)	0	(0.0%)	19	(4.1%)
Everolimus	8	(4.3%)	0	(0.0%)	0	(0.0%)	9	(26.5%)	1	(1.5%)	18	(3.9%)
Epirubicin	16	(8.6%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(1.5%)	17	(3.6%)
Pertuzumab	17	(9.1%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	17	(3.6%)
Fluorouracil	3	(1.6%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	13	(19.1%)	16	(3.4%)
Pemetrexed disodium	0	(0.0%)	0	(0.0%)	16	(14.2%)	0	(0.0%)	0	(0.0%)	16	(3.4%)
Combinations of antineoplastic agents	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	11	(16.2%)	11	(2.4%)

Chemotherapies with missing chemotheray name (N=1) were not included in the analysis.
Some of these chemotherapies may have been given in combination, but have been presented separately in this table.
Chemotherapies are counted as previous chemotherapies if the tick box for previous chemotherapy in the eCRF is ticked with 'Yes' or if the start date of the therapy is prior to day 1 or if the start date is missing and the end date is before day 1 or missing.
WHO Drug Dictionary version 2012 June.

15.2.6.5 Previous chemotherapy by preferred term - by cancer type - FAS

	Breast cancer (N=187)		Prostate cancer (N=64)		Lung cancer (N=113)		Kidney cancer (N=34)		Other cancer type (N=68)		Total (N=466)	
Preferred term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Abiraterone acetate	0	(0.0%)	10	(15.6%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	10	(2.1%)
Paclitaxel albumin	9	(4.8%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(1.5%)	10	(2.1%)
Vinorelbine tartrate	6	(3.2%)	0	(0.0%)	4	(3.5%)	0	(0.0%)	0	(0.0%)	10	(2.1%)
Sunitinib malate	0	(0.0%)	0	(0.0%)	0	(0.0%)	8	(23.5%)	1	(1.5%)	9	(1.9%)
Cabazitaxel	0	(0.0%)	8	(12.5%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	8	(1.7%)
Pazopanib hydrochloride	0	(0.0%)	0	(0.0%)	0	(0.0%)	8	(23.5%)	0	(0.0%)	8	(1.7%)
Topotecan	0	(0.0%)	1	(1.6%)	6	(5.3%)	0	(0.0%)	1	(1.5%)	8	(1.7%)
Cetuximab	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	7	(10.3%)	7	(1.5%)
Fluorouracil w/folinic acid/irinotecan	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	7	(10.3%)	7	(1.5%)
Gemcitabine hydrochloride	0	(0.0%)	1	(1.6%)	1	(0.9%)	1	(2.9%)	4	(5.9%)	7	(1.5%)
Cisplatin w/etoposide	0	(0.0%)	0	(0.0%)	5	(4.4%)	1	(2.9%)	0	(0.0%)	6	(1.3%)
Oxaliplatin	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	6	(8.8%)	6	(1.3%)
Prednisolone	0	(0.0%)	6	(9.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	6	(1.3%)
Sunitinib	0	(0.0%)	0	(0.0%)	0	(0.0%)	6	(17.6%)	0	(0.0%)	6	(1.3%)
Temsirolimus	0	(0.0%)	0	(0.0%)	0	(0.0%)	6	(17.6%)	0	(0.0%)	6	(1.3%)
Eribulin	5	(2.7%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	5	(1.1%)
Erlotinib hydrochloride	0	(0.0%)	0	(0.0%)	5	(4.4%)	0	(0.0%)	0	(0.0%)	5	(1.1%)
Irinotecan	0	(0.0%)	1	(1.6%)	0	(0.0%)	0	(0.0%)	4	(5.9%)	5	(1.1%)
Lapatinib	5	(2.7%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	5	(1.1%)
Sorafenib tosilate	0	(0.0%)	0	(0.0%)	0	(0.0%)	3	(8.8%)	2	(2.9%)	5	(1.1%)

Chemotherapies with missing chemotheray name (N=1) were not included in the analysis.
Some of these chemotherapies may have been given in combination, but have been presented separately in this table.
Chemotherapies are counted as previous chemotherapies if the tick box for previous chemotherapy in the eCRF is ticked with 'Yes' or if the start date of the therapy is prior to day 1 or if the start date is missing and the end date is before day 1 or missing.
WHO Drug Dictionary version 2012 June.

15.2.6.5 Previous chemotherapy by preferred term - by cancer type - FAS

	Breast cancer (N=187)		Prostate cancer (N=64)		Lung cancer (N=113)		Kidney cancer (N=34)		Other cancer type (N=68)		Total (N=466)	
Preferred term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Afatinib	0	(0.0%)	0	(0.0%)	4	(3.5%)	0	(0.0%)	0	(0.0%)	4	(0.9%)
Folinic acid	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	4	(5.9%)	4	(0.9%)
Calcium folinate	1	(0.5%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(2.9%)	3	(0.6%)
Carboplatin w/gemcitabine	2	(1.1%)	0	(0.0%)	1	(0.9%)	0	(0.0%)	0	(0.0%)	3	(0.6%)
Gefitinib	0	(0.0%)	0	(0.0%)	3	(2.7%)	0	(0.0%)	0	(0.0%)	3	(0.6%)
Liposomal doxorubicin hydrochloride	3	(1.6%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	3	(0.6%)
Pazopanib	0	(0.0%)	0	(0.0%)	0	(0.0%)	3	(8.8%)	0	(0.0%)	3	(0.6%)
Pegylated liposomal doxorubicin hydrochloride	3	(1.6%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	3	(0.6%)
Taxol w/carboplatin	0	(0.0%)	0	(0.0%)	1	(0.9%)	0	(0.0%)	2	(2.9%)	3	(0.6%)
Vincristine	0	(0.0%)	1	(1.6%)	2	(1.8%)	0	(0.0%)	0	(0.0%)	3	(0.6%)
Eribulin mesilate	2	(1.1%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.4%)
Estramustine phosphate sodium	0	(0.0%)	2	(3.1%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.4%)
Methotrexate	2	(1.1%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.4%)
Mitoxantrone	0	(0.0%)	2	(3.1%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.4%)
Panitumumab	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(2.9%)	2	(0.4%)
Sorafenib	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(2.9%)	1	(1.5%)	2	(0.4%)
Vinflunine	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(2.9%)	1	(1.5%)	2	(0.4%)
Abiraterone acetate w/prednisolone	0	(0.0%)	1	(1.6%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.2%)
Axitinib	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(2.9%)	0	(0.0%)	1	(0.2%)
Bisphosphonates	1	(0.5%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.2%)

Chemotherapies with missing chemotheray name (N=1) were not included in the analysis.
Some of these chemotherapies may have been given in combination, but have been presented separately in this table.
Chemotherapies are counted as previous chemotherapies if the tick box for previous chemotherapy in the eCRF is ticked with 'Yes' or if the start date of the therapy is prior to day 1 or if the start date is missing and the end date is before day 1 or missing.
WHO Drug Dictionary version 2012 June.

15.2.6.5 Previous chemotherapy by preferred term - by cancer type - FAS

	Breast cancer (N=187)		Prostate cancer (N=64)		Lung cancer (N=113)		Kidney cancer (N=34)		Other cancer type (N=68)		Total (N=466)	
Preferred term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Catumaxomab	1	(0.5%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.2%)
Doxorubicin hydrochloride	0	(0.0%)	0	(0.0%)	1	(0.9%)	0	(0.0%)	0	(0.0%)	1	(0.2%)
Erlotinib	0	(0.0%)	0	(0.0%)	1	(0.9%)	0	(0.0%)	0	(0.0%)	1	(0.2%)
Exemestane	1	(0.5%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.2%)
Folate sodium	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(1.5%)	1	(0.2%)
Folfox-4	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(1.5%)	1	(0.2%)
Fursultiamine hydrochloride	0	(0.0%)	0	(0.0%)	1	(0.9%)	0	(0.0%)	0	(0.0%)	1	(0.2%)
Interferon	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(2.9%)	0	(0.0%)	1	(0.2%)
Irinotecan hydrochloride	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(1.5%)	1	(0.2%)
Letrozole	1	(0.5%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.2%)
Monoclonal antibodies	0	(0.0%)	0	(0.0%)	1	(0.9%)	0	(0.0%)	0	(0.0%)	1	(0.2%)
Other antineoplastic agents	0	(0.0%)	1	(1.6%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.2%)
Ramucirumab	1	(0.5%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.2%)
Streptozocin	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(1.5%)	1	(0.2%)
Taxanes	1	(0.5%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.2%)
Trastuzumab emtansine	1	(0.5%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.2%)
Trofosfamide	1	(0.5%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.2%)
Vemurafenib	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(1.5%)	1	(0.2%)
Vinflunine ditartrate	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(1.5%)	1	(0.2%)

Chemotherapies with missing chemotheray name (N=1) were not included in the analysis.
Some of these chemotherapies may have been given in combination, but have been presented separately in this table.
Chemotherapies are counted as previous chemotherapies if the tick box for previous chemotherapy in the eCRF is ticked with 'Yes' or if the start date of the therapy is prior to day 1 or if the start date is missing and the end date is before day 1 or missing.
WHO Drug Dictionary version 2012 June.

15.2.6.5 Previous chemotherapy by preferred term - by cancer type - FAS

	Breast cancer (N=187)		Prostate cancer (N=64)		Lung cancer (N=113)		Kidney cancer (N=34)		Other cancer type (N=68)		Total (N=466)	
Preferred term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Xelox	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(1.5%)	1	(0.2%)
Zoledronic acid	1	(0.5%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.2%)

Chemotherapies with missing chemotheray name (N=1) were not included in the analysis.
Some of these chemotherapies may have been given in combination, but have been presented separately in this table.
Chemotherapies are counted as previous chemotherapies if the tick box for previous chemotherapy in the eCRF is ticked with 'Yes' or if the start date of the therapy is prior to day 1 or if the start date is missing and the end date is before day 1 or missing.
WHO Drug Dictionary version 2012 June.

15.2.6.6 Previous antihormonal therapy (incl. antibodies and small molecules) by preferred term - by cancer type - FAS

	Breast cancer (N=218)		Prostate cancer (N=192)		Lung cancer (N=1)		Kidney cancer (N=1)		Other cancer type (N=5)		Total (N=417)	
Preferred term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Total	218	(100.0%)	192	(100.0%)	1	(100.0%)	1	(100.0%)	5	(100.0%)	417	(100.0%)
Leuprorelin acetate	0	(0.0%)	88	(45.8%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	88	(21.1%)
Letrozole	81	(37.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	81	(19.4%)
Anastrozole	79	(36.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	79	(18.9%)
Bicalutamide	0	(0.0%)	73	(38.0%)	0	(0.0%)	0	(0.0%)	1	(20.0%)	74	(17.7%)
Tamoxifen	46	(21.1%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	46	(11.0%)
Exemestane	41	(18.8%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(40.0%)	43	(10.3%)
Buserelin acetate	0	(0.0%)	20	(10.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	20	(4.8%)
Leuprorelin	0	(0.0%)	14	(7.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	14	(3.4%)
Degarelix	0	(0.0%)	13	(6.8%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	13	(3.1%)
Abiraterone acetate	0	(0.0%)	12	(6.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	12	(2.9%)
Fulvestrant	11	(5.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	11	(2.6%)
Goserelin	2	(0.9%)	8	(4.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	10	(2.4%)
Triptorelin embonate	0	(0.0%)	10	(5.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	10	(2.4%)
Abiraterone	0	(0.0%)	8	(4.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	8	(1.9%)
Flutamide	0	(0.0%)	8	(4.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	8	(1.9%)
Gonadotropin releasing hormone analogues	1	(0.5%)	4	(2.1%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	5	(1.2%)
Other antineoplastic agents	0	(0.0%)	4	(2.1%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	4	(1.0%)
Aromatase inhibitors	2	(0.9%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.5%)
Cyproterone	0	(0.0%)	2	(1.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.5%)
Cyproterone acetate	0	(0.0%)	2	(1.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.5%)

Antihormonal therapies are counted as previous antihormonal therapies if the tick box for previous antihormonal therapy in the eCRF is ticked with 'Yes' or if the start date of the therapy is prior to day 1 or if the start date is missing and the end date is before day 1 or missing.
WHO Drug Dictionary version 2012 June.

15.2.6.6 Previous antihormonal therapy (incl. antibodies and small molecules) by preferred term - by cancer type - FAS

	Breast cancer (N=218)		Prostate cancer (N=192)		Lung cancer (N=1)		Kidney cancer (N=1)		Other cancer type (N=5)		Total (N=417)	
Preferred term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Everolimus	1	(0.5%)	0	(0.0%)	0	(0.0%)	1	(100.0%)	0	(0.0%)	2	(0.5%)
Histrelin acetate	0	(0.0%)	2	(1.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.5%)
Zoledronic acid	0	(0.0%)	0	(0.0%)	1	(100.0%)	1	(100.0%)	0	(0.0%)	2	(0.5%)
Abarelix	0	(0.0%)	1	(0.5%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.2%)
Alfuzosin	0	(0.0%)	1	(0.5%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.2%)
Gonadorelin	0	(0.0%)	1	(0.5%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.2%)
Medroxyprogesterone acetate	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(20.0%)	1	(0.2%)
Monoclonal antibodies	0	(0.0%)	1	(0.5%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.2%)
Octreotide acetate	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(20.0%)	1	(0.2%)
Pazopanib hydrochloride	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(100.0%)	0	(0.0%)	1	(0.2%)
Prednisone	0	(0.0%)	1	(0.5%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.2%)
Sunitinib malate	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(100.0%)	0	(0.0%)	1	(0.2%)
Trastuzumab	1	(0.5%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.2%)
Triptorelin	0	(0.0%)	1	(0.5%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.2%)

Antihormonal therapies are counted as previous antihormonal therapies if the tick box for previous antihormonal therapy in the eCRF is ticked with 'Yes' or if the start date of the therapy is prior to day 1 or if the start date is missing and the end date is before day 1 or missing.
WHO Drug Dictionary version 2012 June.

15.3.1.1 Persistence at 24 weeks by cancer type - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=480)			Prostate cancer (N=281)			Lung cancer (N=113)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	168	(35.0%)	[30.7%-39.5%]	109	(38.8%)	[33.1%-44.8%]	54	(47.8%)	[38.3%-57.4%]
Yes	312	(65.0%)	[60.5%-69.3%]	172	(61.2%)	[55.2%-66.9%]	59	(52.2%)	[42.6%-61.7%]

	Kidney cancer (N=46)			Other cancer type (N=88)			Total (N=1008)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	13	(28.3%)	[16.0%-43.5%]	44	(50.0%)	[39.1%-60.9%]	388	(38.5%)	[35.5%-41.6%]
Yes	33	(71.7%)	[56.5%-84.0%]	44	(50.0%)	[39.1%-60.9%]	620	(61.5%)	[58.4%-64.5%]

	Breast cancer (N=480)		Prostate cancer (N=281)		Lung cancer (N=113)		Kidney cancer (N=46)		Other cancer type (N=88)		Total (N=1008)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Persistent	312	(65.0%)	172	(61.2%)	59	(52.2%)	33	(71.7%)	44	(50.0%)	620	(61.5%)
Non-persistent: Prem. term. (adverse event)	4	(0.8%)	2	(0.7%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	6	(0.6%)
Non-persistent: Prem. term. (patient refuses to take medication)	7	(1.5%)	5	(1.8%)	3	(2.7%)	1	(2.2%)	6	(6.8%)	22	(2.2%)
Non-persistent: Prem. term. (physician`s decision)	4	(0.8%)	1	(0.4%)	2	(1.8%)	0	(0.0%)	0	(0.0%)	7	(0.7%)
Non-persistent: Prem. term. (other)	4	(0.8%)	1	(0.4%)	1	(0.9%)	0	(0.0%)	2	(2.3%)	8	(0.8%)
Non-persistent: Not enough injections	1	(0.2%)	0	(0.0%)	1	(0.9%)	0	(0.0%)	1	(1.1%)	3	(0.3%)
Non-persistent: Violation of time windows	148	(30.8%)	100	(35.6%)	47	(41.6%)	12	(26.1%)	35	(39.8%)	342	(33.9%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 24 weeks if the subject received at least 6 injections without time window violation. A time window of +/- 7 days is allowed for each injection relative to the previous injection and of +2 weeks after 24 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included.

15.3.1.1 Persistence at 24 weeks by cancer type - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=480)		Prostate cancer (N=281)		Lung cancer (N=113)		Kidney cancer (N=46)		Other cancer type (N=88)		Total (N=1008)	
Number of violated time windows	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Violation of 1 time window	121	(25.2%)	83	(29.5%)	40	(35.4%)	11	(23.9%)	28	(31.8%)	283	(28.1%)
Violation of 2 time windows	24	(5.0%)	13	(4.6%)	6	(5.3%)	1	(2.2%)	6	(6.8%)	50	(5.0%)
Violation of 3 time windows	3	(0.6%)	2	(0.7%)	1	(0.9%)	0	(0.0%)	1	(1.1%)	7	(0.7%)
Violation of more than 3 time windows	0	(0.0%)	2	(0.7%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.2%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 24 weeks if the subject received at least 6 injections without time window violation. A time window of +/- 7 days is allowed for each injection relative to the previous injection and of +2 weeks after 24 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included.

15.3.1.2 Persistence at 24 weeks by cancer type for patients with previous antiresorptive treatment - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=37)			Prostate cancer (N=13)			Lung cancer (N=6)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	13	(35.1%)	[20.2%-52.5%]	7	(53.8%)	[25.1%-80.8%]	4	(66.7%)	[22.3%-95.7%]
Yes	24	(64.9%)	[47.5%-79.8%]	6	(46.2%)	[19.2%-74.9%]	2	(33.3%)	[4.3%-77.7%]

	Kidney cancer (N=4)			Other cancer type (N=4)			Total (N=64)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	2	(50.0%)	[6.8%-93.2%]	4	(100.0%)	[39.8%-100.0%]	30	(46.9%)	[34.3%-59.8%]
Yes	2	(50.0%)	[6.8%-93.2%]	0	(0.0%)	[0.0%-60.2%]	34	(53.1%)	[40.2%-65.7%]

	Breast cancer (N=37)		Prostate cancer (N=13)		Lung cancer (N=6)		Kidney cancer (N=4)		Other cancer type (N=4)		Total (N=64)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Persistent	24	(64.9%)	6	(46.2%)	2	(33.3%)	2	(50.0%)	0	(0.0%)	34	(53.1%)
Non-persistent: Prem. term. (adverse event)	1	(2.7%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(1.6%)
Non-persistent: Prem. term. (patient refuses to take medication)	1	(2.7%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(25.0%)	2	(3.1%)
Non-persistent: Prem. term. (physician`s decision)	0	(0.0%)	0	(0.0%)	1	(16.7%)	0	(0.0%)	0	(0.0%)	1	(1.6%)
Non-persistent: Prem. term. (other)	1	(2.7%)	1	(7.7%)	0	(0.0%)	0	(0.0%)	1	(25.0%)	3	(4.7%)
Non-persistent: Not enough injections	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Non-persistent: Violation of time windows	10	(27.0%)	6	(46.2%)	3	(50.0%)	2	(50.0%)	2	(50.0%)	23	(35.9%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 24 weeks if the subject received at least 6 injections without time window violation. A time window of +/- 7 days is allowed for each injection relative to the previous injection and of +2 weeks after 24 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included.

15.3.1.2 Persistence at 24 weeks by cancer type for patients with previous antiresorptive treatment - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=37)		Prostate cancer (N=13)		Lung cancer (N=6)		Kidney cancer (N=4)		Other cancer type (N=4)		Total (N=64)	
Number of violated time windows	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Violation of 1 time window	10	(27.0%)	5	(38.5%)	3	(50.0%)	2	(50.0%)	2	(50.0%)	22	(34.4%)
Violation of 2 time windows	0	(0.0%)	1	(7.7%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(1.6%)
Violation of 3 time windows	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Violation of more than 3 time windows	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 24 weeks if the subject received at least 6 injections without time window violation. A time window of +/- 7 days is allowed for each injection relative to the previous injection and of +2 weeks after 24 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included.

15.3.1.3 Persistence at 24 weeks by cancer type for patients without previous antiresorptive treatment - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=443)			Prostate cancer (N=268)			Lung cancer (N=107)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	155	(35.0%)	[30.5%-39.6%]	102	(38.1%)	[32.2%-44.2%]	50	(46.7%)	[37.0%-56.6%]
Yes	288	(65.0%)	[60.4%-69.5%]	166	(61.9%)	[55.8%-67.8%]	57	(53.3%)	[43.4%-63.0%]

	Kidney cancer (N=42)			Other cancer type (N=84)			Total (N=944)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	11	(26.2%)	[13.9%-42.0%]	40	(47.6%)	[36.6%-58.8%]	358	(37.9%)	[34.8%-41.1%]
Yes	31	(73.8%)	[58.0%-86.1%]	44	(52.4%)	[41.2%-63.4%]	586	(62.1%)	[58.9%-65.2%]

	Breast cancer (N=443)		Prostate cancer (N=268)		Lung cancer (N=107)		Kidney cancer (N=42)		Other cancer type (N=84)		Total (N=944)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Persistent	288	(65.0%)	166	(61.9%)	57	(53.3%)	31	(73.8%)	44	(52.4%)	586	(62.1%)
Non-persistent: Prem. term. (adverse event)	3	(0.7%)	2	(0.7%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	5	(0.5%)
Non-persistent: Prem. term. (patient refuses to take medication)	6	(1.4%)	5	(1.9%)	3	(2.8%)	1	(2.4%)	5	(6.0%)	20	(2.1%)
Non-persistent: Prem. term. (physician`s decision)	4	(0.9%)	1	(0.4%)	1	(0.9%)	0	(0.0%)	0	(0.0%)	6	(0.6%)
Non-persistent: Prem. term. (other)	3	(0.7%)	0	(0.0%)	1	(0.9%)	0	(0.0%)	1	(1.2%)	5	(0.5%)
Non-persistent: Not enough injections	1	(0.2%)	0	(0.0%)	1	(0.9%)	0	(0.0%)	1	(1.2%)	3	(0.3%)
Non-persistent: Violation of time windows	138	(31.2%)	94	(35.1%)	44	(41.1%)	10	(23.8%)	33	(39.3%)	319	(33.8%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 24 weeks if the subject received at least 6 injections without time window violation. A time window of +/- 7 days is allowed for each injection relative to the previous injection and of +2 weeks after 24 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included.

15.3.1.3 Persistence at 24 weeks by cancer type for patients without previous antiresorptive treatment - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=443)		Prostate cancer (N=268)		Lung cancer (N=107)		Kidney cancer (N=42)		Other cancer type (N=84)		Total (N=944)	
Number of violated time windows	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Violation of 1 time window	111	(25.1%)	78	(29.1%)	37	(34.6%)	9	(21.4%)	26	(31.0%)	261	(27.6%)
Violation of 2 time windows	24	(5.4%)	12	(4.5%)	6	(5.6%)	1	(2.4%)	6	(7.1%)	49	(5.2%)
Violation of 3 time windows	3	(0.7%)	2	(0.7%)	1	(0.9%)	0	(0.0%)	1	(1.2%)	7	(0.7%)
Violation of more than 3 time windows	0	(0.0%)	2	(0.7%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.2%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 24 weeks if the subject received at least 6 injections without time window violation. A time window of +/- 7 days is allowed for each injection relative to the previous injection and of +2 weeks after 24 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included.

15.3.1.4 Persistence at 24 weeks by cancer type for patients who underwent previous surgery - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=77)			Prostate cancer (N=23)			Lung cancer (N=20)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	30	(39.0%)	[28.0%-50.8%]	6	(26.1%)	[10.2%-48.4%]	8	(40.0%)	[19.1%-63.9%]
Yes	47	(61.0%)	[49.2%-72.0%]	17	(73.9%)	[51.6%-89.8%]	12	(60.0%)	[36.1%-80.9%]

	Kidney cancer (N=18)			Other cancer type (N=26)			Total (N=164)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	3	(16.7%)	[3.6%-41.4%]	9	(34.6%)	[17.2%-55.7%]	56	(34.1%)	[26.9%-41.9%]
Yes	15	(83.3%)	[58.6%-96.4%]	17	(65.4%)	[44.3%-82.8%]	108	(65.9%)	[58.1%-73.1%]

	Breast cancer (N=77)		Prostate cancer (N=23)		Lung cancer (N=20)		Kidney cancer (N=18)		Other cancer type (N=26)		Total (N=164)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Persistent	47	(61.0%)	17	(73.9%)	12	(60.0%)	15	(83.3%)	17	(65.4%)	108	(65.9%)
Non-persistent: Prem. term. (adverse event)	0	(0.0%)	1	(4.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.6%)
Non-persistent: Prem. term. (patient refuses to take medication)	3	(3.9%)	0	(0.0%)	0	(0.0%)	1	(5.6%)	1	(3.8%)	5	(3.0%)
Non-persistent: Prem. term. (physician`s decision)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Non-persistent: Prem. term. (other)	1	(1.3%)	0	(0.0%)	1	(5.0%)	0	(0.0%)	0	(0.0%)	2	(1.2%)
Non-persistent: Not enough injections	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(3.8%)	1	(0.6%)
Non-persistent: Violation of time windows	26	(33.8%)	5	(21.7%)	7	(35.0%)	2	(11.1%)	7	(26.9%)	47	(28.7%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 24 weeks if the subject received at least 6 injections without time window violation. A time window of +/- 7 days is allowed for each injection relative to the previous injection and of +2 weeks after 24 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included.

15.3.1.4 Persistence at 24 weeks by cancer type for patients who underwent previous surgery - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=77)		Prostate cancer (N=23)		Lung cancer (N=20)		Kidney cancer (N=18)		Other cancer type (N=26)		Total (N=164)	
Number of violated time windows	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Violation of 1 time window	21	(27.3%)	4	(17.4%)	6	(30.0%)	2	(11.1%)	7	(26.9%)	40	(24.4%)
Violation of 2 time windows	5	(6.5%)	1	(4.3%)	1	(5.0%)	0	(0.0%)	0	(0.0%)	7	(4.3%)
Violation of 3 time windows	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Violation of more than 3 time windows	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 24 weeks if the subject received at least 6 injections without time window violation. A time window of +/- 7 days is allowed for each injection relative to the previous injection and of +2 weeks after 24 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included.

15.3.1.5 Persistence at 24 weeks by cancer type for patients who did not undergo previous surgery - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=403)			Prostate cancer (N=258)			Lung cancer (N=93)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	138	(34.2%)	[29.6%-39.1%]	103	(39.9%)	[33.9%-46.2%]	46	(49.5%)	[38.9%-60.0%]
Yes	265	(65.8%)	[60.9%-70.4%]	155	(60.1%)	[53.8%-66.1%]	47	(50.5%)	[40.0%-61.1%]

	Kidney cancer (N=28)			Other cancer type (N=62)			Total (N=844)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	10	(35.7%)	[18.6%-55.9%]	35	(56.5%)	[43.3%-69.0%]	332	(39.3%)	[36.0%-42.7%]
Yes	18	(64.3%)	[44.1%-81.4%]	27	(43.5%)	[31.0%-56.7%]	512	(60.7%)	[57.3%-64.0%]

	Breast cancer (N=403)		Prostate cancer (N=258)		Lung cancer (N=93)		Kidney cancer (N=28)		Other cancer type (N=62)		Total (N=844)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Persistent	265	(65.8%)	155	(60.1%)	47	(50.5%)	18	(64.3%)	27	(43.5%)	512	(60.7%)
Non-persistent: Prem. term. (adverse event)	4	(1.0%)	1	(0.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	5	(0.6%)
Non-persistent: Prem. term. (patient refuses to take medication)	4	(1.0%)	5	(1.9%)	3	(3.2%)	0	(0.0%)	5	(8.1%)	17	(2.0%)
Non-persistent: Prem. term. (physician`s decision)	4	(1.0%)	1	(0.4%)	2	(2.2%)	0	(0.0%)	0	(0.0%)	7	(0.8%)
Non-persistent: Prem. term. (other)	3	(0.7%)	1	(0.4%)	0	(0.0%)	0	(0.0%)	2	(3.2%)	6	(0.7%)
Non-persistent: Not enough injections	1	(0.2%)	0	(0.0%)	1	(1.1%)	0	(0.0%)	0	(0.0%)	2	(0.2%)
Non-persistent: Violation of time windows	122	(30.3%)	95	(36.8%)	40	(43.0%)	10	(35.7%)	28	(45.2%)	295	(35.0%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 24 weeks if the subject received at least 6 injections without time window violation. A time window of +/- 7 days is allowed for each injection relative to the previous injection and of +2 weeks after 24 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included.

15.3.1.5 Persistence at 24 weeks by cancer type for patients who did not undergo previous surgery - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=403)		Prostate cancer (N=258)		Lung cancer (N=93)		Kidney cancer (N=28)		Other cancer type (N=62)		Total (N=844)	
Number of violated time windows	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Violation of 1 time window	100	(24.8%)	79	(30.6%)	34	(36.6%)	9	(32.1%)	21	(33.9%)	243	(28.8%)
Violation of 2 time windows	19	(4.7%)	12	(4.7%)	5	(5.4%)	1	(3.6%)	6	(9.7%)	43	(5.1%)
Violation of 3 time windows	3	(0.7%)	2	(0.8%)	1	(1.1%)	0	(0.0%)	1	(1.6%)	7	(0.8%)
Violation of more than 3 time windows	0	(0.0%)	2	(0.8%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.2%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 24 weeks if the subject received at least 6 injections without time window violation. A time window of +/- 7 days is allowed for each injection relative to the previous injection and of +2 weeks after 24 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included.

15.3.1.6 Persistence at 24 weeks by cancer type for patients who underwent previous chemotherapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=171)			Prostate cancer (N=58)			Lung cancer (N=84)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	59	(34.5%)	[27.4%-42.1%]	27	(46.6%)	[33.3%-60.1%]	39	(46.4%)	[35.5%-57.6%]
Yes	112	(65.5%)	[57.9%-72.6%]	31	(53.4%)	[39.9%-66.7%]	45	(53.6%)	[42.4%-64.5%]

	Kidney cancer (N=30)			Other cancer type (N=50)			Total (N=393)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	10	(33.3%)	[17.3%-52.8%]	27	(54.0%)	[39.3%-68.2%]	162	(41.2%)	[36.3%-46.3%]
Yes	20	(66.7%)	[47.2%-82.7%]	23	(46.0%)	[31.8%-60.7%]	231	(58.8%)	[53.7%-63.7%]

	Breast cancer (N=171)		Prostate cancer (N=58)		Lung cancer (N=84)		Kidney cancer (N=30)		Other cancer type (N=50)		Total (N=393)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Persistent	112	(65.5%)	31	(53.4%)	45	(53.6%)	20	(66.7%)	23	(46.0%)	231	(58.8%)
Non-persistent: Prem. term. (adverse event)	0	(0.0%)	1	(1.7%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.3%)
Non-persistent: Prem. term. (patient refuses to take medication)	2	(1.2%)	3	(5.2%)	2	(2.4%)	1	(3.3%)	4	(8.0%)	12	(3.1%)
Non-persistent: Prem. term. (physician`s decision)	1	(0.6%)	0	(0.0%)	2	(2.4%)	0	(0.0%)	0	(0.0%)	3	(0.8%)
Non-persistent: Prem. term. (other)	1	(0.6%)	0	(0.0%)	1	(1.2%)	0	(0.0%)	2	(4.0%)	4	(1.0%)
Non-persistent: Not enough injections	0	(0.0%)	0	(0.0%)	1	(1.2%)	0	(0.0%)	1	(2.0%)	2	(0.5%)
Non-persistent: Violation of time windows	55	(32.2%)	23	(39.7%)	33	(39.3%)	9	(30.0%)	20	(40.0%)	140	(35.6%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 24 weeks if the subject received at least 6 injections without time window violation. A time window of +/- 7 days is allowed for each injection relative to the previous injection and of +2 weeks after 24 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included.

15.3.1.6 Persistence at 24 weeks by cancer type for patients who underwent previous chemotherapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=171)		Prostate cancer (N=58)		Lung cancer (N=84)		Kidney cancer (N=30)		Other cancer type (N=50)		Total (N=393)	
Number of violated time windows	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Violation of 1 time window	45	(26.3%)	19	(32.8%)	30	(35.7%)	8	(26.7%)	17	(34.0%)	119	(30.3%)
Violation of 2 time windows	9	(5.3%)	4	(6.9%)	3	(3.6%)	1	(3.3%)	3	(6.0%)	20	(5.1%)
Violation of 3 time windows	1	(0.6%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.3%)
Violation of more than 3 time windows	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 24 weeks if the subject received at least 6 injections without time window violation. A time window of +/- 7 days is allowed for each injection relative to the previous injection and of +2 weeks after 24 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included.

15.3.1.7 Persistence at 24 weeks by cancer type for patients who did not undergo previous chemotherapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=309)			Prostate cancer (N=223)			Lung cancer (N=29)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	109	(35.3%)	[29.9%-40.9%]	82	(36.8%)	[30.4%-43.5%]	15	(51.7%)	[32.5%-70.6%]
Yes	200	(64.7%)	[59.1%-70.1%]	141	(63.2%)	[56.5%-69.6%]	14	(48.3%)	[29.4%-67.5%]

	Kidney cancer (N=16)			Other cancer type (N=38)			Total (N=615)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	3	(18.8%)	[4.0%-45.6%]	17	(44.7%)	[28.6%-61.7%]	226	(36.7%)	[32.9%-40.7%]
Yes	13	(81.3%)	[54.4%-96.0%]	21	(55.3%)	[38.3%-71.4%]	389	(63.3%)	[59.3%-67.1%]

	Breast cancer (N=309)		Prostate cancer (N=223)		Lung cancer (N=29)		Kidney cancer (N=16)		Other cancer type (N=38)		Total (N=615)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Persistent	200	(64.7%)	141	(63.2%)	14	(48.3%)	13	(81.3%)	21	(55.3%)	389	(63.3%)
Non-persistent: Prem. term. (adverse event)	4	(1.3%)	1	(0.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	5	(0.8%)
Non-persistent: Prem. term. (patient refuses to take medication)	5	(1.6%)	2	(0.9%)	1	(3.4%)	0	(0.0%)	2	(5.3%)	10	(1.6%)
Non-persistent: Prem. term. (physician`s decision)	3	(1.0%)	1	(0.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	4	(0.7%)
Non-persistent: Prem. term. (other)	3	(1.0%)	1	(0.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	4	(0.7%)
Non-persistent: Not enough injections	1	(0.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.2%)
Non-persistent: Violation of time windows	93	(30.1%)	77	(34.5%)	14	(48.3%)	3	(18.8%)	15	(39.5%)	202	(32.8%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 24 weeks if the subject received at least 6 injections without time window violation. A time window of +/- 7 days is allowed for each injection relative to the previous injection and of +2 weeks after 24 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included.

15.3.1.7 Persistence at 24 weeks by cancer type for patients who did not undergo previous chemotherapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=309)		Prostate cancer (N=223)		Lung cancer (N=29)		Kidney cancer (N=16)		Other cancer type (N=38)		Total (N=615)	
Number of violated time windows	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Violation of 1 time window	76	(24.6%)	64	(28.7%)	10	(34.5%)	3	(18.8%)	11	(28.9%)	164	(26.7%)
Violation of 2 time windows	15	(4.9%)	9	(4.0%)	3	(10.3%)	0	(0.0%)	3	(7.9%)	30	(4.9%)
Violation of 3 time windows	2	(0.6%)	2	(0.9%)	1	(3.4%)	0	(0.0%)	1	(2.6%)	6	(1.0%)
Violation of more than 3 time windows	0	(0.0%)	2	(0.9%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.3%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 24 weeks if the subject received at least 6 injections without time window violation. A time window of +/- 7 days is allowed for each injection relative to the previous injection and of +2 weeks after 24 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included.

15.3.1.8 Persistence at 24 weeks by cancer type for patients who underwent previous radiotherapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=134)			Prostate cancer (N=34)			Lung cancer (N=37)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	46	(34.3%)	[26.3%-43.0%]	17	(50.0%)	[32.4%-67.6%]	15	(40.5%)	[24.8%-57.9%]
Yes	88	(65.7%)	[57.0%-73.7%]	17	(50.0%)	[32.4%-67.6%]	22	(59.5%)	[42.1%-75.2%]

	Kidney cancer (N=18)			Other cancer type (N=30)			Total (N=253)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	7	(38.9%)	[17.3%-64.3%]	14	(46.7%)	[28.3%-65.7%]	99	(39.1%)	[33.1%-45.4%]
Yes	11	(61.1%)	[35.7%-82.7%]	16	(53.3%)	[34.3%-71.7%]	154	(60.9%)	[54.6%-66.9%]

	Breast cancer (N=134)		Prostate cancer (N=34)		Lung cancer (N=37)		Kidney cancer (N=18)		Other cancer type (N=30)		Total (N=253)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Persistent	88	(65.7%)	17	(50.0%)	22	(59.5%)	11	(61.1%)	16	(53.3%)	154	(60.9%)
Non-persistent: Prem. term. (adverse event)	2	(1.5%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.8%)
Non-persistent: Prem. term. (patient refuses to take medication)	1	(0.7%)	0	(0.0%)	0	(0.0%)	1	(5.6%)	2	(6.7%)	4	(1.6%)
Non-persistent: Prem. term. (physician`s decision)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Non-persistent: Prem. term. (other)	2	(1.5%)	1	(2.9%)	1	(2.7%)	0	(0.0%)	0	(0.0%)	4	(1.6%)
Non-persistent: Not enough injections	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Non-persistent: Violation of time windows	41	(30.6%)	16	(47.1%)	14	(37.8%)	6	(33.3%)	12	(40.0%)	89	(35.2%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 24 weeks if the subject received at least 6 injections without time window violation. A time window of +/- 7 days is allowed for each injection relative to the previous injection and of +2 weeks after 24 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included.

15.3.1.8 Persistence at 24 weeks by cancer type for patients who underwent previous radiotherapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=134)		Prostate cancer (N=34)		Lung cancer (N=37)		Kidney cancer (N=18)		Other cancer type (N=30)		Total (N=253)	
Number of violated time windows	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Violation of 1 time window	33	(24.6%)	12	(35.3%)	13	(35.1%)	5	(27.8%)	9	(30.0%)	72	(28.5%)
Violation of 2 time windows	7	(5.2%)	3	(8.8%)	1	(2.7%)	1	(5.6%)	3	(10.0%)	15	(5.9%)
Violation of 3 time windows	1	(0.7%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.4%)
Violation of more than 3 time windows	0	(0.0%)	1	(2.9%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.4%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 24 weeks if the subject received at least 6 injections without time window violation. A time window of +/- 7 days is allowed for each injection relative to the previous injection and of +2 weeks after 24 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included.

15.3.1.9 Persistence at 24 weeks by cancer type for patients who did not undergo previous radiotherapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=346)			Prostate cancer (N=247)			Lung cancer (N=76)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	122	(35.3%)	[30.2%-40.5%]	92	(37.2%)	[31.2%-43.6%]	39	(51.3%)	[39.6%-63.0%]
Yes	224	(64.7%)	[59.5%-69.8%]	155	(62.8%)	[56.4%-68.8%]	37	(48.7%)	[37.0%-60.4%]

	Kidney cancer (N=28)			Other cancer type (N=58)			Total (N=755)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	6	(21.4%)	[8.3%-41.0%]	30	(51.7%)	[38.2%-65.0%]	289	(38.3%)	[34.8%-41.9%]
Yes	22	(78.6%)	[59.0%-91.7%]	28	(48.3%)	[35.0%-61.8%]	466	(61.7%)	[58.1%-65.2%]

	Breast cancer (N=346)		Prostate cancer (N=247)		Lung cancer (N=76)		Kidney cancer (N=28)		Other cancer type (N=58)		Total (N=755)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Persistent	224	(64.7%)	155	(62.8%)	37	(48.7%)	22	(78.6%)	28	(48.3%)	466	(61.7%)
Non-persistent: Prem. term. (adverse event)	2	(0.6%)	2	(0.8%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	4	(0.5%)
Non-persistent: Prem. term. (patient refuses to take medication)	6	(1.7%)	5	(2.0%)	3	(3.9%)	0	(0.0%)	4	(6.9%)	18	(2.4%)
Non-persistent: Prem. term. (physician`s decision)	4	(1.2%)	1	(0.4%)	2	(2.6%)	0	(0.0%)	0	(0.0%)	7	(0.9%)
Non-persistent: Prem. term. (other)	2	(0.6%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(3.4%)	4	(0.5%)
Non-persistent: Not enough injections	1	(0.3%)	0	(0.0%)	1	(1.3%)	0	(0.0%)	1	(1.7%)	3	(0.4%)
Non-persistent: Violation of time windows	107	(30.9%)	84	(34.0%)	33	(43.4%)	6	(21.4%)	23	(39.7%)	253	(33.5%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 24 weeks if the subject received at least 6 injections without time window violation. A time window of +/- 7 days is allowed for each injection relative to the previous injection and of +2 weeks after 24 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included.

15.3.1.9 Persistence at 24 weeks by cancer type for patients who did not undergo previous radiotherapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=346)		Prostate cancer (N=247)		Lung cancer (N=76)		Kidney cancer (N=28)		Other cancer type (N=58)		Total (N=755)	
Number of violated time windows	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Violation of 1 time window	88	(25.4%)	71	(28.7%)	27	(35.5%)	6	(21.4%)	19	(32.8%)	211	(27.9%)
Violation of 2 time windows	17	(4.9%)	10	(4.0%)	5	(6.6%)	0	(0.0%)	3	(5.2%)	35	(4.6%)
Violation of 3 time windows	2	(0.6%)	2	(0.8%)	1	(1.3%)	0	(0.0%)	1	(1.7%)	6	(0.8%)
Violation of more than 3 time windows	0	(0.0%)	1	(0.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 24 weeks if the subject received at least 6 injections without time window violation. A time window of +/- 7 days is allowed for each injection relative to the previous injection and of +2 weeks after 24 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included.

15.3.1.10 Persistence at 24 weeks by cancer type for patients who underwent previous antihormonal therapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=210)			Prostate cancer (N=182)			Kidney cancer (N=1)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	69	(32.9%)	[26.5%-39.7%]	69	(37.9%)	[30.8%-45.4%]	1	(100.0%)	[2.5%-100.0%]
Yes	141	(67.1%)	[60.3%-73.5%]	113	(62.1%)	[54.6%-69.2%]	0	(0.0%)	[0.0%-97.5%]

	Other cancer type (N=4)			Total (N=397)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	3	(75.0%)	[19.4%-99.4%]	142	(35.8%)	[31.0%-40.7%]
Yes	1	(25.0%)	[0.6%-80.6%]	255	(64.2%)	[59.3%-69.0%]

	Breast cancer (N=210)		Prostate cancer (N=182)		Kidney cancer (N=1)		Other cancer type (N=4)		Total (N=397)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Persistent	141	(67.1%)	113	(62.1%)	0	(0.0%)	1	(25.0%)	255	(64.2%)
Non-persistent: Prem. term. (adverse event)	3	(1.4%)	1	(0.5%)	0	(0.0%)	0	(0.0%)	4	(1.0%)
Non-persistent: Prem. term. (patient refuses to take medication)	3	(1.4%)	4	(2.2%)	0	(0.0%)	0	(0.0%)	7	(1.8%)
Non-persistent: Prem. term. (physician`s decision)	2	(1.0%)	1	(0.5%)	0	(0.0%)	0	(0.0%)	3	(0.8%)
Non-persistent: Prem. term. (other)	3	(1.4%)	1	(0.5%)	0	(0.0%)	0	(0.0%)	4	(1.0%)
Non-persistent: Not enough injections	1	(0.5%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.3%)
Non-persistent: Violation of time windows	57	(27.1%)	62	(34.1%)	1	(100.0%)	3	(75.0%)	123	(31.0%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 24 weeks if the subject received at least 6 injections without time window violation. A time window of +/- 7 days is allowed for each injection relative to the previous injection and of +2 weeks after 24 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included.

15.3.1.10 Persistence at 24 weeks by cancer type for patients who underwent previous antihormonal therapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=210)		Prostate cancer (N=182)		Kidney cancer (N=1)		Other cancer type (N=4)		Total (N=397)	
Number of violated time windows	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Violation of 1 time window	47	(22.4%)	50	(27.5%)	1	(100.0%)	3	(75.0%)	101	(25.4%)
Violation of 2 time windows	8	(3.8%)	10	(5.5%)	0	(0.0%)	0	(0.0%)	18	(4.5%)
Violation of 3 time windows	2	(1.0%)	2	(1.1%)	0	(0.0%)	0	(0.0%)	4	(1.0%)
Violation of more than 3 time windows	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 24 weeks if the subject received at least 6 injections without time window violation. A time window of +/- 7 days is allowed for each injection relative to the previous injection and of +2 weeks after 24 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included.

15.3.1.11 Persistence at 24 weeks by cancer type for patients who did not undergo previous antihormonal therapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=270)			Prostate cancer (N=99)			Lung cancer (N=113)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	99	(36.7%)	[30.9%-42.7%]	40	(40.4%)	[30.7%-50.7%]	54	(47.8%)	[38.3%-57.4%]
Yes	171	(63.3%)	[57.3%-69.1%]	59	(59.6%)	[49.3%-69.3%]	59	(52.2%)	[42.6%-61.7%]

	Kidney cancer (N=45)			Other cancer type (N=84)			Total (N=611)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	12	(26.7%)	[14.6%-41.9%]	41	(48.8%)	[37.7%-60.0%]	246	(40.3%)	[36.3%-44.3%]
Yes	33	(73.3%)	[58.1%-85.4%]	43	(51.2%)	[40.0%-62.3%]	365	(59.7%)	[55.7%-63.7%]

	Breast cancer (N=270)		Prostate cancer (N=99)		Lung cancer (N=113)		Kidney cancer (N=45)		Other cancer type (N=84)		Total (N=611)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Persistent	171	(63.3%)	59	(59.6%)	59	(52.2%)	33	(73.3%)	43	(51.2%)	365	(59.7%)
Non-persistent: Prem. term. (adverse event)	1	(0.4%)	1	(1.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.3%)
Non-persistent: Prem. term. (patient refuses to take medication)	4	(1.5%)	1	(1.0%)	3	(2.7%)	1	(2.2%)	6	(7.1%)	15	(2.5%)
Non-persistent: Prem. term. (physician`s decision)	2	(0.7%)	0	(0.0%)	2	(1.8%)	0	(0.0%)	0	(0.0%)	4	(0.7%)
Non-persistent: Prem. term. (other)	1	(0.4%)	0	(0.0%)	1	(0.9%)	0	(0.0%)	2	(2.4%)	4	(0.7%)
Non-persistent: Not enough injections	0	(0.0%)	0	(0.0%)	1	(0.9%)	0	(0.0%)	1	(1.2%)	2	(0.3%)
Non-persistent: Violation of time windows	91	(33.7%)	38	(38.4%)	47	(41.6%)	11	(24.4%)	32	(38.1%)	219	(35.8%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 24 weeks if the subject received at least 6 injections without time window violation. A time window of +/- 7 days is allowed for each injection relative to the previous injection and of +2 weeks after 24 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included.

15.3.1.11 Persistence at 24 weeks by cancer type for patients who did not undergo previous antihormonal therapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=270)		Prostate cancer (N=99)		Lung cancer (N=113)		Kidney cancer (N=45)		Other cancer type (N=84)		Total (N=611)	
Number of violated time windows	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Violation of 1 time window	74	(27.4%)	33	(33.3%)	40	(35.4%)	10	(22.2%)	25	(29.8%)	182	(29.8%)
Violation of 2 time windows	16	(5.9%)	3	(3.0%)	6	(5.3%)	1	(2.2%)	6	(7.1%)	32	(5.2%)
Violation of 3 time windows	1	(0.4%)	0	(0.0%)	1	(0.9%)	0	(0.0%)	1	(1.2%)	3	(0.5%)
Violation of more than 3 time windows	0	(0.0%)	2	(2.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.3%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 24 weeks if the subject received at least 6 injections without time window violation. A time window of +/- 7 days is allowed for each injection relative to the previous injection and of +2 weeks after 24 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included.

15.3.2.1 Persistence at 48 weeks by cancer type - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=455)			Prostate cancer (N=267)			Lung cancer (N=88)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	257	(56.5%)	[51.8%-61.1%]	172	(64.4%)	[58.4%-70.2%]	62	(70.5%)	[59.8%-79.7%]
Yes	198	(43.5%)	[38.9%-48.2%]	95	(35.6%)	[29.8%-41.6%]	26	(29.5%)	[20.3%-40.2%]

	Kidney cancer (N=39)			Other cancer type (N=79)			Total (N=928)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	24	(61.5%)	[44.6%-76.6%]	63	(79.7%)	[69.2%-88.0%]	578	(62.3%)	[59.1%-65.4%]
Yes	15	(38.5%)	[23.4%-55.4%]	16	(20.3%)	[12.0%-30.8%]	350	(37.7%)	[34.6%-40.9%]

	Breast cancer (N=455)		Prostate cancer (N=267)		Lung cancer (N=88)		Kidney cancer (N=39)		Other cancer type (N=79)		Total (N=928)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Persistent	198	(43.5%)	95	(35.6%)	26	(29.5%)	15	(38.5%)	16	(20.3%)	350	(37.7%)
Non-persistent: Prem. term. (adverse event)	4	(0.9%)	2	(0.7%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	6	(0.6%)
Non-persistent: Prem. term. (patient refuses to take medication)	13	(2.9%)	11	(4.1%)	3	(3.4%)	2	(5.1%)	9	(11.4%)	38	(4.1%)
Non-persistent: Prem. term. (physician`s decision)	6	(1.3%)	4	(1.5%)	2	(2.3%)	1	(2.6%)	1	(1.3%)	14	(1.5%)
Non-persistent: Prem. term. (other)	6	(1.3%)	2	(0.7%)	2	(2.3%)	0	(0.0%)	4	(5.1%)	14	(1.5%)
Non-persistent: Not enough injections	1	(0.2%)	3	(1.1%)	0	(0.0%)	0	(0.0%)	1	(1.3%)	5	(0.5%)
Non-persistent: Violation of time windows	227	(49.9%)	150	(56.2%)	55	(62.5%)	21	(53.8%)	48	(60.8%)	501	(54.0%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 48 weeks if the subject received at least 12 injections without time window violation. A time window of +/- 7 days is allowed for each injection relative to the previous injection and of +7 weeks after 48 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included.

15.3.2.1 Persistence at 48 weeks by cancer type - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=455)		Prostate cancer (N=267)		Lung cancer (N=88)		Kidney cancer (N=39)		Other cancer type (N=79)		Total (N=928)	
Number of violated time windows	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Violation of 1 time window	141	(31.0%)	84	(31.5%)	39	(44.3%)	15	(38.5%)	29	(36.7%)	308	(33.2%)
Violation of 2 time windows	58	(12.7%)	38	(14.2%)	12	(13.6%)	5	(12.8%)	11	(13.9%)	124	(13.4%)
Violation of 3 time windows	15	(3.3%)	21	(7.9%)	3	(3.4%)	0	(0.0%)	5	(6.3%)	44	(4.7%)
Violation of more than 3 time windows	13	(2.9%)	7	(2.6%)	1	(1.1%)	1	(2.6%)	3	(3.8%)	25	(2.7%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 48 weeks if the subject received at least 12 injections without time window violation. A time window of +/- 7 days is allowed for each injection relative to the previous injection and of +7 weeks after 48 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included.

15.3.2.2 Persistence at 48 weeks by cancer type for patients with previous antiresorptive treatment - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=34)			Prostate cancer (N=12)			Lung cancer (N=4)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	17	(50.0%)	[32.4%-67.6%]	10	(83.3%)	[51.6%-97.9%]	4	(100.0%)	[39.8%-100.0%]
Yes	17	(50.0%)	[32.4%-67.6%]	2	(16.7%)	[2.1%-48.4%]	0	(0.0%)	[0.0%-60.2%]

	Kidney cancer (N=4)			Other cancer type (N=4)			Total (N=58)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	3	(75.0%)	[19.4%-99.4%]	4	(100.0%)	[39.8%-100.0%]	38	(65.5%)	[51.9%-77.5%]
Yes	1	(25.0%)	[0.6%-80.6%]	0	(0.0%)	[0.0%-60.2%]	20	(34.5%)	[22.5%-48.1%]

	Breast cancer (N=34)		Prostate cancer (N=12)		Lung cancer (N=4)		Kidney cancer (N=4)		Other cancer type (N=4)		Total (N=58)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Persistent	17	(50.0%)	2	(16.7%)	0	(0.0%)	1	(25.0%)	0	(0.0%)	20	(34.5%)
Non-persistent: Prem. term. (adverse event)	1	(2.9%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(1.7%)
Non-persistent: Prem. term. (patient refuses to take medication)	1	(2.9%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(25.0%)	2	(3.4%)
Non-persistent: Prem. term. (physician`s decision)	1	(2.9%)	1	(8.3%)	1	(25.0%)	0	(0.0%)	0	(0.0%)	3	(5.2%)
Non-persistent: Prem. term. (other)	2	(5.9%)	1	(8.3%)	0	(0.0%)	0	(0.0%)	1	(25.0%)	4	(6.9%)
Non-persistent: Not enough injections	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Non-persistent: Violation of time windows	12	(35.3%)	8	(66.7%)	3	(75.0%)	3	(75.0%)	2	(50.0%)	28	(48.3%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 48 weeks if the subject received at least 12 injections without time window violation. A time window of +/- 7 days is allowed for each injection relative to the previous injection and of +7 weeks after 48 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included.

15.3.2.2 Persistence at 48 weeks by cancer type for patients with previous antiresorptive treatment - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=34)		Prostate cancer (N=12)		Lung cancer (N=4)		Kidney cancer (N=4)		Other cancer type (N=4)		Total (N=58)	
Number of violated time windows	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Violation of 1 time window	9	(26.5%)	5	(41.7%)	3	(75.0%)	2	(50.0%)	1	(25.0%)	20	(34.5%)
Violation of 2 time windows	2	(5.9%)	3	(25.0%)	0	(0.0%)	1	(25.0%)	1	(25.0%)	7	(12.1%)
Violation of 3 time windows	1	(2.9%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(1.7%)
Violation of more than 3 time windows	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 48 weeks if the subject received at least 12 injections without time window violation. A time window of +/- 7 days is allowed for each injection relative to the previous injection and of +7 weeks after 48 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included.

15.3.2.3 Persistence at 48 weeks by cancer type for patients without previous antiresorptive treatment - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=421)			Prostate cancer (N=255)			Lung cancer (N=84)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	240	(57.0%)	[52.1%-61.8%]	162	(63.5%)	[57.3%-69.4%]	58	(69.0%)	[58.0%-78.7%]
Yes	181	(43.0%)	[38.2%-47.9%]	93	(36.5%)	[30.6%-42.7%]	26	(31.0%)	[21.3%-42.0%]

	Kidney cancer (N=35)			Other cancer type (N=75)			Total (N=870)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	21	(60.0%)	[42.1%-76.1%]	59	(78.7%)	[67.7%-87.3%]	540	(62.1%)	[58.8%-65.3%]
Yes	14	(40.0%)	[23.9%-57.9%]	16	(21.3%)	[12.7%-32.3%]	330	(37.9%)	[34.7%-41.2%]

	Breast cancer (N=421)		Prostate cancer (N=255)		Lung cancer (N=84)		Kidney cancer (N=35)		Other cancer type (N=75)		Total (N=870)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Persistent	181	(43.0%)	93	(36.5%)	26	(31.0%)	14	(40.0%)	16	(21.3%)	330	(37.9%)
Non-persistent: Prem. term. (adverse event)	3	(0.7%)	2	(0.8%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	5	(0.6%)
Non-persistent: Prem. term. (patient refuses to take medication)	12	(2.9%)	11	(4.3%)	3	(3.6%)	2	(5.7%)	8	(10.7%)	36	(4.1%)
Non-persistent: Prem. term. (physician`s decision)	5	(1.2%)	3	(1.2%)	1	(1.2%)	1	(2.9%)	1	(1.3%)	11	(1.3%)
Non-persistent: Prem. term. (other)	4	(1.0%)	1	(0.4%)	2	(2.4%)	0	(0.0%)	3	(4.0%)	10	(1.1%)
Non-persistent: Not enough injections	1	(0.2%)	3	(1.2%)	0	(0.0%)	0	(0.0%)	1	(1.3%)	5	(0.6%)
Non-persistent: Violation of time windows	215	(51.1%)	142	(55.7%)	52	(61.9%)	18	(51.4%)	46	(61.3%)	473	(54.4%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 48 weeks if the subject received at least 12 injections without time window violation. A time window of +/- 7 days is allowed for each injection relative to the previous injection and of +7 weeks after 48 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included.

15.3.2.3 Persistence at 48 weeks by cancer type for patients without previous antiresorptive treatment - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=421)		Prostate cancer (N=255)		Lung cancer (N=84)		Kidney cancer (N=35)		Other cancer type (N=75)		Total (N=870)	
Number of violated time windows	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Violation of 1 time window	132	(31.4%)	79	(31.0%)	36	(42.9%)	13	(37.1%)	28	(37.3%)	288	(33.1%)
Violation of 2 time windows	56	(13.3%)	35	(13.7%)	12	(14.3%)	4	(11.4%)	10	(13.3%)	117	(13.4%)
Violation of 3 time windows	14	(3.3%)	21	(8.2%)	3	(3.6%)	0	(0.0%)	5	(6.7%)	43	(4.9%)
Violation of more than 3 time windows	13	(3.1%)	7	(2.7%)	1	(1.2%)	1	(2.9%)	3	(4.0%)	25	(2.9%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 48 weeks if the subject received at least 12 injections without time window violation. A time window of +/- 7 days is allowed for each injection relative to the previous injection and of +7 weeks after 48 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included.

15.3.2.4 Persistence at 48 weeks by cancer type for patients who underwent previous surgery - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=76)			Prostate cancer (N=19)			Lung cancer (N=14)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	46	(60.5%)	[48.6%-71.6%]	12	(63.2%)	[38.4%-83.7%]	8	(57.1%)	[28.9%-82.3%]
Yes	30	(39.5%)	[28.4%-51.4%]	7	(36.8%)	[16.3%-61.6%]	6	(42.9%)	[17.7%-71.1%]

	Kidney cancer (N=13)			Other cancer type (N=22)			Total (N=144)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	8	(61.5%)	[31.6%-86.1%]	16	(72.7%)	[49.8%-89.3%]	90	(62.5%)	[54.1%-70.4%]
Yes	5	(38.5%)	[13.9%-68.4%]	6	(27.3%)	[10.7%-50.2%]	54	(37.5%)	[29.6%-45.9%]

	Breast cancer (N=76)		Prostate cancer (N=19)		Lung cancer (N=14)		Kidney cancer (N=13)		Other cancer type (N=22)		Total (N=144)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Persistent	30	(39.5%)	7	(36.8%)	6	(42.9%)	5	(38.5%)	6	(27.3%)	54	(37.5%)
Non-persistent: Prem. term. (adverse event)	0	(0.0%)	1	(5.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.7%)
Non-persistent: Prem. term. (patient refuses to take medication)	4	(5.3%)	2	(10.5%)	0	(0.0%)	1	(7.7%)	2	(9.1%)	9	(6.3%)
Non-persistent: Prem. term. (physician`s decision)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(7.7%)	1	(4.5%)	2	(1.4%)
Non-persistent: Prem. term. (other)	2	(2.6%)	0	(0.0%)	1	(7.1%)	0	(0.0%)	2	(9.1%)	5	(3.5%)
Non-persistent: Not enough injections	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(4.5%)	1	(0.7%)
Non-persistent: Violation of time windows	40	(52.6%)	9	(47.4%)	7	(50.0%)	6	(46.2%)	10	(45.5%)	72	(50.0%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 48 weeks if the subject received at least 12 injections without time window violation. A time window of +/- 7 days is allowed for each injection relative to the previous injection and of +7 weeks after 48 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included.

15.3.2.4 Persistence at 48 weeks by cancer type for patients who underwent previous surgery - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=76)		Prostate cancer (N=19)		Lung cancer (N=14)		Kidney cancer (N=13)		Other cancer type (N=22)		Total (N=144)	
Number of violated time windows	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Violation of 1 time window	28	(36.8%)	6	(31.6%)	4	(28.6%)	4	(30.8%)	8	(36.4%)	50	(34.7%)
Violation of 2 time windows	7	(9.2%)	1	(5.3%)	1	(7.1%)	1	(7.7%)	2	(9.1%)	12	(8.3%)
Violation of 3 time windows	2	(2.6%)	2	(10.5%)	1	(7.1%)	0	(0.0%)	0	(0.0%)	5	(3.5%)
Violation of more than 3 time windows	3	(3.9%)	0	(0.0%)	1	(7.1%)	1	(7.7%)	0	(0.0%)	5	(3.5%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 48 weeks if the subject received at least 12 injections without time window violation. A time window of +/- 7 days is allowed for each injection relative to the previous injection and of +7 weeks after 48 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included.

15.3.2.5 Persistence at 48 weeks by cancer type for patients who did not undergo previous surgery - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=379)			Prostate cancer (N=248)			Lung cancer (N=74)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	211	(55.7%)	[50.5%-60.7%]	160	(64.5%)	[58.2%-70.5%]	54	(73.0%)	[61.4%-82.6%]
Yes	168	(44.3%)	[39.3%-49.5%]	88	(35.5%)	[29.5%-41.8%]	20	(27.0%)	[17.4%-38.6%]

	Kidney cancer (N=26)			Other cancer type (N=57)			Total (N=784)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	16	(61.5%)	[40.6%-79.8%]	47	(82.5%)	[70.1%-91.3%]	488	(62.2%)	[58.7%-65.7%]
Yes	10	(38.5%)	[20.2%-59.4%]	10	(17.5%)	[8.7%-29.9%]	296	(37.8%)	[34.3%-41.3%]

	Breast cancer (N=379)		Prostate cancer (N=248)		Lung cancer (N=74)		Kidney cancer (N=26)		Other cancer type (N=57)		Total (N=784)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Persistent	168	(44.3%)	88	(35.5%)	20	(27.0%)	10	(38.5%)	10	(17.5%)	296	(37.8%)
Non-persistent: Prem. term. (adverse event)	4	(1.1%)	1	(0.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	5	(0.6%)
Non-persistent: Prem. term. (patient refuses to take medication)	9	(2.4%)	9	(3.6%)	3	(4.1%)	1	(3.8%)	7	(12.3%)	29	(3.7%)
Non-persistent: Prem. term. (physician`s decision)	6	(1.6%)	4	(1.6%)	2	(2.7%)	0	(0.0%)	0	(0.0%)	12	(1.5%)
Non-persistent: Prem. term. (other)	4	(1.1%)	2	(0.8%)	1	(1.4%)	0	(0.0%)	2	(3.5%)	9	(1.1%)
Non-persistent: Not enough injections	1	(0.3%)	3	(1.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	4	(0.5%)
Non-persistent: Violation of time windows	187	(49.3%)	141	(56.9%)	48	(64.9%)	15	(57.7%)	38	(66.7%)	429	(54.7%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 48 weeks if the subject received at least 12 injections without time window violation. A time window of +/- 7 days is allowed for each injection relative to the previous injection and of +7 weeks after 48 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included.

15.3.2.5 Persistence at 48 weeks by cancer type for patients who did not undergo previous surgery - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=379)		Prostate cancer (N=248)		Lung cancer (N=74)		Kidney cancer (N=26)		Other cancer type (N=57)		Total (N=784)	
Number of violated time windows	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Violation of 1 time window	113	(29.8%)	78	(31.5%)	35	(47.3%)	11	(42.3%)	21	(36.8%)	258	(32.9%)
Violation of 2 time windows	51	(13.5%)	37	(14.9%)	11	(14.9%)	4	(15.4%)	9	(15.8%)	112	(14.3%)
Violation of 3 time windows	13	(3.4%)	19	(7.7%)	2	(2.7%)	0	(0.0%)	5	(8.8%)	39	(5.0%)
Violation of more than 3 time windows	10	(2.6%)	7	(2.8%)	0	(0.0%)	0	(0.0%)	3	(5.3%)	20	(2.6%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 48 weeks if the subject received at least 12 injections without time window violation. A time window of +/- 7 days is allowed for each injection relative to the previous injection and of +7 weeks after 48 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included.

15.3.2.6 Persistence at 48 weeks by cancer type for patients who underwent previous chemotherapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=161)			Prostate cancer (N=55)			Lung cancer (N=67)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	105	(65.2%)	[57.3%-72.5%]	40	(72.7%)	[59.0%-83.9%]	46	(68.7%)	[56.2%-79.4%]
Yes	56	(34.8%)	[27.5%-42.7%]	15	(27.3%)	[16.1%-41.0%]	21	(31.3%)	[20.6%-43.8%]

	Kidney cancer (N=26)			Other cancer type (N=46)			Total (N=355)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	16	(61.5%)	[40.6%-79.8%]	38	(82.6%)	[68.6%-92.2%]	245	(69.0%)	[63.9%-73.8%]
Yes	10	(38.5%)	[20.2%-59.4%]	8	(17.4%)	[7.8%-31.4%]	110	(31.0%)	[26.2%-36.1%]

	Breast cancer (N=161)		Prostate cancer (N=55)		Lung cancer (N=67)		Kidney cancer (N=26)		Other cancer type (N=46)		Total (N=355)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Persistent	56	(34.8%)	15	(27.3%)	21	(31.3%)	10	(38.5%)	8	(17.4%)	110	(31.0%)
Non-persistent: Prem. term. (adverse event)	0	(0.0%)	1	(1.8%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.3%)
Non-persistent: Prem. term. (patient refuses to take medication)	4	(2.5%)	5	(9.1%)	2	(3.0%)	2	(7.7%)	6	(13.0%)	19	(5.4%)
Non-persistent: Prem. term. (physician`s decision)	1	(0.6%)	1	(1.8%)	2	(3.0%)	1	(3.8%)	1	(2.2%)	6	(1.7%)
Non-persistent: Prem. term. (other)	2	(1.2%)	1	(1.8%)	2	(3.0%)	0	(0.0%)	3	(6.5%)	8	(2.3%)
Non-persistent: Not enough injections	1	(0.6%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(2.2%)	2	(0.6%)
Non-persistent: Violation of time windows	97	(60.2%)	32	(58.2%)	40	(59.7%)	13	(50.0%)	27	(58.7%)	209	(58.9%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 48 weeks if the subject received at least 12 injections without time window violation. A time window of +/- 7 days is allowed for each injection relative to the previous injection and of +7 weeks after 48 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included.

15.3.2.6 Persistence at 48 weeks by cancer type for patients who underwent previous chemotherapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=161)		Prostate cancer (N=55)		Lung cancer (N=67)		Kidney cancer (N=26)		Other cancer type (N=46)		Total (N=355)	
Number of violated time windows	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Violation of 1 time window	55	(34.2%)	16	(29.1%)	29	(43.3%)	11	(42.3%)	18	(39.1%)	129	(36.3%)
Violation of 2 time windows	26	(16.1%)	8	(14.5%)	10	(14.9%)	2	(7.7%)	6	(13.0%)	52	(14.6%)
Violation of 3 time windows	10	(6.2%)	8	(14.5%)	1	(1.5%)	0	(0.0%)	3	(6.5%)	22	(6.2%)
Violation of more than 3 time windows	6	(3.7%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	6	(1.7%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 48 weeks if the subject received at least 12 injections without time window violation. A time window of +/- 7 days is allowed for each injection relative to the previous injection and of +7 weeks after 48 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included.

15.3.2.7 Persistence at 48 weeks by cancer type for patients who did not undergo previous chemotherapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=294)			Prostate cancer (N=212)			Lung cancer (N=21)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	152	(51.7%)	[45.8%-57.5%]	132	(62.3%)	[55.4%-68.8%]	16	(76.2%)	[52.8%-91.8%]
Yes	142	(48.3%)	[42.5%-54.2%]	80	(37.7%)	[31.2%-44.6%]	5	(23.8%)	[8.2%-47.2%]

	Kidney cancer (N=13)			Other cancer type (N=33)			Total (N=573)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	8	(61.5%)	[31.6%-86.1%]	25	(75.8%)	[57.7%-88.9%]	333	(58.1%)	[54.0%-62.2%]
Yes	5	(38.5%)	[13.9%-68.4%]	8	(24.2%)	[11.1%-42.3%]	240	(41.9%)	[37.8%-46.0%]

	Breast cancer (N=294)		Prostate cancer (N=212)		Lung cancer (N=21)		Kidney cancer (N=13)		Other cancer type (N=33)		Total (N=573)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Persistent	142	(48.3%)	80	(37.7%)	5	(23.8%)	5	(38.5%)	8	(24.2%)	240	(41.9%)
Non-persistent: Prem. term. (adverse event)	4	(1.4%)	1	(0.5%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	5	(0.9%)
Non-persistent: Prem. term. (patient refuses to take medication)	9	(3.1%)	6	(2.8%)	1	(4.8%)	0	(0.0%)	3	(9.1%)	19	(3.3%)
Non-persistent: Prem. term. (physician`s decision)	5	(1.7%)	3	(1.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	8	(1.4%)
Non-persistent: Prem. term. (other)	4	(1.4%)	1	(0.5%)	0	(0.0%)	0	(0.0%)	1	(3.0%)	6	(1.0%)
Non-persistent: Not enough injections	0	(0.0%)	3	(1.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	3	(0.5%)
Non-persistent: Violation of time windows	130	(44.2%)	118	(55.7%)	15	(71.4%)	8	(61.5%)	21	(63.6%)	292	(51.0%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 48 weeks if the subject received at least 12 injections without time window violation. A time window of +/- 7 days is allowed for each injection relative to the previous injection and of +7 weeks after 48 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included.

15.3.2.7 Persistence at 48 weeks by cancer type for patients who did not undergo previous chemotherapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=294)		Prostate cancer (N=212)		Lung cancer (N=21)		Kidney cancer (N=13)		Other cancer type (N=33)		Total (N=573)	
Number of violated time windows	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Violation of 1 time window	86	(29.3%)	68	(32.1%)	10	(47.6%)	4	(30.8%)	11	(33.3%)	179	(31.2%)
Violation of 2 time windows	32	(10.9%)	30	(14.2%)	2	(9.5%)	3	(23.1%)	5	(15.2%)	72	(12.6%)
Violation of 3 time windows	5	(1.7%)	13	(6.1%)	2	(9.5%)	0	(0.0%)	2	(6.1%)	22	(3.8%)
Violation of more than 3 time windows	7	(2.4%)	7	(3.3%)	1	(4.8%)	1	(7.7%)	3	(9.1%)	19	(3.3%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 48 weeks if the subject received at least 12 injections without time window violation. A time window of +/- 7 days is allowed for each injection relative to the previous injection and of +7 weeks after 48 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included.

15.3.2.8 Persistence at 48 weeks by cancer type for patients who underwent previous radiotherapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=130)			Prostate cancer (N=30)			Lung cancer (N=28)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	69	(53.1%)	[44.1%-61.9%]	22	(73.3%)	[54.1%-87.7%]	16	(57.1%)	[37.2%-75.5%]
Yes	61	(46.9%)	[38.1%-55.9%]	8	(26.7%)	[12.3%-45.9%]	12	(42.9%)	[24.5%-62.8%]

	Kidney cancer (N=17)			Other cancer type (N=29)			Total (N=234)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	9	(52.9%)	[27.8%-77.0%]	22	(75.9%)	[56.5%-89.7%]	138	(59.0%)	[52.4%-65.3%]
Yes	8	(47.1%)	[23.0%-72.2%]	7	(24.1%)	[10.3%-43.5%]	96	(41.0%)	[34.7%-47.6%]

	Breast cancer (N=130)		Prostate cancer (N=30)		Lung cancer (N=28)		Kidney cancer (N=17)		Other cancer type (N=29)		Total (N=234)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Persistent	61	(46.9%)	8	(26.7%)	12	(42.9%)	8	(47.1%)	7	(24.1%)	96	(41.0%)
Non-persistent: Prem. term. (adverse event)	2	(1.5%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.9%)
Non-persistent: Prem. term. (patient refuses to take medication)	3	(2.3%)	1	(3.3%)	0	(0.0%)	1	(5.9%)	4	(13.8%)	9	(3.8%)
Non-persistent: Prem. term. (physician`s decision)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Non-persistent: Prem. term. (other)	2	(1.5%)	1	(3.3%)	1	(3.6%)	0	(0.0%)	1	(3.4%)	5	(2.1%)
Non-persistent: Not enough injections	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Non-persistent: Violation of time windows	62	(47.7%)	20	(66.7%)	15	(53.6%)	8	(47.1%)	17	(58.6%)	122	(52.1%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 48 weeks if the subject received at least 12 injections without time window violation. A time window of +/- 7 days is allowed for each injection relative to the previous injection and of +7 weeks after 48 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included.

15.3.2.8 Persistence at 48 weeks by cancer type for patients who underwent previous radiotherapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=130)		Prostate cancer (N=30)		Lung cancer (N=28)		Kidney cancer (N=17)		Other cancer type (N=29)		Total (N=234)	
Number of violated time windows	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Violation of 1 time window	40	(30.8%)	10	(33.3%)	10	(35.7%)	5	(29.4%)	10	(34.5%)	75	(32.1%)
Violation of 2 time windows	14	(10.8%)	7	(23.3%)	4	(14.3%)	2	(11.8%)	3	(10.3%)	30	(12.8%)
Violation of 3 time windows	4	(3.1%)	2	(6.7%)	1	(3.6%)	0	(0.0%)	3	(10.3%)	10	(4.3%)
Violation of more than 3 time windows	4	(3.1%)	1	(3.3%)	0	(0.0%)	1	(5.9%)	1	(3.4%)	7	(3.0%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 48 weeks if the subject received at least 12 injections without time window violation. A time window of +/- 7 days is allowed for each injection relative to the previous injection and of +7 weeks after 48 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included.

15.3.2.9 Persistence at 48 weeks by cancer type for patients who did not undergo previous radiotherapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=325)			Prostate cancer (N=237)			Lung cancer (N=60)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	188	(57.8%)	[52.3%-63.3%]	150	(63.3%)	[56.8%-69.4%]	46	(76.7%)	[64.0%-86.6%]
Yes	137	(42.2%)	[36.7%-47.7%]	87	(36.7%)	[30.6%-43.2%]	14	(23.3%)	[13.4%-36.0%]

	Kidney cancer (N=22)			Other cancer type (N=50)			Total (N=694)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	15	(68.2%)	[45.1%-86.1%]	41	(82.0%)	[68.6%-91.4%]	440	(63.4%)	[59.7%-67.0%]
Yes	7	(31.8%)	[13.9%-54.9%]	9	(18.0%)	[8.6%-31.4%]	254	(36.6%)	[33.0%-40.3%]

	Breast cancer (N=325)		Prostate cancer (N=237)		Lung cancer (N=60)		Kidney cancer (N=22)		Other cancer type (N=50)		Total (N=694)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Persistent	137	(42.2%)	87	(36.7%)	14	(23.3%)	7	(31.8%)	9	(18.0%)	254	(36.6%)
Non-persistent: Prem. term. (adverse event)	2	(0.6%)	2	(0.8%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	4	(0.6%)
Non-persistent: Prem. term. (patient refuses to take medication)	10	(3.1%)	10	(4.2%)	3	(5.0%)	1	(4.5%)	5	(10.0%)	29	(4.2%)
Non-persistent: Prem. term. (physician`s decision)	6	(1.8%)	4	(1.7%)	2	(3.3%)	1	(4.5%)	1	(2.0%)	14	(2.0%)
Non-persistent: Prem. term. (other)	4	(1.2%)	1	(0.4%)	1	(1.7%)	0	(0.0%)	3	(6.0%)	9	(1.3%)
Non-persistent: Not enough injections	1	(0.3%)	3	(1.3%)	0	(0.0%)	0	(0.0%)	1	(2.0%)	5	(0.7%)
Non-persistent: Violation of time windows	165	(50.8%)	130	(54.9%)	40	(66.7%)	13	(59.1%)	31	(62.0%)	379	(54.6%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 48 weeks if the subject received at least 12 injections without time window violation. A time window of +/- 7 days is allowed for each injection relative to the previous injection and of +7 weeks after 48 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included.

15.3.2.9 Persistence at 48 weeks by cancer type for patients who did not undergo previous radiotherapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=325)		Prostate cancer (N=237)		Lung cancer (N=60)		Kidney cancer (N=22)		Other cancer type (N=50)		Total (N=694)	
Number of violated time windows	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Violation of 1 time window	101	(31.1%)	74	(31.2%)	29	(48.3%)	10	(45.5%)	19	(38.0%)	233	(33.6%)
Violation of 2 time windows	44	(13.5%)	31	(13.1%)	8	(13.3%)	3	(13.6%)	8	(16.0%)	94	(13.5%)
Violation of 3 time windows	11	(3.4%)	19	(8.0%)	2	(3.3%)	0	(0.0%)	2	(4.0%)	34	(4.9%)
Violation of more than 3 time windows	9	(2.8%)	6	(2.5%)	1	(1.7%)	0	(0.0%)	2	(4.0%)	18	(2.6%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 48 weeks if the subject received at least 12 injections without time window violation. A time window of +/- 7 days is allowed for each injection relative to the previous injection and of +7 weeks after 48 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included.

15.3.2.10 Persistence at 48 weeks by cancer type for patients who underwent previous antihormonal therapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=200)			Prostate cancer (N=174)			Kidney cancer (N=1)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	107	(53.5%)	[46.3%-60.6%]	110	(63.2%)	[55.6%-70.4%]	1	(100.0%)	[2.5%-100.0%]
Yes	93	(46.5%)	[39.4%-53.7%]	64	(36.8%)	[29.6%-44.4%]	0	(0.0%)	[0.0%-97.5%]

	Other cancer type (N=4)			Total (N=379)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	3	(75.0%)	[19.4%-99.4%]	221	(58.3%)	[53.2%-63.3%]
Yes	1	(25.0%)	[0.6%-80.6%]	158	(41.7%)	[36.7%-46.8%]

	Breast cancer (N=200)		Prostate cancer (N=174)		Kidney cancer (N=1)		Other cancer type (N=4)		Total (N=379)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Persistent	93	(46.5%)	64	(36.8%)	0	(0.0%)	1	(25.0%)	158	(41.7%)
Non-persistent: Prem. term. (adverse event)	3	(1.5%)	1	(0.6%)	0	(0.0%)	0	(0.0%)	4	(1.1%)
Non-persistent: Prem. term. (patient refuses to take medication)	7	(3.5%)	9	(5.2%)	0	(0.0%)	0	(0.0%)	16	(4.2%)
Non-persistent: Prem. term. (physician`s decision)	4	(2.0%)	4	(2.3%)	0	(0.0%)	0	(0.0%)	8	(2.1%)
Non-persistent: Prem. term. (other)	3	(1.5%)	1	(0.6%)	0	(0.0%)	0	(0.0%)	4	(1.1%)
Non-persistent: Not enough injections	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Non-persistent: Violation of time windows	90	(45.0%)	95	(54.6%)	1	(100.0%)	3	(75.0%)	189	(49.9%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 48 weeks if the subject received at least 12 injections without time window violation. A time window of +/- 7 days is allowed for each injection relative to the previous injection and of +7 weeks after 48 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included.

15.3.2.10 Persistence at 48 weeks by cancer type for patients who underwent previous antihormonal therapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=200)		Prostate cancer (N=174)		Kidney cancer (N=1)		Other cancer type (N=4)		Total (N=379)	
Number of violated time windows	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Violation of 1 time window	58	(29.0%)	52	(29.9%)	0	(0.0%)	3	(75.0%)	113	(29.8%)
Violation of 2 time windows	23	(11.5%)	25	(14.4%)	0	(0.0%)	0	(0.0%)	48	(12.7%)
Violation of 3 time windows	5	(2.5%)	14	(8.0%)	0	(0.0%)	0	(0.0%)	19	(5.0%)
Violation of more than 3 time windows	4	(2.0%)	4	(2.3%)	1	(100.0%)	0	(0.0%)	9	(2.4%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 48 weeks if the subject received at least 12 injections without time window violation. A time window of +/- 7 days is allowed for each injection relative to the previous injection and of +7 weeks after 48 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included.

15.3.2.11 Persistence at 48 weeks by cancer type for patients who did not undergo previous antihormonal therapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=255)			Prostate cancer (N=93)			Lung cancer (N=88)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	150	(58.8%)	[52.5%-64.9%]	62	(66.7%)	[56.1%-76.1%]	62	(70.5%)	[59.8%-79.7%]
Yes	105	(41.2%)	[35.1%-47.5%]	31	(33.3%)	[23.9%-43.9%]	26	(29.5%)	[20.3%-40.2%]

	Kidney cancer (N=38)			Other cancer type (N=75)			Total (N=549)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	23	(60.5%)	[43.4%-76.0%]	60	(80.0%)	[69.2%-88.4%]	357	(65.0%)	[60.9%-69.0%]
Yes	15	(39.5%)	[24.0%-56.6%]	15	(20.0%)	[11.6%-30.8%]	192	(35.0%)	[31.0%-39.1%]

	Breast cancer (N=255)		Prostate cancer (N=93)		Lung cancer (N=88)		Kidney cancer (N=38)		Other cancer type (N=75)		Total (N=549)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Persistent	105	(41.2%)	31	(33.3%)	26	(29.5%)	15	(39.5%)	15	(20.0%)	192	(35.0%)
Non-persistent: Prem. term. (adverse event)	1	(0.4%)	1	(1.1%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.4%)
Non-persistent: Prem. term. (patient refuses to take medication)	6	(2.4%)	2	(2.2%)	3	(3.4%)	2	(5.3%)	9	(12.0%)	22	(4.0%)
Non-persistent: Prem. term. (physician`s decision)	2	(0.8%)	0	(0.0%)	2	(2.3%)	1	(2.6%)	1	(1.3%)	6	(1.1%)
Non-persistent: Prem. term. (other)	3	(1.2%)	1	(1.1%)	2	(2.3%)	0	(0.0%)	4	(5.3%)	10	(1.8%)
Non-persistent: Not enough injections	1	(0.4%)	3	(3.2%)	0	(0.0%)	0	(0.0%)	1	(1.3%)	5	(0.9%)
Non-persistent: Violation of time windows	137	(53.7%)	55	(59.1%)	55	(62.5%)	20	(52.6%)	45	(60.0%)	312	(56.8%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 48 weeks if the subject received at least 12 injections without time window violation. A time window of +/- 7 days is allowed for each injection relative to the previous injection and of +7 weeks after 48 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included.

15.3.2.11 Persistence at 48 weeks by cancer type for patients who did not undergo previous antihormonal therapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=255)		Prostate cancer (N=93)		Lung cancer (N=88)		Kidney cancer (N=38)		Other cancer type (N=75)		Total (N=549)	
Number of violated time windows	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Violation of 1 time window	83	(32.5%)	32	(34.4%)	39	(44.3%)	15	(39.5%)	26	(34.7%)	195	(35.5%)
Violation of 2 time windows	35	(13.7%)	13	(14.0%)	12	(13.6%)	5	(13.2%)	11	(14.7%)	76	(13.8%)
Violation of 3 time windows	10	(3.9%)	7	(7.5%)	3	(3.4%)	0	(0.0%)	5	(6.7%)	25	(4.6%)
Violation of more than 3 time windows	9	(3.5%)	3	(3.2%)	1	(1.1%)	0	(0.0%)	3	(4.0%)	16	(2.9%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 48 weeks if the subject received at least 12 injections without time window violation. A time window of +/- 7 days is allowed for each injection relative to the previous injection and of +7 weeks after 48 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included.

15.3.3.1 Persistence at 24 weeks - sensitivity analysis - by cancer type - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=475)			Prostate cancer (N=279)			Lung cancer (N=106)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	99	(20.8%)	[17.3%-24.8%]	66	(23.7%)	[18.8%-29.1%]	35	(33.0%)	[24.2%-42.8%]
Yes	376	(79.2%)	[75.2%-82.7%]	213	(76.3%)	[70.9%-81.2%]	71	(67.0%)	[57.2%-75.8%]

	Kidney cancer (N=46)			Other cancer type (N=84)			Total (N=990)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	12	(26.1%)	[14.3%-41.1%]	24	(28.6%)	[19.2%-39.5%]	236	(23.8%)	[21.2%-26.6%]
Yes	34	(73.9%)	[58.9%-85.7%]	60	(71.4%)	[60.5%-80.8%]	754	(76.2%)	[73.4%-78.8%]

	Breast cancer (N=475)		Prostate cancer (N=279)		Lung cancer (N=106)		Kidney cancer (N=46)		Other cancer type (N=84)		Total (N=990)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Persistent	376	(79.2%)	213	(76.3%)	71	(67.0%)	34	(73.9%)	60	(71.4%)	754	(76.2%)
Non-persistent: Prem. term. (adverse event)	4	(0.8%)	2	(0.7%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	6	(0.6%)
Non-persistent: Prem. term. (patient refuses to take medication)	8	(1.7%)	5	(1.8%)	3	(2.8%)	1	(2.2%)	6	(7.1%)	23	(2.3%)
Non-persistent: Prem. term. (physician`s decision)	5	(1.1%)	1	(0.4%)	4	(3.8%)	0	(0.0%)	1	(1.2%)	11	(1.1%)
Non-persistent: Prem. term. (other)	4	(0.8%)	1	(0.4%)	2	(1.9%)	0	(0.0%)	2	(2.4%)	9	(0.9%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 24 weeks if he received at least 6 injections without time window violation. A time window of +/- 14 days is allowed for each injection relative to the previous injection and of +4 weeks after 24 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included. I.e. more patients are excluded for sensitivity analyses compared to normal analyses.

15.3.3.1 Persistence at 24 weeks - sensitivity analysis - by cancer type - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=475)		Prostate cancer (N=279)		Lung cancer (N=106)		Kidney cancer (N=46)		Other cancer type (N=84)		Total (N=990)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Non-persistent: Not enough injections	0	(0.0%)	1	(0.4%)	2	(1.9%)	0	(0.0%)	0	(0.0%)	3	(0.3%)
Non-persistent: Violation of time windows	78	(16.4%)	56	(20.1%)	24	(22.6%)	11	(23.9%)	15	(17.9%)	184	(18.6%)

	Breast cancer (N=475)		Prostate cancer (N=279)		Lung cancer (N=106)		Kidney cancer (N=46)		Other cancer type (N=84)		Total (N=990)	
Number of violated time windows	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Violation of 1 time window	72	(15.2%)	49	(17.6%)	22	(20.8%)	11	(23.9%)	13	(15.5%)	167	(16.9%)
Violation of 2 time windows	5	(1.1%)	6	(2.2%)	2	(1.9%)	0	(0.0%)	2	(2.4%)	15	(1.5%)
Violation of 3 time windows	1	(0.2%)	1	(0.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.2%)
Violation of more than 3 time windows	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 24 weeks if he received at least 6 injections without time window violation. A time window of +/- 14 days is allowed for each injection relative to the previous injection and of +4 weeks after 24 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included. I.e. more patients are excluded for sensitivity analyses compared to normal analyses.

15.3.3.2 Persistence at 24 weeks - sensitivity analysis - by cancer type for patients with previous antiresorptive treatment - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=37)			Prostate cancer (N=12)			Lung cancer (N=5)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	8	(21.6%)	[9.8%-38.2%]	3	(25.0%)	[5.5%-57.2%]	3	(60.0%)	[14.7%-94.7%]
Yes	29	(78.4%)	[61.8%-90.2%]	9	(75.0%)	[42.8%-94.5%]	2	(40.0%)	[5.3%-85.3%]

	Kidney cancer (N=4)			Other cancer type (N=4)			Total (N=62)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	2	(50.0%)	[6.8%-93.2%]	2	(50.0%)	[6.8%-93.2%]	18	(29.0%)	[18.2%-41.9%]
Yes	2	(50.0%)	[6.8%-93.2%]	2	(50.0%)	[6.8%-93.2%]	44	(71.0%)	[58.1%-81.8%]

	Breast cancer (N=37)		Prostate cancer (N=12)		Lung cancer (N=5)		Kidney cancer (N=4)		Other cancer type (N=4)		Total (N=62)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Persistent	29	(78.4%)	9	(75.0%)	2	(40.0%)	2	(50.0%)	2	(50.0%)	44	(71.0%)
Non-persistent: Prem. term. (adverse event)	1	(2.7%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(1.6%)
Non-persistent: Prem. term. (patient refuses to take medication)	1	(2.7%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(25.0%)	2	(3.2%)
Non-persistent: Prem. term. (physician`s decision)	0	(0.0%)	0	(0.0%)	1	(20.0%)	0	(0.0%)	0	(0.0%)	1	(1.6%)
Non-persistent: Prem. term. (other)	1	(2.7%)	1	(8.3%)	0	(0.0%)	0	(0.0%)	1	(25.0%)	3	(4.8%)
Non-persistent: Not enough injections	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Non-persistent: Violation of time windows	5	(13.5%)	2	(16.7%)	2	(40.0%)	2	(50.0%)	0	(0.0%)	11	(17.7%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 24 weeks if he received at least 6 injections without time window violation. A time window of +/- 14 days is allowed for each injection relative to the previous injection and of +4 weeks after 24 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included. I.e. more patients are excluded for sensitivity analyses compared to normal analyses.

15.3.3.2 Persistence at 24 weeks - sensitivity analysis - by cancer type for patients with previous antiresorptive treatment - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=37)		Prostate cancer (N=12)		Lung cancer (N=5)		Kidney cancer (N=4)		Other cancer type (N=4)		Total (N=62)	
Number of violated time windows	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Violation of 1 time window	5	(13.5%)	2	(16.7%)	2	(40.0%)	2	(50.0%)	0	(0.0%)	11	(17.7%)
Violation of 2 time windows	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Violation of 3 time windows	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Violation of more than 3 time windows	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 24 weeks if he received at least 6 injections without time window violation. A time window of +/- 14 days is allowed for each injection relative to the previous injection and of +4 weeks after 24 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included. I.e. more patients are excluded for sensitivity analyses compared to normal analyses.

15.3.3.3 Persistence at 24 weeks - sensitivity analysis - by cancer type for patients without previous antiresorptive treatment - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=438)			Prostate cancer (N=267)			Lung cancer (N=101)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	91	(20.8%)	[17.1%-24.9%]	63	(23.6%)	[18.6%-29.2%]	32	(31.7%)	[22.8%-41.7%]
Yes	347	(79.2%)	[75.1%-82.9%]	204	(76.4%)	[70.8%-81.4%]	69	(68.3%)	[58.3%-77.2%]

	Kidney cancer (N=42)			Other cancer type (N=80)			Total (N=928)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	10	(23.8%)	[12.1%-39.5%]	22	(27.5%)	[18.1%-38.6%]	218	(23.5%)	[20.8%-26.4%]
Yes	32	(76.2%)	[60.5%-87.9%]	58	(72.5%)	[61.4%-81.9%]	710	(76.5%)	[73.6%-79.2%]

	Breast cancer (N=438)		Prostate cancer (N=267)		Lung cancer (N=101)		Kidney cancer (N=42)		Other cancer type (N=80)		Total (N=928)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Persistent	347	(79.2%)	204	(76.4%)	69	(68.3%)	32	(76.2%)	58	(72.5%)	710	(76.5%)
Non-persistent: Prem. term. (adverse event)	3	(0.7%)	2	(0.7%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	5	(0.5%)
Non-persistent: Prem. term. (patient refuses to take medication)	7	(1.6%)	5	(1.9%)	3	(3.0%)	1	(2.4%)	5	(6.3%)	21	(2.3%)
Non-persistent: Prem. term. (physician`s decision)	5	(1.1%)	1	(0.4%)	3	(3.0%)	0	(0.0%)	1	(1.3%)	10	(1.1%)
Non-persistent: Prem. term. (other)	3	(0.7%)	0	(0.0%)	2	(2.0%)	0	(0.0%)	1	(1.3%)	6	(0.6%)
Non-persistent: Not enough injections	0	(0.0%)	1	(0.4%)	2	(2.0%)	0	(0.0%)	0	(0.0%)	3	(0.3%)
Non-persistent: Violation of time windows	73	(16.7%)	54	(20.2%)	22	(21.8%)	9	(21.4%)	15	(18.8%)	173	(18.6%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 24 weeks if he received at least 6 injections without time window violation. A time window of +/- 14 days is allowed for each injection relative to the previous injection and of +4 weeks after 24 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included. I.e. more patients are excluded for sensitivity analyses compared to normal analyses.

15.3.3.3 Persistence at 24 weeks - sensitivity analysis - by cancer type for patients without previous antiresorptive treatment - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=438)		Prostate cancer (N=267)		Lung cancer (N=101)		Kidney cancer (N=42)		Other cancer type (N=80)		Total (N=928)	
Number of violated time windows	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Violation of 1 time window	67	(15.3%)	47	(17.6%)	20	(19.8%)	9	(21.4%)	13	(16.3%)	156	(16.8%)
Violation of 2 time windows	5	(1.1%)	6	(2.2%)	2	(2.0%)	0	(0.0%)	2	(2.5%)	15	(1.6%)
Violation of 3 time windows	1	(0.2%)	1	(0.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.2%)
Violation of more than 3 time windows	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 24 weeks if he received at least 6 injections without time window violation. A time window of +/- 14 days is allowed for each injection relative to the previous injection and of +4 weeks after 24 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included. I.e. more patients are excluded for sensitivity analyses compared to normal analyses.

15.3.3.4 Persistence at 24 weeks - sensitivity analysis - by cancer type for patients who underwent previous surgery - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=77)			Prostate cancer (N=23)			Lung cancer (N=20)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	20	(26.0%)	[16.6%-37.2%]	2	(8.7%)	[1.1%-28.0%]	7	(35.0%)	[15.4%-59.2%]
Yes	57	(74.0%)	[62.8%-83.4%]	21	(91.3%)	[72.0%-98.9%]	13	(65.0%)	[40.8%-84.6%]

	Kidney cancer (N=18)			Other cancer type (N=26)			Total (N=164)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	3	(16.7%)	[3.6%-41.4%]	4	(15.4%)	[4.4%-34.9%]	36	(22.0%)	[15.9%-29.1%]
Yes	15	(83.3%)	[58.6%-96.4%]	22	(84.6%)	[65.1%-95.6%]	128	(78.0%)	[70.9%-84.1%]

	Breast cancer (N=77)		Prostate cancer (N=23)		Lung cancer (N=20)		Kidney cancer (N=18)		Other cancer type (N=26)		Total (N=164)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Persistent	57	(74.0%)	21	(91.3%)	13	(65.0%)	15	(83.3%)	22	(84.6%)	128	(78.0%)
Non-persistent: Prem. term. (adverse event)	0	(0.0%)	1	(4.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.6%)
Non-persistent: Prem. term. (patient refuses to take medication)	3	(3.9%)	0	(0.0%)	0	(0.0%)	1	(5.6%)	1	(3.8%)	5	(3.0%)
Non-persistent: Prem. term. (physician`s decision)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(3.8%)	1	(0.6%)
Non-persistent: Prem. term. (other)	1	(1.3%)	0	(0.0%)	1	(5.0%)	0	(0.0%)	0	(0.0%)	2	(1.2%)
Non-persistent: Not enough injections	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Non-persistent: Violation of time windows	16	(20.8%)	1	(4.3%)	6	(30.0%)	2	(11.1%)	2	(7.7%)	27	(16.5%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 24 weeks if he received at least 6 injections without time window violation. A time window of +/- 14 days is allowed for each injection relative to the previous injection and of +4 weeks after 24 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included. I.e. more patients are excluded for sensitivity analyses compared to normal analyses.

15.3.3.4 Persistence at 24 weeks - sensitivity analysis - by cancer type for patients who underwent previous surgery - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=77)		Prostate cancer (N=23)		Lung cancer (N=20)		Kidney cancer (N=18)		Other cancer type (N=26)		Total (N=164)	
Number of violated time windows	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Violation of 1 time window	15	(19.5%)	0	(0.0%)	6	(30.0%)	2	(11.1%)	2	(7.7%)	25	(15.2%)
Violation of 2 time windows	1	(1.3%)	1	(4.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(1.2%)
Violation of 3 time windows	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Violation of more than 3 time windows	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 24 weeks if he received at least 6 injections without time window violation. A time window of +/- 14 days is allowed for each injection relative to the previous injection and of +4 weeks after 24 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included. I.e. more patients are excluded for sensitivity analyses compared to normal analyses.

15.3.3.5 Persistence at 24 weeks - sensitivity analysis - by cancer type for patients who did not undergo previous surgery - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=398)			Prostate cancer (N=256)			Lung cancer (N=86)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	79	(19.8%)	[16.0%-24.1%]	64	(25.0%)	[19.8%-30.8%]	28	(32.6%)	[22.8%-43.5%]
Yes	319	(80.2%)	[75.9%-84.0%]	192	(75.0%)	[69.2%-80.2%]	58	(67.4%)	[56.5%-77.2%]

	Kidney cancer (N=28)			Other cancer type (N=58)			Total (N=826)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	9	(32.1%)	[15.9%-52.4%]	20	(34.5%)	[22.5%-48.1%]	200	(24.2%)	[21.3%-27.3%]
Yes	19	(67.9%)	[47.6%-84.1%]	38	(65.5%)	[51.9%-77.5%]	626	(75.8%)	[72.7%-78.7%]

	Breast cancer (N=398)		Prostate cancer (N=256)		Lung cancer (N=86)		Kidney cancer (N=28)		Other cancer type (N=58)		Total (N=826)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Persistent	319	(80.2%)	192	(75.0%)	58	(67.4%)	19	(67.9%)	38	(65.5%)	626	(75.8%)
Non-persistent: Prem. term. (adverse event)	4	(1.0%)	1	(0.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	5	(0.6%)
Non-persistent: Prem. term. (patient refuses to take medication)	5	(1.3%)	5	(2.0%)	3	(3.5%)	0	(0.0%)	5	(8.6%)	18	(2.2%)
Non-persistent: Prem. term. (physician`s decision)	5	(1.3%)	1	(0.4%)	4	(4.7%)	0	(0.0%)	0	(0.0%)	10	(1.2%)
Non-persistent: Prem. term. (other)	3	(0.8%)	1	(0.4%)	1	(1.2%)	0	(0.0%)	2	(3.4%)	7	(0.8%)
Non-persistent: Not enough injections	0	(0.0%)	1	(0.4%)	2	(2.3%)	0	(0.0%)	0	(0.0%)	3	(0.4%)
Non-persistent: Violation of time windows	62	(15.6%)	55	(21.5%)	18	(20.9%)	9	(32.1%)	13	(22.4%)	157	(19.0%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 24 weeks if he received at least 6 injections without time window violation. A time window of +/- 14 days is allowed for each injection relative to the previous injection and of +4 weeks after 24 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included. I.e. more patients are excluded for sensitivity analyses compared to normal analyses.

15.3.3.5 Persistence at 24 weeks - sensitivity analysis - by cancer type for patients who did not undergo previous surgery - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=398)		Prostate cancer (N=256)		Lung cancer (N=86)		Kidney cancer (N=28)		Other cancer type (N=58)		Total (N=826)	
Number of violated time windows	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Violation of 1 time window	57	(14.3%)	49	(19.1%)	16	(18.6%)	9	(32.1%)	11	(19.0%)	142	(17.2%)
Violation of 2 time windows	4	(1.0%)	5	(2.0%)	2	(2.3%)	0	(0.0%)	2	(3.4%)	13	(1.6%)
Violation of 3 time windows	1	(0.3%)	1	(0.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.2%)
Violation of more than 3 time windows	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 24 weeks if he received at least 6 injections without time window violation. A time window of +/- 14 days is allowed for each injection relative to the previous injection and of +4 weeks after 24 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included. I.e. more patients are excluded for sensitivity analyses compared to normal analyses.

15.3.3.6 Persistence at 24 weeks - sensitivity analysis - by cancer type for patients who underwent previous chemotherapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=168)			Prostate cancer (N=57)			Lung cancer (N=78)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	28	(16.7%)	[11.4%-23.2%]	18	(31.6%)	[19.9%-45.2%]	24	(30.8%)	[20.8%-42.2%]
Yes	140	(83.3%)	[76.8%-88.6%]	39	(68.4%)	[54.8%-80.1%]	54	(69.2%)	[57.8%-79.2%]

	Kidney cancer (N=30)			Other cancer type (N=46)			Total (N=379)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	9	(30.0%)	[14.7%-49.4%]	16	(34.8%)	[21.4%-50.2%]	95	(25.1%)	[20.8%-29.7%]
Yes	21	(70.0%)	[50.6%-85.3%]	30	(65.2%)	[49.8%-78.6%]	284	(74.9%)	[70.3%-79.2%]

	Breast cancer (N=168)		Prostate cancer (N=57)		Lung cancer (N=78)		Kidney cancer (N=30)		Other cancer type (N=46)		Total (N=379)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Persistent	140	(83.3%)	39	(68.4%)	54	(69.2%)	21	(70.0%)	30	(65.2%)	284	(74.9%)
Non-persistent: Prem. term. (adverse event)	0	(0.0%)	1	(1.8%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.3%)
Non-persistent: Prem. term. (patient refuses to take medication)	2	(1.2%)	3	(5.3%)	2	(2.6%)	1	(3.3%)	4	(8.7%)	12	(3.2%)
Non-persistent: Prem. term. (physician`s decision)	1	(0.6%)	0	(0.0%)	3	(3.8%)	0	(0.0%)	1	(2.2%)	5	(1.3%)
Non-persistent: Prem. term. (other)	1	(0.6%)	0	(0.0%)	2	(2.6%)	0	(0.0%)	2	(4.3%)	5	(1.3%)
Non-persistent: Not enough injections	0	(0.0%)	1	(1.8%)	1	(1.3%)	0	(0.0%)	0	(0.0%)	2	(0.5%)
Non-persistent: Violation of time windows	24	(14.3%)	13	(22.8%)	16	(20.5%)	8	(26.7%)	9	(19.6%)	70	(18.5%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 24 weeks if he received at least 6 injections without time window violation. A time window of +/- 14 days is allowed for each injection relative to the previous injection and of +4 weeks after 24 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included. I.e. more patients are excluded for sensitivity analyses compared to normal analyses.

15.3.3.6 Persistence at 24 weeks - sensitivity analysis - by cancer type for patients who underwent previous chemotherapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=168)		Prostate cancer (N=57)		Lung cancer (N=78)		Kidney cancer (N=30)		Other cancer type (N=46)		Total (N=379)	
Number of violated time windows	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Violation of 1 time window	21	(12.5%)	10	(17.5%)	16	(20.5%)	8	(26.7%)	9	(19.6%)	64	(16.9%)
Violation of 2 time windows	3	(1.8%)	3	(5.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	6	(1.6%)
Violation of 3 time windows	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Violation of more than 3 time windows	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 24 weeks if he received at least 6 injections without time window violation. A time window of +/- 14 days is allowed for each injection relative to the previous injection and of +4 weeks after 24 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included. I.e. more patients are excluded for sensitivity analyses compared to normal analyses.

15.3.3.7 Persistence at 24 weeks - sensitivity analysis - by cancer type for patients who did not undergo previous chemotherapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=307)			Prostate cancer (N=222)			Lung cancer (N=28)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	71	(23.1%)	[18.5%-28.3%]	48	(21.6%)	[16.4%-27.6%]	11	(39.3%)	[21.5%-59.4%]
Yes	236	(76.9%)	[71.7%-81.5%]	174	(78.4%)	[72.4%-83.6%]	17	(60.7%)	[40.6%-78.5%]

	Kidney cancer (N=16)			Other cancer type (N=38)			Total (N=611)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	3	(18.8%)	[4.0%-45.6%]	8	(21.1%)	[9.6%-37.3%]	141	(23.1%)	[19.8%-26.6%]
Yes	13	(81.3%)	[54.4%-96.0%]	30	(78.9%)	[62.7%-90.4%]	470	(76.9%)	[73.4%-80.2%]

	Breast cancer (N=307)		Prostate cancer (N=222)		Lung cancer (N=28)		Kidney cancer (N=16)		Other cancer type (N=38)		Total (N=611)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Persistent	236	(76.9%)	174	(78.4%)	17	(60.7%)	13	(81.3%)	30	(78.9%)	470	(76.9%)
Non-persistent: Prem. term. (adverse event)	4	(1.3%)	1	(0.5%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	5	(0.8%)
Non-persistent: Prem. term. (patient refuses to take medication)	6	(2.0%)	2	(0.9%)	1	(3.6%)	0	(0.0%)	2	(5.3%)	11	(1.8%)
Non-persistent: Prem. term. (physician`s decision)	4	(1.3%)	1	(0.5%)	1	(3.6%)	0	(0.0%)	0	(0.0%)	6	(1.0%)
Non-persistent: Prem. term. (other)	3	(1.0%)	1	(0.5%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	4	(0.7%)
Non-persistent: Not enough injections	0	(0.0%)	0	(0.0%)	1	(3.6%)	0	(0.0%)	0	(0.0%)	1	(0.2%)
Non-persistent: Violation of time windows	54	(17.6%)	43	(19.4%)	8	(28.6%)	3	(18.8%)	6	(15.8%)	114	(18.7%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 24 weeks if he received at least 6 injections without time window violation. A time window of +/- 14 days is allowed for each injection relative to the previous injection and of +4 weeks after 24 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included. I.e. more patients are excluded for sensitivity analyses compared to normal analyses.

15.3.3.7 Persistence at 24 weeks - sensitivity analysis - by cancer type for patients who did not undergo previous chemotherapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=307)		Prostate cancer (N=222)		Lung cancer (N=28)		Kidney cancer (N=16)		Other cancer type (N=38)		Total (N=611)	
Number of violated time windows	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Violation of 1 time window	51	(16.6%)	39	(17.6%)	6	(21.4%)	3	(18.8%)	4	(10.5%)	103	(16.9%)
Violation of 2 time windows	2	(0.7%)	3	(1.4%)	2	(7.1%)	0	(0.0%)	2	(5.3%)	9	(1.5%)
Violation of 3 time windows	1	(0.3%)	1	(0.5%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.3%)
Violation of more than 3 time windows	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 24 weeks if he received at least 6 injections without time window violation. A time window of +/- 14 days is allowed for each injection relative to the previous injection and of +4 weeks after 24 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included. I.e. more patients are excluded for sensitivity analyses compared to normal analyses.

15.3.3.8 Persistence at 24 weeks - sensitivity analysis - by cancer type for patients who underwent previous radiotherapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=133)			Prostate cancer (N=34)			Lung cancer (N=35)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	29	(21.8%)	[15.1%-29.8%]	11	(32.4%)	[17.4%-50.5%]	9	(25.7%)	[12.5%-43.3%]
Yes	104	(78.2%)	[70.2%-84.9%]	23	(67.6%)	[49.5%-82.6%]	26	(74.3%)	[56.7%-87.5%]

	Kidney cancer (N=18)			Other cancer type (N=28)			Total (N=248)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	6	(33.3%)	[13.3%-59.0%]	6	(21.4%)	[8.3%-41.0%]	61	(24.6%)	[19.4%-30.4%]
Yes	12	(66.7%)	[41.0%-86.7%]	22	(78.6%)	[59.0%-91.7%]	187	(75.4%)	[69.6%-80.6%]

	Breast cancer (N=133)		Prostate cancer (N=34)		Lung cancer (N=35)		Kidney cancer (N=18)		Other cancer type (N=28)		Total (N=248)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Persistent	104	(78.2%)	23	(67.6%)	26	(74.3%)	12	(66.7%)	22	(78.6%)	187	(75.4%)
Non-persistent: Prem. term. (adverse event)	2	(1.5%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.8%)
Non-persistent: Prem. term. (patient refuses to take medication)	1	(0.8%)	0	(0.0%)	0	(0.0%)	1	(5.6%)	2	(7.1%)	4	(1.6%)
Non-persistent: Prem. term. (physician`s decision)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Non-persistent: Prem. term. (other)	2	(1.5%)	1	(2.9%)	1	(2.9%)	0	(0.0%)	0	(0.0%)	4	(1.6%)
Non-persistent: Not enough injections	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Non-persistent: Violation of time windows	24	(18.0%)	10	(29.4%)	8	(22.9%)	5	(27.8%)	4	(14.3%)	51	(20.6%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 24 weeks if he received at least 6 injections without time window violation. A time window of +/- 14 days is allowed for each injection relative to the previous injection and of +4 weeks after 24 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included. I.e. more patients are excluded for sensitivity analyses compared to normal analyses.

15.3.3.8 Persistence at 24 weeks - sensitivity analysis - by cancer type for patients who underwent previous radiotherapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=133)		Prostate cancer (N=34)		Lung cancer (N=35)		Kidney cancer (N=18)		Other cancer type (N=28)		Total (N=248)	
Number of violated time windows	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Violation of 1 time window	22	(16.5%)	8	(23.5%)	8	(22.9%)	5	(27.8%)	3	(10.7%)	46	(18.5%)
Violation of 2 time windows	2	(1.5%)	2	(5.9%)	0	(0.0%)	0	(0.0%)	1	(3.6%)	5	(2.0%)
Violation of 3 time windows	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Violation of more than 3 time windows	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 24 weeks if he received at least 6 injections without time window violation. A time window of +/- 14 days is allowed for each injection relative to the previous injection and of +4 weeks after 24 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included. I.e. more patients are excluded for sensitivity analyses compared to normal analyses.

15.3.3.9 Persistence at 24 weeks - sensitivity analysis - by cancer type for patients who did not undergo previous radiotherapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=342)			Prostate cancer (N=245)			Lung cancer (N=71)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	70	(20.5%)	[16.3%-25.1%]	55	(22.4%)	[17.4%-28.2%]	26	(36.6%)	[25.5%-48.9%]
Yes	272	(79.5%)	[74.9%-83.7%]	190	(77.6%)	[71.8%-82.6%]	45	(63.4%)	[51.1%-74.5%]

	Kidney cancer (N=28)			Other cancer type (N=56)			Total (N=742)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	6	(21.4%)	[8.3%-41.0%]	18	(32.1%)	[20.3%-46.0%]	175	(23.6%)	[20.6%-26.8%]
Yes	22	(78.6%)	[59.0%-91.7%]	38	(67.9%)	[54.0%-79.7%]	567	(76.4%)	[73.2%-79.4%]

	Breast cancer (N=342)		Prostate cancer (N=245)		Lung cancer (N=71)		Kidney cancer (N=28)		Other cancer type (N=56)		Total (N=742)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Persistent	272	(79.5%)	190	(77.6%)	45	(63.4%)	22	(78.6%)	38	(67.9%)	567	(76.4%)
Non-persistent: Prem. term. (adverse event)	2	(0.6%)	2	(0.8%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	4	(0.5%)
Non-persistent: Prem. term. (patient refuses to take medication)	7	(2.0%)	5	(2.0%)	3	(4.2%)	0	(0.0%)	4	(7.1%)	19	(2.6%)
Non-persistent: Prem. term. (physician`s decision)	5	(1.5%)	1	(0.4%)	4	(5.6%)	0	(0.0%)	1	(1.8%)	11	(1.5%)
Non-persistent: Prem. term. (other)	2	(0.6%)	0	(0.0%)	1	(1.4%)	0	(0.0%)	2	(3.6%)	5	(0.7%)
Non-persistent: Not enough injections	0	(0.0%)	1	(0.4%)	2	(2.8%)	0	(0.0%)	0	(0.0%)	3	(0.4%)
Non-persistent: Violation of time windows	54	(15.8%)	46	(18.8%)	16	(22.5%)	6	(21.4%)	11	(19.6%)	133	(17.9%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 24 weeks if he received at least 6 injections without time window violation. A time window of +/- 14 days is allowed for each injection relative to the previous injection and of +4 weeks after 24 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included. I.e. more patients are excluded for sensitivity analyses compared to normal analyses.

15.3.3.9 Persistence at 24 weeks - sensitivity analysis - by cancer type for patients who did not undergo previous radiotherapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=342)		Prostate cancer (N=245)		Lung cancer (N=71)		Kidney cancer (N=28)		Other cancer type (N=56)		Total (N=742)	
Number of violated time windows	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Violation of 1 time window	50	(14.6%)	41	(16.7%)	14	(19.7%)	6	(21.4%)	10	(17.9%)	121	(16.3%)
Violation of 2 time windows	3	(0.9%)	4	(1.6%)	2	(2.8%)	0	(0.0%)	1	(1.8%)	10	(1.3%)
Violation of 3 time windows	1	(0.3%)	1	(0.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.3%)
Violation of more than 3 time windows	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 24 weeks if he received at least 6 injections without time window violation. A time window of +/- 14 days is allowed for each injection relative to the previous injection and of +4 weeks after 24 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included. I.e. more patients are excluded for sensitivity analyses compared to normal analyses.

15.3.3.10 Persistence at 24 weeks - sensitivity analysis - by cancer type for patients who underwent previous antihormonal therapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=209)			Prostate cancer (N=180)			Kidney cancer (N=1)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	45	(21.5%)	[16.2%-27.7%]	42	(23.3%)	[17.4%-30.2%]	1	(100.0%)	[2.5%-100.0%]
Yes	164	(78.5%)	[72.3%-83.8%]	138	(76.7%)	[69.8%-82.6%]	0	(0.0%)	[0.0%-97.5%]

	Other cancer type (N=4)			Total (N=394)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	0	(0.0%)	[0.0%-60.2%]	88	(22.3%)	[18.3%-26.8%]
Yes	4	(100.0%)	[39.8%-100.0%]	306	(77.7%)	[73.2%-81.7%]

	Breast cancer (N=209)		Prostate cancer (N=180)		Kidney cancer (N=1)		Other cancer type (N=4)		Total (N=394)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Persistent	164	(78.5%)	138	(76.7%)	0	(0.0%)	4	(100.0%)	306	(77.7%)
Non-persistent: Prem. term. (adverse event)	3	(1.4%)	1	(0.6%)	0	(0.0%)	0	(0.0%)	4	(1.0%)
Non-persistent: Prem. term. (patient refuses to take medication)	4	(1.9%)	4	(2.2%)	0	(0.0%)	0	(0.0%)	8	(2.0%)
Non-persistent: Prem. term. (physician`s decision)	3	(1.4%)	1	(0.6%)	0	(0.0%)	0	(0.0%)	4	(1.0%)
Non-persistent: Prem. term. (other)	3	(1.4%)	1	(0.6%)	0	(0.0%)	0	(0.0%)	4	(1.0%)
Non-persistent: Not enough injections	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Non-persistent: Violation of time windows	32	(15.3%)	35	(19.4%)	1	(100.0%)	0	(0.0%)	68	(17.3%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 24 weeks if he received at least 6 injections without time window violation. A time window of +/- 14 days is allowed for each injection relative to the previous injection and of +4 weeks after 24 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included. I.e. more patients are excluded for sensitivity analyses compared to normal analyses.

15.3.3.10 Persistence at 24 weeks - sensitivity analysis - by cancer type for patients who underwent previous antihormonal therapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=209)		Prostate cancer (N=180)		Kidney cancer (N=1)		Other cancer type (N=4)		Total (N=394)	
Number of violated time windows	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Violation of 1 time window	29	(13.9%)	30	(16.7%)	1	(100.0%)	0	(0.0%)	60	(15.2%)
Violation of 2 time windows	2	(1.0%)	4	(2.2%)	0	(0.0%)	0	(0.0%)	6	(1.5%)
Violation of 3 time windows	1	(0.5%)	1	(0.6%)	0	(0.0%)	0	(0.0%)	2	(0.5%)
Violation of more than 3 time windows	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 24 weeks if he received at least 6 injections without time window violation. A time window of +/- 14 days is allowed for each injection relative to the previous injection and of +4 weeks after 24 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included. I.e. more patients are excluded for sensitivity analyses compared to normal analyses.

15.3.3.11 Persistence at 24 weeks - sensitivity analysis - by cancer type for patients who did not undergo previous antihormonal therapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=266)			Prostate cancer (N=99)			Lung cancer (N=106)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	54	(20.3%)	[15.6%-25.6%]	24	(24.2%)	[16.2%-33.9%]	35	(33.0%)	[24.2%-42.8%]
Yes	212	(79.7%)	[74.4%-84.4%]	75	(75.8%)	[66.1%-83.8%]	71	(67.0%)	[57.2%-75.8%]

	Kidney cancer (N=45)			Other cancer type (N=80)			Total (N=596)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	11	(24.4%)	[12.9%-39.5%]	24	(30.0%)	[20.3%-41.3%]	148	(24.8%)	[21.4%-28.5%]
Yes	34	(75.6%)	[60.5%-87.1%]	56	(70.0%)	[58.7%-79.7%]	448	(75.2%)	[71.5%-78.6%]

	Breast cancer (N=266)		Prostate cancer (N=99)		Lung cancer (N=106)		Kidney cancer (N=45)		Other cancer type (N=80)		Total (N=596)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Persistent	212	(79.7%)	75	(75.8%)	71	(67.0%)	34	(75.6%)	56	(70.0%)	448	(75.2%)
Non-persistent: Prem. term. (adverse event)	1	(0.4%)	1	(1.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.3%)
Non-persistent: Prem. term. (patient refuses to take medication)	4	(1.5%)	1	(1.0%)	3	(2.8%)	1	(2.2%)	6	(7.5%)	15	(2.5%)
Non-persistent: Prem. term. (physician`s decision)	2	(0.8%)	0	(0.0%)	4	(3.8%)	0	(0.0%)	1	(1.3%)	7	(1.2%)
Non-persistent: Prem. term. (other)	1	(0.4%)	0	(0.0%)	2	(1.9%)	0	(0.0%)	2	(2.5%)	5	(0.8%)
Non-persistent: Not enough injections	0	(0.0%)	1	(1.0%)	2	(1.9%)	0	(0.0%)	0	(0.0%)	3	(0.5%)
Non-persistent: Violation of time windows	46	(17.3%)	21	(21.2%)	24	(22.6%)	10	(22.2%)	15	(18.8%)	116	(19.5%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 24 weeks if he received at least 6 injections without time window violation. A time window of +/- 14 days is allowed for each injection relative to the previous injection and of +4 weeks after 24 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included. I.e. more patients are excluded for sensitivity analyses compared to normal analyses.

15.3.3.11 Persistence at 24 weeks - sensitivity analysis - by cancer type for patients who did not undergo previous antihormonal therapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=266)		Prostate cancer (N=99)		Lung cancer (N=106)		Kidney cancer (N=45)		Other cancer type (N=80)		Total (N=596)	
Number of violated time windows	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Violation of 1 time window	43	(16.2%)	19	(19.2%)	22	(20.8%)	10	(22.2%)	13	(16.3%)	107	(18.0%)
Violation of 2 time windows	3	(1.1%)	2	(2.0%)	2	(1.9%)	0	(0.0%)	2	(2.5%)	9	(1.5%)
Violation of 3 time windows	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Violation of more than 3 time windows	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 24 weeks if he received at least 6 injections without time window violation. A time window of +/- 14 days is allowed for each injection relative to the previous injection and of +4 weeks after 24 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included. I.e. more patients are excluded for sensitivity analyses compared to normal analyses.

15.3.4.1 Persistence at 48 weeks - sensitivity analysis - by cancer type - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=437)			Prostate cancer (N=260)			Lung cancer (N=72)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	172	(39.4%)	[34.7%-44.1%]	113	(43.5%)	[37.3%-49.7%]	39	(54.2%)	[42.0%-66.0%]
Yes	265	(60.6%)	[55.9%-65.3%]	147	(56.5%)	[50.3%-62.7%]	33	(45.8%)	[34.0%-58.0%]

	Kidney cancer (N=37)			Other cancer type (N=69)			Total (N=875)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	21	(56.8%)	[39.5%-72.9%]	42	(60.9%)	[48.4%-72.4%]	387	(44.2%)	[40.9%-47.6%]
Yes	16	(43.2%)	[27.1%-60.5%]	27	(39.1%)	[27.6%-51.6%]	488	(55.8%)	[52.4%-59.1%]

	Breast cancer (N=437)		Prostate cancer (N=260)		Lung cancer (N=72)		Kidney cancer (N=37)		Other cancer type (N=69)		Total (N=875)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Persistent	265	(60.6%)	147	(56.5%)	33	(45.8%)	16	(43.2%)	27	(39.1%)	488	(55.8%)
Non-persistent: Prem. term. (adverse event)	4	(0.9%)	3	(1.2%)	1	(1.4%)	0	(0.0%)	0	(0.0%)	8	(0.9%)
Non-persistent: Prem. term. (patient refuses to take medication)	15	(3.4%)	13	(5.0%)	3	(4.2%)	2	(5.4%)	10	(14.5%)	43	(4.9%)
Non-persistent: Prem. term. (physician`s decision)	11	(2.5%)	5	(1.9%)	5	(6.9%)	1	(2.7%)	1	(1.4%)	23	(2.6%)
Non-persistent: Prem. term. (other)	7	(1.6%)	2	(0.8%)	3	(4.2%)	0	(0.0%)	4	(5.8%)	16	(1.8%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 48 weeks if he received at least 12 injections without time window violation. A time window of +/- 14 days is allowed for each injection relative to the previous injection and of +10 weeks after 48 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included. I.e. more patients are excluded for sensitivity analyses compared to normal analyses.

15.3.4.1 Persistence at 48 weeks - sensitivity analysis - by cancer type - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=437)		Prostate cancer (N=260)		Lung cancer (N=72)		Kidney cancer (N=37)		Other cancer type (N=69)		Total (N=875)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Non-persistent: Not enough injections	2	(0.5%)	3	(1.2%)	0	(0.0%)	1	(2.7%)	1	(1.4%)	7	(0.8%)
Non-persistent: Violation of time windows	133	(30.4%)	87	(33.5%)	27	(37.5%)	17	(45.9%)	26	(37.7%)	290	(33.1%)

	Breast cancer (N=437)		Prostate cancer (N=260)		Lung cancer (N=72)		Kidney cancer (N=37)		Other cancer type (N=69)		Total (N=875)	
Number of violated time windows	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Violation of 1 time window	104	(23.8%)	66	(25.4%)	22	(30.6%)	12	(32.4%)	20	(29.0%)	224	(25.6%)
Violation of 2 time windows	20	(4.6%)	15	(5.8%)	5	(6.9%)	5	(13.5%)	4	(5.8%)	49	(5.6%)
Violation of 3 time windows	8	(1.8%)	5	(1.9%)	0	(0.0%)	0	(0.0%)	2	(2.9%)	15	(1.7%)
Violation of more than 3 time windows	1	(0.2%)	1	(0.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.2%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 48 weeks if he received at least 12 injections without time window violation. A time window of +/- 14 days is allowed for each injection relative to the previous injection and of +10 weeks after 48 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included. I.e. more patients are excluded for sensitivity analyses compared to normal analyses.

15.3.4.2 Persistence at 48 weeks - sensitivity analysis - by cancer type for patients with previous antiresorptive treatment - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=33)			Prostate cancer (N=10)			Lung cancer (N=3)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	13	(39.4%)	[22.9%-57.9%]	6	(60.0%)	[26.2%-87.8%]	3	(100.0%)	[29.2%-100.0%]
Yes	20	(60.6%)	[42.1%-77.1%]	4	(40.0%)	[12.2%-73.8%]	0	(0.0%)	[0.0%-70.8%]

	Kidney cancer (N=4)			Other cancer type (N=2)			Total (N=52)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	3	(75.0%)	[19.4%-99.4%]	2	(100.0%)	[15.8%-100.0%]	27	(51.9%)	[37.6%-66.0%]
Yes	1	(25.0%)	[0.6%-80.6%]	0	(0.0%)	[0.0%-84.2%]	25	(48.1%)	[34.0%-62.4%]

	Breast cancer (N=33)		Prostate cancer (N=10)		Lung cancer (N=3)		Kidney cancer (N=4)		Other cancer type (N=2)		Total (N=52)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Persistent	20	(60.6%)	4	(40.0%)	0	(0.0%)	1	(25.0%)	0	(0.0%)	25	(48.1%)
Non-persistent: Prem. term. (adverse event)	1	(3.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(1.9%)
Non-persistent: Prem. term. (patient refuses to take medication)	1	(3.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(50.0%)	2	(3.8%)
Non-persistent: Prem. term. (physician`s decision)	2	(6.1%)	1	(10.0%)	1	(33.3%)	0	(0.0%)	0	(0.0%)	4	(7.7%)
Non-persistent: Prem. term. (other)	2	(6.1%)	1	(10.0%)	0	(0.0%)	0	(0.0%)	1	(50.0%)	4	(7.7%)
Non-persistent: Not enough injections	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Non-persistent: Violation of time windows	7	(21.2%)	4	(40.0%)	2	(66.7%)	3	(75.0%)	0	(0.0%)	16	(30.8%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 48 weeks if he received at least 12 injections without time window violation. A time window of +/- 14 days is allowed for each injection relative to the previous injection and of +10 weeks after 48 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included. I.e. more patients are excluded for sensitivity analyses compared to normal analyses.

15.3.4.2 Persistence at 48 weeks - sensitivity analysis - by cancer type for patients with previous antiresorptive treatment - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=33)		Prostate cancer (N=10)		Lung cancer (N=3)		Kidney cancer (N=4)		Other cancer type (N=2)		Total (N=52)	
Number of violated time windows	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Violation of 1 time window	5	(15.2%)	4	(40.0%)	2	(66.7%)	2	(50.0%)	0	(0.0%)	13	(25.0%)
Violation of 2 time windows	2	(6.1%)	0	(0.0%)	0	(0.0%)	1	(25.0%)	0	(0.0%)	3	(5.8%)
Violation of 3 time windows	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Violation of more than 3 time windows	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 48 weeks if he received at least 12 injections without time window violation. A time window of +/- 14 days is allowed for each injection relative to the previous injection and of +10 weeks after 48 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included. I.e. more patients are excluded for sensitivity analyses compared to normal analyses.

15.3.4.3 Persistence at 48 weeks - sensitivity analysis - by cancer type for patients without previous antiresorptive treatment - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=404)			Prostate cancer (N=250)			Lung cancer (N=69)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	159	(39.4%)	[34.6%-44.3%]	107	(42.8%)	[36.6%-49.2%]	36	(52.2%)	[39.8%-64.4%]
Yes	245	(60.6%)	[55.7%-65.4%]	143	(57.2%)	[50.8%-63.4%]	33	(47.8%)	[35.6%-60.2%]

	Kidney cancer (N=33)			Other cancer type (N=67)			Total (N=823)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	18	(54.5%)	[36.4%-71.9%]	40	(59.7%)	[47.0%-71.5%]	360	(43.7%)	[40.3%-47.2%]
Yes	15	(45.5%)	[28.1%-63.6%]	27	(40.3%)	[28.5%-53.0%]	463	(56.3%)	[52.8%-59.7%]

	Breast cancer (N=404)		Prostate cancer (N=250)		Lung cancer (N=69)		Kidney cancer (N=33)		Other cancer type (N=67)		Total (N=823)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Persistent	245	(60.6%)	143	(57.2%)	33	(47.8%)	15	(45.5%)	27	(40.3%)	463	(56.3%)
Non-persistent: Prem. term. (adverse event)	3	(0.7%)	3	(1.2%)	1	(1.4%)	0	(0.0%)	0	(0.0%)	7	(0.9%)
Non-persistent: Prem. term. (patient refuses to take medication)	14	(3.5%)	13	(5.2%)	3	(4.3%)	2	(6.1%)	9	(13.4%)	41	(5.0%)
Non-persistent: Prem. term. (physician`s decision)	9	(2.2%)	4	(1.6%)	4	(5.8%)	1	(3.0%)	1	(1.5%)	19	(2.3%)
Non-persistent: Prem. term. (other)	5	(1.2%)	1	(0.4%)	3	(4.3%)	0	(0.0%)	3	(4.5%)	12	(1.5%)
Non-persistent: Not enough injections	2	(0.5%)	3	(1.2%)	0	(0.0%)	1	(3.0%)	1	(1.5%)	7	(0.9%)
Non-persistent: Violation of time windows	126	(31.2%)	83	(33.2%)	25	(36.2%)	14	(42.4%)	26	(38.8%)	274	(33.3%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 48 weeks if he received at least 12 injections without time window violation. A time window of +/- 14 days is allowed for each injection relative to the previous injection and of +10 weeks after 48 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included. I.e. more patients are excluded for sensitivity analyses compared to normal analyses.

15.3.4.3 Persistence at 48 weeks - sensitivity analysis - by cancer type for patients without previous antiresorptive treatment - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=404)		Prostate cancer (N=250)		Lung cancer (N=69)		Kidney cancer (N=33)		Other cancer type (N=67)		Total (N=823)	
Number of violated time windows	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Violation of 1 time window	99	(24.5%)	62	(24.8%)	20	(29.0%)	10	(30.3%)	20	(29.9%)	211	(25.6%)
Violation of 2 time windows	18	(4.5%)	15	(6.0%)	5	(7.2%)	4	(12.1%)	4	(6.0%)	46	(5.6%)
Violation of 3 time windows	8	(2.0%)	5	(2.0%)	0	(0.0%)	0	(0.0%)	2	(3.0%)	15	(1.8%)
Violation of more than 3 time windows	1	(0.2%)	1	(0.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.2%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 48 weeks if he received at least 12 injections without time window violation. A time window of +/- 14 days is allowed for each injection relative to the previous injection and of +10 weeks after 48 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included. I.e. more patients are excluded for sensitivity analyses compared to normal analyses.

15.3.4.4 Persistence at 48 weeks - sensitivity analysis - by cancer type for patients who underwent previous surgery - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=73)			Prostate cancer (N=18)			Lung cancer (N=14)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	38	(52.1%)	[40.0%-63.9%]	8	(44.4%)	[21.5%-69.2%]	8	(57.1%)	[28.9%-82.3%]
Yes	35	(47.9%)	[36.1%-60.0%]	10	(55.6%)	[30.8%-78.5%]	6	(42.9%)	[17.7%-71.1%]

	Kidney cancer (N=12)			Other cancer type (N=20)			Total (N=137)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	7	(58.3%)	[27.7%-84.8%]	11	(55.0%)	[31.5%-76.9%]	72	(52.6%)	[43.9%-61.1%]
Yes	5	(41.7%)	[15.2%-72.3%]	9	(45.0%)	[23.1%-68.5%]	65	(47.4%)	[38.9%-56.1%]

	Breast cancer (N=73)		Prostate cancer (N=18)		Lung cancer (N=14)		Kidney cancer (N=12)		Other cancer type (N=20)		Total (N=137)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Persistent	35	(47.9%)	10	(55.6%)	6	(42.9%)	5	(41.7%)	9	(45.0%)	65	(47.4%)
Non-persistent: Prem. term. (adverse event)	0	(0.0%)	1	(5.6%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.7%)
Non-persistent: Prem. term. (patient refuses to take medication)	4	(5.5%)	2	(11.1%)	0	(0.0%)	1	(8.3%)	2	(10.0%)	9	(6.6%)
Non-persistent: Prem. term. (physician`s decision)	3	(4.1%)	0	(0.0%)	1	(7.1%)	1	(8.3%)	1	(5.0%)	6	(4.4%)
Non-persistent: Prem. term. (other)	2	(2.7%)	0	(0.0%)	1	(7.1%)	0	(0.0%)	2	(10.0%)	5	(3.6%)
Non-persistent: Not enough injections	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(8.3%)	1	(5.0%)	2	(1.5%)
Non-persistent: Violation of time windows	29	(39.7%)	5	(27.8%)	6	(42.9%)	4	(33.3%)	5	(25.0%)	49	(35.8%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 48 weeks if he received at least 12 injections without time window violation. A time window of +/- 14 days is allowed for each injection relative to the previous injection and of +10 weeks after 48 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included. I.e. more patients are excluded for sensitivity analyses compared to normal analyses.

15.3.4.4 Persistence at 48 weeks - sensitivity analysis - by cancer type for patients who underwent previous surgery - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=73)		Prostate cancer (N=18)		Lung cancer (N=14)		Kidney cancer (N=12)		Other cancer type (N=20)		Total (N=137)	
Number of violated time windows	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Violation of 1 time window	24	(32.9%)	4	(22.2%)	5	(35.7%)	2	(16.7%)	5	(25.0%)	40	(29.2%)
Violation of 2 time windows	5	(6.8%)	0	(0.0%)	1	(7.1%)	2	(16.7%)	0	(0.0%)	8	(5.8%)
Violation of 3 time windows	0	(0.0%)	1	(5.6%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.7%)
Violation of more than 3 time windows	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 48 weeks if he received at least 12 injections without time window violation. A time window of +/- 14 days is allowed for each injection relative to the previous injection and of +10 weeks after 48 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included. I.e. more patients are excluded for sensitivity analyses compared to normal analyses.

15.3.4.5 Persistence at 48 weeks - sensitivity analysis - by cancer type for patients who did not undergo previous surgery - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=364)			Prostate cancer (N=242)			Lung cancer (N=58)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	134	(36.8%)	[31.8%-42.0%]	105	(43.4%)	[37.1%-49.9%]	31	(53.4%)	[39.9%-66.7%]
Yes	230	(63.2%)	[58.0%-68.2%]	137	(56.6%)	[50.1%-62.9%]	27	(46.6%)	[33.3%-60.1%]

	Kidney cancer (N=25)			Other cancer type (N=49)			Total (N=738)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	14	(56.0%)	[34.9%-75.6%]	31	(63.3%)	[48.3%-76.6%]	315	(42.7%)	[39.1%-46.3%]
Yes	11	(44.0%)	[24.4%-65.1%]	18	(36.7%)	[23.4%-51.7%]	423	(57.3%)	[53.7%-60.9%]

	Breast cancer (N=364)		Prostate cancer (N=242)		Lung cancer (N=58)		Kidney cancer (N=25)		Other cancer type (N=49)		Total (N=738)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Persistent	230	(63.2%)	137	(56.6%)	27	(46.6%)	11	(44.0%)	18	(36.7%)	423	(57.3%)
Non-persistent: Prem. term. (adverse event)	4	(1.1%)	2	(0.8%)	1	(1.7%)	0	(0.0%)	0	(0.0%)	7	(0.9%)
Non-persistent: Prem. term. (patient refuses to take medication)	11	(3.0%)	11	(4.5%)	3	(5.2%)	1	(4.0%)	8	(16.3%)	34	(4.6%)
Non-persistent: Prem. term. (physician`s decision)	8	(2.2%)	5	(2.1%)	4	(6.9%)	0	(0.0%)	0	(0.0%)	17	(2.3%)
Non-persistent: Prem. term. (other)	5	(1.4%)	2	(0.8%)	2	(3.4%)	0	(0.0%)	2	(4.1%)	11	(1.5%)
Non-persistent: Not enough injections	2	(0.5%)	3	(1.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	5	(0.7%)
Non-persistent: Violation of time windows	104	(28.6%)	82	(33.9%)	21	(36.2%)	13	(52.0%)	21	(42.9%)	241	(32.7%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 48 weeks if he received at least 12 injections without time window violation. A time window of +/- 14 days is allowed for each injection relative to the previous injection and of +10 weeks after 48 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included. I.e. more patients are excluded for sensitivity analyses compared to normal analyses.

15.3.4.5 Persistence at 48 weeks - sensitivity analysis - by cancer type for patients who did not undergo previous surgery - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=364)		Prostate cancer (N=242)		Lung cancer (N=58)		Kidney cancer (N=25)		Other cancer type (N=49)		Total (N=738)	
Number of violated time windows	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Violation of 1 time window	80	(22.0%)	62	(25.6%)	17	(29.3%)	10	(40.0%)	15	(30.6%)	184	(24.9%)
Violation of 2 time windows	15	(4.1%)	15	(6.2%)	4	(6.9%)	3	(12.0%)	4	(8.2%)	41	(5.6%)
Violation of 3 time windows	8	(2.2%)	4	(1.7%)	0	(0.0%)	0	(0.0%)	2	(4.1%)	14	(1.9%)
Violation of more than 3 time windows	1	(0.3%)	1	(0.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.3%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 48 weeks if he received at least 12 injections without time window violation. A time window of +/- 14 days is allowed for each injection relative to the previous injection and of +10 weeks after 48 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included. I.e. more patients are excluded for sensitivity analyses compared to normal analyses.

15.3.4.6 Persistence at 48 weeks - sensitivity analysis - by cancer type for patients who underwent previous chemotherapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=148)			Prostate cancer (N=54)			Lung cancer (N=55)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	66	(44.6%)	[36.4%-53.0%]	32	(59.3%)	[45.0%-72.4%]	29	(52.7%)	[38.8%-66.3%]
Yes	82	(55.4%)	[47.0%-63.6%]	22	(40.7%)	[27.6%-55.0%]	26	(47.3%)	[33.7%-61.2%]

	Kidney cancer (N=25)			Other cancer type (N=38)			Total (N=320)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	15	(60.0%)	[38.7%-78.9%]	26	(68.4%)	[51.3%-82.5%]	168	(52.5%)	[46.9%-58.1%]
Yes	10	(40.0%)	[21.1%-61.3%]	12	(31.6%)	[17.5%-48.7%]	152	(47.5%)	[41.9%-53.1%]

	Breast cancer (N=148)		Prostate cancer (N=54)		Lung cancer (N=55)		Kidney cancer (N=25)		Other cancer type (N=38)		Total (N=320)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Persistent	82	(55.4%)	22	(40.7%)	26	(47.3%)	10	(40.0%)	12	(31.6%)	152	(47.5%)
Non-persistent: Prem. term. (adverse event)	0	(0.0%)	2	(3.7%)	1	(1.8%)	0	(0.0%)	0	(0.0%)	3	(0.9%)
Non-persistent: Prem. term. (patient refuses to take medication)	4	(2.7%)	5	(9.3%)	2	(3.6%)	2	(8.0%)	6	(15.8%)	19	(5.9%)
Non-persistent: Prem. term. (physician`s decision)	4	(2.7%)	1	(1.9%)	4	(7.3%)	1	(4.0%)	1	(2.6%)	11	(3.4%)
Non-persistent: Prem. term. (other)	2	(1.4%)	1	(1.9%)	3	(5.5%)	0	(0.0%)	3	(7.9%)	9	(2.8%)
Non-persistent: Not enough injections	1	(0.7%)	0	(0.0%)	0	(0.0%)	1	(4.0%)	1	(2.6%)	3	(0.9%)
Non-persistent: Violation of time windows	55	(37.2%)	23	(42.6%)	19	(34.5%)	11	(44.0%)	15	(39.5%)	123	(38.4%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 48 weeks if he received at least 12 injections without time window violation. A time window of +/- 14 days is allowed for each injection relative to the previous injection and of +10 weeks after 48 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included. I.e. more patients are excluded for sensitivity analyses compared to normal analyses.

15.3.4.6 Persistence at 48 weeks - sensitivity analysis - by cancer type for patients who underwent previous chemotherapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=148)		Prostate cancer (N=54)		Lung cancer (N=55)		Kidney cancer (N=25)		Other cancer type (N=38)		Total (N=320)	
Number of violated time windows	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Violation of 1 time window	41	(27.7%)	20	(37.0%)	17	(30.9%)	10	(40.0%)	14	(36.8%)	102	(31.9%)
Violation of 2 time windows	10	(6.8%)	1	(1.9%)	2	(3.6%)	1	(4.0%)	1	(2.6%)	15	(4.7%)
Violation of 3 time windows	3	(2.0%)	2	(3.7%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	5	(1.6%)
Violation of more than 3 time windows	1	(0.7%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.3%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 48 weeks if he received at least 12 injections without time window violation. A time window of +/- 14 days is allowed for each injection relative to the previous injection and of +10 weeks after 48 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included. I.e. more patients are excluded for sensitivity analyses compared to normal analyses.

15.3.4.7 Persistence at 48 weeks - sensitivity analysis - by cancer type for patients who did not undergo previous chemotherapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=289)			Prostate cancer (N=206)			Lung cancer (N=17)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	106	(36.7%)	[31.1%-42.5%]	81	(39.3%)	[32.6%-46.3%]	10	(58.8%)	[32.9%-81.6%]
Yes	183	(63.3%)	[57.5%-68.9%]	125	(60.7%)	[53.7%-67.4%]	7	(41.2%)	[18.4%-67.1%]

	Kidney cancer (N=12)			Other cancer type (N=31)			Total (N=555)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	6	(50.0%)	[21.1%-78.9%]	16	(51.6%)	[33.1%-69.8%]	219	(39.5%)	[35.4%-43.7%]
Yes	6	(50.0%)	[21.1%-78.9%]	15	(48.4%)	[30.2%-66.9%]	336	(60.5%)	[56.3%-64.6%]

	Breast cancer (N=289)		Prostate cancer (N=206)		Lung cancer (N=17)		Kidney cancer (N=12)		Other cancer type (N=31)		Total (N=555)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Persistent	183	(63.3%)	125	(60.7%)	7	(41.2%)	6	(50.0%)	15	(48.4%)	336	(60.5%)
Non-persistent: Prem. term. (adverse event)	4	(1.4%)	1	(0.5%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	5	(0.9%)
Non-persistent: Prem. term. (patient refuses to take medication)	11	(3.8%)	8	(3.9%)	1	(5.9%)	0	(0.0%)	4	(12.9%)	24	(4.3%)
Non-persistent: Prem. term. (physician`s decision)	7	(2.4%)	4	(1.9%)	1	(5.9%)	0	(0.0%)	0	(0.0%)	12	(2.2%)
Non-persistent: Prem. term. (other)	5	(1.7%)	1	(0.5%)	0	(0.0%)	0	(0.0%)	1	(3.2%)	7	(1.3%)
Non-persistent: Not enough injections	1	(0.3%)	3	(1.5%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	4	(0.7%)
Non-persistent: Violation of time windows	78	(27.0%)	64	(31.1%)	8	(47.1%)	6	(50.0%)	11	(35.5%)	167	(30.1%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 48 weeks if he received at least 12 injections without time window violation. A time window of +/- 14 days is allowed for each injection relative to the previous injection and of +10 weeks after 48 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included. I.e. more patients are excluded for sensitivity analyses compared to normal analyses.

15.3.4.7 Persistence at 48 weeks - sensitivity analysis - by cancer type for patients who did not undergo previous chemotherapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=289)		Prostate cancer (N=206)		Lung cancer (N=17)		Kidney cancer (N=12)		Other cancer type (N=31)		Total (N=555)	
Number of violated time windows	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Violation of 1 time window	63	(21.8%)	46	(22.3%)	5	(29.4%)	2	(16.7%)	6	(19.4%)	122	(22.0%)
Violation of 2 time windows	10	(3.5%)	14	(6.8%)	3	(17.6%)	4	(33.3%)	3	(9.7%)	34	(6.1%)
Violation of 3 time windows	5	(1.7%)	3	(1.5%)	0	(0.0%)	0	(0.0%)	2	(6.5%)	10	(1.8%)
Violation of more than 3 time windows	0	(0.0%)	1	(0.5%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.2%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 48 weeks if he received at least 12 injections without time window violation. A time window of +/- 14 days is allowed for each injection relative to the previous injection and of +10 weeks after 48 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included. I.e. more patients are excluded for sensitivity analyses compared to normal analyses.

15.3.4.8 Persistence at 48 weeks - sensitivity analysis - by cancer type for patients who underwent previous radiotherapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=125)			Prostate cancer (N=29)			Lung cancer (N=24)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	48	(38.4%)	[29.8%-47.5%]	15	(51.7%)	[32.5%-70.6%]	11	(45.8%)	[25.6%-67.2%]
Yes	77	(61.6%)	[52.5%-70.2%]	14	(48.3%)	[29.4%-67.5%]	13	(54.2%)	[32.8%-74.4%]

	Kidney cancer (N=15)			Other cancer type (N=25)			Total (N=218)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	7	(46.7%)	[21.3%-73.4%]	15	(60.0%)	[38.7%-78.9%]	96	(44.0%)	[37.3%-50.9%]
Yes	8	(53.3%)	[26.6%-78.7%]	10	(40.0%)	[21.1%-61.3%]	122	(56.0%)	[49.1%-62.7%]

	Breast cancer (N=125)		Prostate cancer (N=29)		Lung cancer (N=24)		Kidney cancer (N=15)		Other cancer type (N=25)		Total (N=218)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Persistent	77	(61.6%)	14	(48.3%)	13	(54.2%)	8	(53.3%)	10	(40.0%)	122	(56.0%)
Non-persistent: Prem. term. (adverse event)	2	(1.6%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.9%)
Non-persistent: Prem. term. (patient refuses to take medication)	4	(3.2%)	1	(3.4%)	0	(0.0%)	1	(6.7%)	4	(16.0%)	10	(4.6%)
Non-persistent: Prem. term. (physician`s decision)	2	(1.6%)	0	(0.0%)	1	(4.2%)	0	(0.0%)	0	(0.0%)	3	(1.4%)
Non-persistent: Prem. term. (other)	2	(1.6%)	1	(3.4%)	1	(4.2%)	0	(0.0%)	1	(4.0%)	5	(2.3%)
Non-persistent: Not enough injections	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Non-persistent: Violation of time windows	38	(30.4%)	13	(44.8%)	9	(37.5%)	6	(40.0%)	10	(40.0%)	76	(34.9%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 48 weeks if he received at least 12 injections without time window violation. A time window of +/- 14 days is allowed for each injection relative to the previous injection and of +10 weeks after 48 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included. I.e. more patients are excluded for sensitivity analyses compared to normal analyses.

15.3.4.8 Persistence at 48 weeks - sensitivity analysis - by cancer type for patients who underwent previous radiotherapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=125)		Prostate cancer (N=29)		Lung cancer (N=24)		Kidney cancer (N=15)		Other cancer type (N=25)		Total (N=218)	
Number of violated time windows	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Violation of 1 time window	29	(23.2%)	9	(31.0%)	7	(29.2%)	4	(26.7%)	6	(24.0%)	55	(25.2%)
Violation of 2 time windows	6	(4.8%)	2	(6.9%)	2	(8.3%)	2	(13.3%)	3	(12.0%)	15	(6.9%)
Violation of 3 time windows	3	(2.4%)	2	(6.9%)	0	(0.0%)	0	(0.0%)	1	(4.0%)	6	(2.8%)
Violation of more than 3 time windows	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 48 weeks if he received at least 12 injections without time window violation. A time window of +/- 14 days is allowed for each injection relative to the previous injection and of +10 weeks after 48 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included. I.e. more patients are excluded for sensitivity analyses compared to normal analyses.

15.3.4.9 Persistence at 48 weeks - sensitivity analysis - by cancer type for patients who did not undergo previous radiotherapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=312)			Prostate cancer (N=231)			Lung cancer (N=48)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	124	(39.7%)	[34.3%-45.4%]	98	(42.4%)	[36.0%-49.1%]	28	(58.3%)	[43.2%-72.4%]
Yes	188	(60.3%)	[54.6%-65.7%]	133	(57.6%)	[50.9%-64.0%]	20	(41.7%)	[27.6%-56.8%]

	Kidney cancer (N=22)			Other cancer type (N=44)			Total (N=657)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	14	(63.6%)	[40.7%-82.8%]	27	(61.4%)	[45.5%-75.6%]	291	(44.3%)	[40.5%-48.2%]
Yes	8	(36.4%)	[17.2%-59.3%]	17	(38.6%)	[24.4%-54.5%]	366	(55.7%)	[51.8%-59.5%]

	Breast cancer (N=312)		Prostate cancer (N=231)		Lung cancer (N=48)		Kidney cancer (N=22)		Other cancer type (N=44)		Total (N=657)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Persistent	188	(60.3%)	133	(57.6%)	20	(41.7%)	8	(36.4%)	17	(38.6%)	366	(55.7%)
Non-persistent: Prem. term. (adverse event)	2	(0.6%)	3	(1.3%)	1	(2.1%)	0	(0.0%)	0	(0.0%)	6	(0.9%)
Non-persistent: Prem. term. (patient refuses to take medication)	11	(3.5%)	12	(5.2%)	3	(6.3%)	1	(4.5%)	6	(13.6%)	33	(5.0%)
Non-persistent: Prem. term. (physician`s decision)	9	(2.9%)	5	(2.2%)	4	(8.3%)	1	(4.5%)	1	(2.3%)	20	(3.0%)
Non-persistent: Prem. term. (other)	5	(1.6%)	1	(0.4%)	2	(4.2%)	0	(0.0%)	3	(6.8%)	11	(1.7%)
Non-persistent: Not enough injections	2	(0.6%)	3	(1.3%)	0	(0.0%)	1	(4.5%)	1	(2.3%)	7	(1.1%)
Non-persistent: Violation of time windows	95	(30.4%)	74	(32.0%)	18	(37.5%)	11	(50.0%)	16	(36.4%)	214	(32.6%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 48 weeks if he received at least 12 injections without time window violation. A time window of +/- 14 days is allowed for each injection relative to the previous injection and of +10 weeks after 48 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included. I.e. more patients are excluded for sensitivity analyses compared to normal analyses.

15.3.4.9 Persistence at 48 weeks - sensitivity analysis - by cancer type for patients who did not undergo previous radiotherapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=312)		Prostate cancer (N=231)		Lung cancer (N=48)		Kidney cancer (N=22)		Other cancer type (N=44)		Total (N=657)	
Number of violated time windows	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Violation of 1 time window	75	(24.0%)	57	(24.7%)	15	(31.3%)	8	(36.4%)	14	(31.8%)	169	(25.7%)
Violation of 2 time windows	14	(4.5%)	13	(5.6%)	3	(6.3%)	3	(13.6%)	1	(2.3%)	34	(5.2%)
Violation of 3 time windows	5	(1.6%)	3	(1.3%)	0	(0.0%)	0	(0.0%)	1	(2.3%)	9	(1.4%)
Violation of more than 3 time windows	1	(0.3%)	1	(0.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.3%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 48 weeks if he received at least 12 injections without time window violation. A time window of +/- 14 days is allowed for each injection relative to the previous injection and of +10 weeks after 48 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included. I.e. more patients are excluded for sensitivity analyses compared to normal analyses.

15.3.4.10 Persistence at 48 weeks - sensitivity analysis - by cancer type for patients who underwent previous antihormonal therapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=195)			Prostate cancer (N=167)			Kidney cancer (N=1)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	74	(37.9%)	[31.1%-45.2%]	64	(38.3%)	[30.9%-46.2%]	1	(100.0%)	[2.5%-100.0%]
Yes	121	(62.1%)	[54.8%-68.9%]	103	(61.7%)	[53.8%-69.1%]	0	(0.0%)	[0.0%-97.5%]

	Other cancer type (N=4)			Total (N=367)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	1	(25.0%)	[0.6%-80.6%]	140	(38.1%)	[33.2%-43.3%]
Yes	3	(75.0%)	[19.4%-99.4%]	227	(61.9%)	[56.7%-66.8%]

	Breast cancer (N=195)		Prostate cancer (N=167)		Kidney cancer (N=1)		Other cancer type (N=4)		Total (N=367)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Persistent	121	(62.1%)	103	(61.7%)	0	(0.0%)	3	(75.0%)	227	(61.9%)
Non-persistent: Prem. term. (adverse event)	3	(1.5%)	1	(0.6%)	0	(0.0%)	0	(0.0%)	4	(1.1%)
Non-persistent: Prem. term. (patient refuses to take medication)	8	(4.1%)	10	(6.0%)	0	(0.0%)	1	(25.0%)	19	(5.2%)
Non-persistent: Prem. term. (physician`s decision)	6	(3.1%)	4	(2.4%)	0	(0.0%)	0	(0.0%)	10	(2.7%)
Non-persistent: Prem. term. (other)	4	(2.1%)	1	(0.6%)	0	(0.0%)	0	(0.0%)	5	(1.4%)
Non-persistent: Not enough injections	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Non-persistent: Violation of time windows	53	(27.2%)	48	(28.7%)	1	(100.0%)	0	(0.0%)	102	(27.8%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 48 weeks if he received at least 12 injections without time window violation. A time window of +/- 14 days is allowed for each injection relative to the previous injection and of +10 weeks after 48 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included. I.e. more patients are excluded for sensitivity analyses compared to normal analyses.

15.3.4.10 Persistence at 48 weeks - sensitivity analysis - by cancer type for patients who underwent previous antihormonal therapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=195)		Prostate cancer (N=167)		Kidney cancer (N=1)		Other cancer type (N=4)		Total (N=367)	
Number of violated time windows	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Violation of 1 time window	43	(22.1%)	32	(19.2%)	0	(0.0%)	0	(0.0%)	75	(20.4%)
Violation of 2 time windows	7	(3.6%)	13	(7.8%)	1	(100.0%)	0	(0.0%)	21	(5.7%)
Violation of 3 time windows	3	(1.5%)	2	(1.2%)	0	(0.0%)	0	(0.0%)	5	(1.4%)
Violation of more than 3 time windows	0	(0.0%)	1	(0.6%)	0	(0.0%)	0	(0.0%)	1	(0.3%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 48 weeks if he received at least 12 injections without time window violation. A time window of +/- 14 days is allowed for each injection relative to the previous injection and of +10 weeks after 48 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included. I.e. more patients are excluded for sensitivity analyses compared to normal analyses.

15.3.4.11 Persistence at 48 weeks - sensitivity analysis - by cancer type for patients who did not undergo previous antihormonal therapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=242)			Prostate cancer (N=93)			Lung cancer (N=72)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	98	(40.5%)	[34.3%-47.0%]	49	(52.7%)	[42.1%-63.1%]	39	(54.2%)	[42.0%-66.0%]
Yes	144	(59.5%)	[53.0%-65.7%]	44	(47.3%)	[36.9%-57.9%]	33	(45.8%)	[34.0%-58.0%]

	Kidney cancer (N=36)			Other cancer type (N=65)			Total (N=508)		
Persistence	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**	**n**	**(%)**	**CI**
No	20	(55.6%)	[38.1%-72.1%]	41	(63.1%)	[50.2%-74.7%]	247	(48.6%)	[44.2%-53.1%]
Yes	16	(44.4%)	[27.9%-61.9%]	24	(36.9%)	[25.3%-49.8%]	261	(51.4%)	[46.9%-55.8%]

	Breast cancer (N=242)		Prostate cancer (N=93)		Lung cancer (N=72)		Kidney cancer (N=36)		Other cancer type (N=65)		Total (N=508)	
Persistence	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Persistent	144	(59.5%)	44	(47.3%)	33	(45.8%)	16	(44.4%)	24	(36.9%)	261	(51.4%)
Non-persistent: Prem. term. (adverse event)	1	(0.4%)	2	(2.2%)	1	(1.4%)	0	(0.0%)	0	(0.0%)	4	(0.8%)
Non-persistent: Prem. term. (patient refuses to take medication)	7	(2.9%)	3	(3.2%)	3	(4.2%)	2	(5.6%)	9	(13.8%)	24	(4.7%)
Non-persistent: Prem. term. (physician`s decision)	5	(2.1%)	1	(1.1%)	5	(6.9%)	1	(2.8%)	1	(1.5%)	13	(2.6%)
Non-persistent: Prem. term. (other)	3	(1.2%)	1	(1.1%)	3	(4.2%)	0	(0.0%)	4	(6.2%)	11	(2.2%)
Non-persistent: Not enough injections	2	(0.8%)	3	(3.2%)	0	(0.0%)	1	(2.8%)	1	(1.5%)	7	(1.4%)
Non-persistent: Violation of time windows	80	(33.1%)	39	(41.9%)	27	(37.5%)	16	(44.4%)	26	(40.0%)	188	(37.0%)

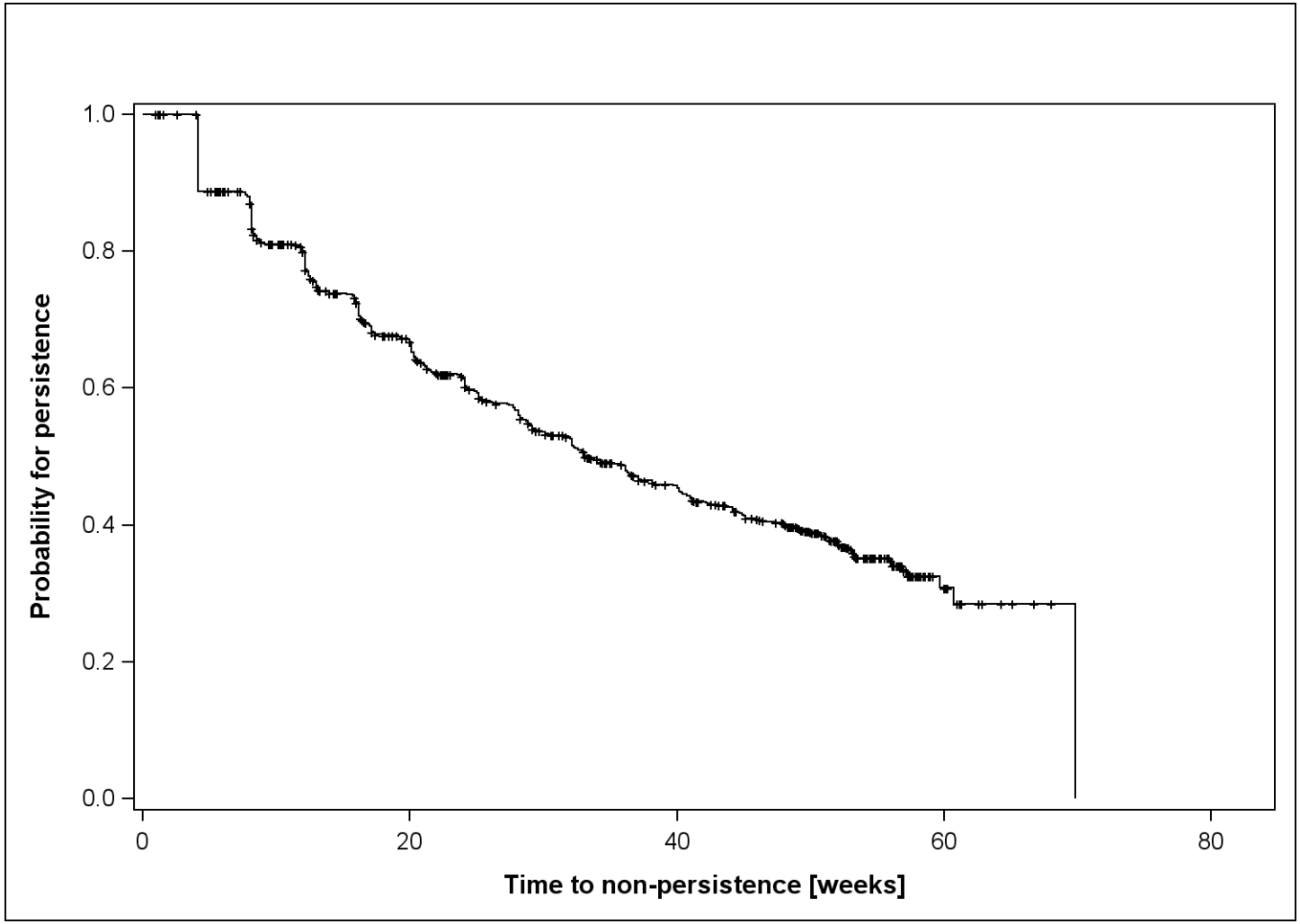
Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 48 weeks if he received at least 12 injections without time window violation. A time window of +/- 14 days is allowed for each injection relative to the previous injection and of +10 weeks after 48 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included. I.e. more patients are excluded for sensitivity analyses compared to normal analyses.

15.3.4.11 Persistence at 48 weeks - sensitivity analysis - by cancer type for patients who did not undergo previous antihormonal therapy - FAS, excluding subjects who died, withdrew consent or lost to follow-up before persistence assessment

	Breast cancer (N=242)		Prostate cancer (N=93)		Lung cancer (N=72)		Kidney cancer (N=36)		Other cancer type (N=65)		Total (N=508)	
Number of violated time windows	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Violation of 1 time window	61	(25.2%)	34	(36.6%)	22	(30.6%)	12	(33.3%)	20	(30.8%)	149	(29.3%)
Violation of 2 time windows	13	(5.4%)	2	(2.2%)	5	(6.9%)	4	(11.1%)	4	(6.2%)	28	(5.5%)
Violation of 3 time windows	5	(2.1%)	3	(3.2%)	0	(0.0%)	0	(0.0%)	2	(3.1%)	10	(2.0%)
Violation of more than 3 time windows	1	(0.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.2%)

Perm. term.: Premature termination
CI: Exact 2-sided Clopper-Pearson 95%-confidence interval
Subject is considered as persistence at 48 weeks if he received at least 12 injections without time window violation. A time window of +/- 14 days is allowed for each injection relative to the previous injection and of +10 weeks after 48 weeks endpoint. Subjects who died, withdrew consent or who were lost to follow-up after being non-persistent were included. I.e. more patients are excluded for sensitivity analyses compared to normal analyses.

15.3.5.1.1 Time to non-persistence [weeks] - overall analysis Kaplan-Meier curve - FAS



15.3.5.1.2 Time to non-persistence [weeks] - overall analysis Kaplan-Meier estimates - FAS

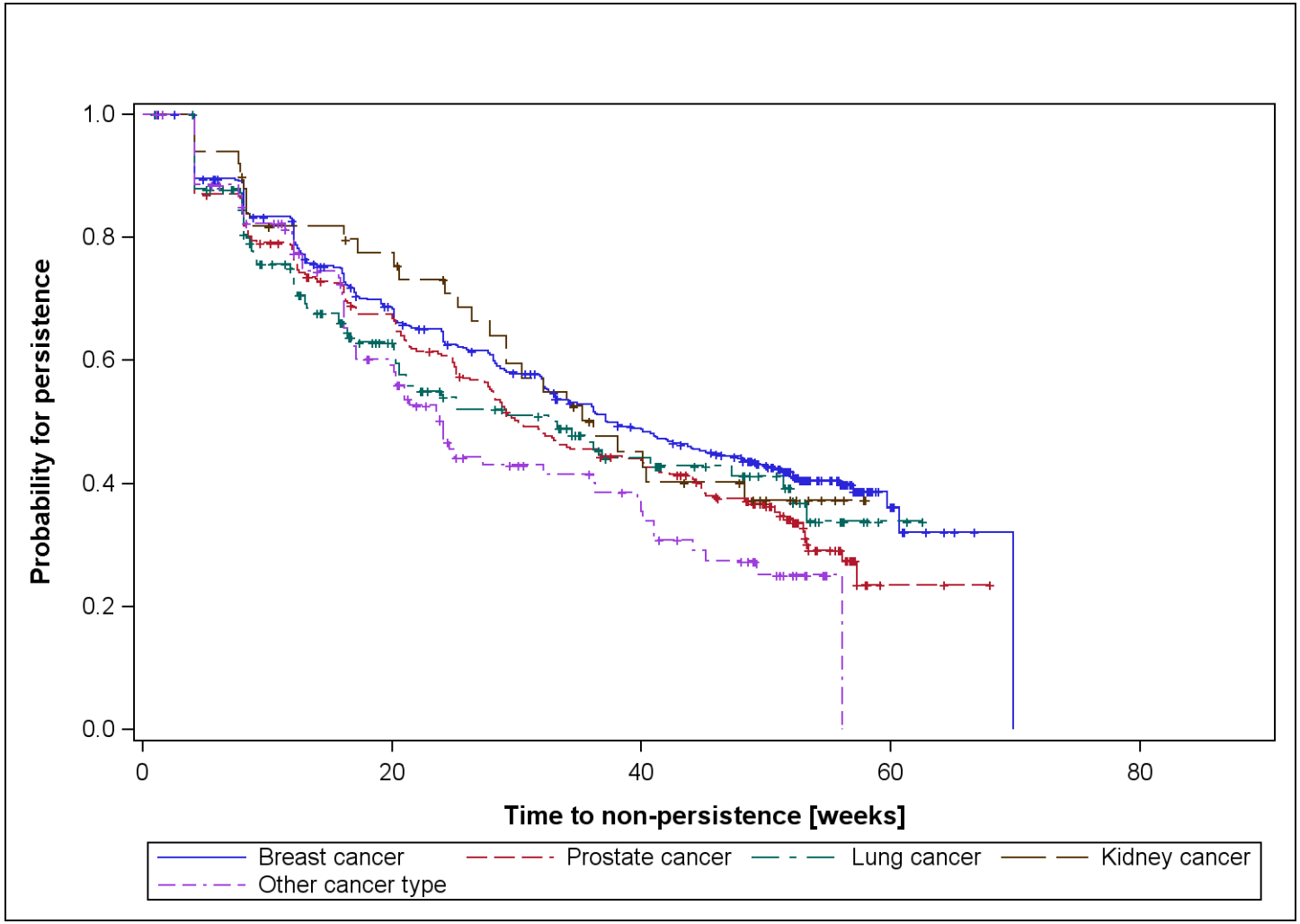
	Kaplan-Meier Quartiles [weeks]			
			95% CI	
	Quartile	Point Estimate	Lower Limit	Upper Limit
Overall (N=1128)	1st Quartile	13.00	12.14	16.14
	Median	33.29	31.71	37.14
	3rd Quartile	69.86	60.71	69.86

Probability for persistence at 24 weeks [%]
61.4

15.3.5.1.2 Time to non-persistence [weeks] - overall analysis Kaplan-Meier estimates - FAS

Weeks	Number of patients at risk
0.00	1128
4.00	1122
8.00	973
12.00	870
16.00	769
20.00	686
24.00	615
28.00	558
32.00	508
36.00	456
40.00	419
44.00	379
48.00	348
52.00	244
56.00	95
60.00	18
64.00	6
68.00	2
72.00	1

15.3.5.2.1 Time to non-persistence [weeks] - analysis by cancer type Kaplan-Meier curve - FAS



15.3.5.2.2 Time to non-persistence [weeks] - analysis by cancer type Kaplan-Meier estimates - FAS

	Kaplan-Meier Quartiles [weeks]			
			95% CI	
Cancer type	Quartile	Point Estimate	Lower Limit	Upper Limit
Breast cancer (N=509)	1st Quartile	15.86	12.29	17.00
	Median	37.29	33.14	44.14
	3rd Quartile	69.86	60.71	69.86
Kidney cancer (N=50)	1st Quartile	20.57	8.29	29.14
	Median	36.14	27.86	not estimable
	3rd Quartile	not estimable	48.29	not estimable
Lung cancer (N=159)	1st Quartile	11.86	8.14	13.29
	Median	33.29	20.57	51.43
	3rd Quartile	not estimable	53.29	not estimable
Other cancer type (N=116)	1st Quartile	12.86	8.14	16.14
	Median	24.14	19.86	36.14
	3rd Quartile	56.14	40.14	56.14
Prostate cancer (N=294)	1st Quartile	12.43	8.71	16.14
	Median	30.14	27.71	38.43
	3rd Quartile	57.29	53.29	not estimable

15.3.5.2.2 Time to non-persistence [weeks] - analysis by cancer type Kaplan-Meier estimates - FAS

Cancer type	Probability for persistence at 24 weeks [%]
Breast cancer (N=509)	64.7
Kidney cancer (N=50)	73.2
Lung cancer (N=159)	54.1
Other cancer type (N=116)	50.3
Prostate cancer (N=294)	60.8

15.3.5.2.2 Time to non-persistence [weeks] - analysis by cancer type Kaplan-Meier estimates - FAS

Cancer type	Weeks	Number of patients at risk
Breast cancer	0.00	509
	4.00	507
	8.00	448
	12.00	416
	16.00	369
	20.00	333
	24.00	313
	28.00	291
	32.00	270
	36.00	245
	40.00	225
	44.00	209
	48.00	197
	52.00	147
	56.00	63
	60.00	14
	64.00	4
	68.00	1
	72.00	1

15.3.5.2.2 Time to non-persistence [weeks] - analysis by cancer type Kaplan-Meier estimates - FAS

Cancer type	Weeks	Number of patients at risk
Prostate cancer	0.00	294
	4.00	293
	8.00	252
	12.00	227
	16.00	204
	20.00	189
	24.00	170
	28.00	153
	32.00	134
	36.00	125
	40.00	118
	44.00	108
	48.00	95
	52.00	62
	56.00	19
	60.00	2
	64.00	2
	68.00	1
	72.00	1

15.3.5.2.2 Time to non-persistence [weeks] - analysis by cancer type Kaplan-Meier estimates - FAS

Cancer type	Weeks	Number of patients at risk
Lung cancer	0.00	159
	4.00	158
	8.00	131
	12.00	104
	16.00	86
	20.00	72
	24.00	57
	28.00	53
	32.00	49
	36.00	38
	40.00	34
	44.00	29
	48.00	26
	52.00	18
	56.00	8
	60.00	2
	64.00	1
	68.00	1
	72.00	1

15.3.5.2.2 Time to non-persistence [weeks] - analysis by cancer type Kaplan-Meier estimates - FAS

Cancer type	Weeks	Number of patients at risk
Kidney cancer	0.00	50
	4.00	50
	8.00	45
	12.00	39
	16.00	39
	20.00	36
	24.00	33
	28.00	28
	32.00	25
	36.00	20
	40.00	18
	44.00	15
	48.00	14
	52.00	9
	56.00	4
	60.00	1
	64.00	1
	68.00	1
	72.00	1

15.3.5.2.2 Time to non-persistence [weeks] - analysis by cancer type Kaplan-Meier estimates - FAS

Cancer type	Weeks	Number of patients at risk
Other cancer type	0.00	116
	4.00	114
	8.00	97
	12.00	84
	16.00	71
	20.00	56
	24.00	42
	28.00	33
	32.00	30
	36.00	28
	40.00	24
	44.00	18
	48.00	16
	52.00	8
	56.00	1
	60.00	1
	64.00	1
	68.00	1
	72.00	1

15.3.6 Time to non-persistence [days] - analysis using a proportional hazards model - FAS

Summary of Event and Censored Observations			
N total	N event	N censored	Percent censored
1099	640	459	41.77

Type 3 Analysis			
Variable	Degrees of freedom	Wald Statistic	p-value for Wald test
Age	1	1.5646	0.2110
Gender	1	0.7140	0.3981
	4	4.4052	0.3539
Visceral metastases	1	11.6528	0.0006
Previous antineoplastic therapy	1	0.0008	0.9779
SREs and/or tumor induced hypercalcemias	1	1.8097	0.1785
ECOG score	2	6.5376	0.0381
Previous antiresorptive therapy	1	1.5638	0.2111

Hazard Ratio Estimates		
Variable	Hazard Ratio*	95% CI for Hazard Ratio
Age: Unit=1 y	1.005	[0.997, 1.013]
Gender: Male vs Female	1.137	[0.844, 1.532]

Patients with missing information on previous SREs and/or tumor induced hypercalcemias or missing ECOG status were deleted from analysis.
The explanatory variable 'previous antineoplastic therapy' contains information on previous surgery, previous chemotherapy, previous radiotherapy and previous antihormonal therapy. If a patient had at least one of these four therapies, the explanatory variable 'previous antineoplastic therapy' is defined as 'yes'.
Explanatory variable 'Bone metastases yes/no' was not included in the model because reference category 'no' does not exist.
The number of events for 'time to non-persistence' differs from the number of 'persistence at 48 weeks' because for 'persistence at 48 weeks' subjects who died, withdrew consent or lost to follow-up before persistence assessment are excluded.
* Hazard Ratios are adjusted for all covariates in the model.

15.3.6 Time to non-persistence [days] - analysis using a proportional hazards model - FAS

Hazard Ratio Estimates		
Variable	**Hazard Ratio***	**95% CI for Hazard Ratio**
Cancer type: Breast cancer vs Other	0.766	[0.558, 1.050]
Cancer type: Kidney cancer vs Other	0.666	[0.422, 1.052]
Cancer type: Lung cancer vs Other	0.811	[0.584, 1.125]
Cancer type: Prostate cancer vs Other	0.881	[0.637, 1.219]
Visceral metastases: Yes vs No	1.355	[1.138, 1.614]
Previous antineoplastic therapy: Yes vs No	0.997	[0.821, 1.211]
SREs and/or tumor induced hypercalcemias: Yes vs No	0.839	[0.650, 1.083]
ECOG status: 0 vs 2	0.716	[0.552, 0.929]
ECOG status: 1 vs 2	0.828	[0.653, 1.051]
Previous antiresorptive therapy: Yes vs No	1.230	[0.889, 1.702]

Patients with missing information on previous SREs and/or tumor induced hypercalcemias or missing ECOG status were deleted from analysis.

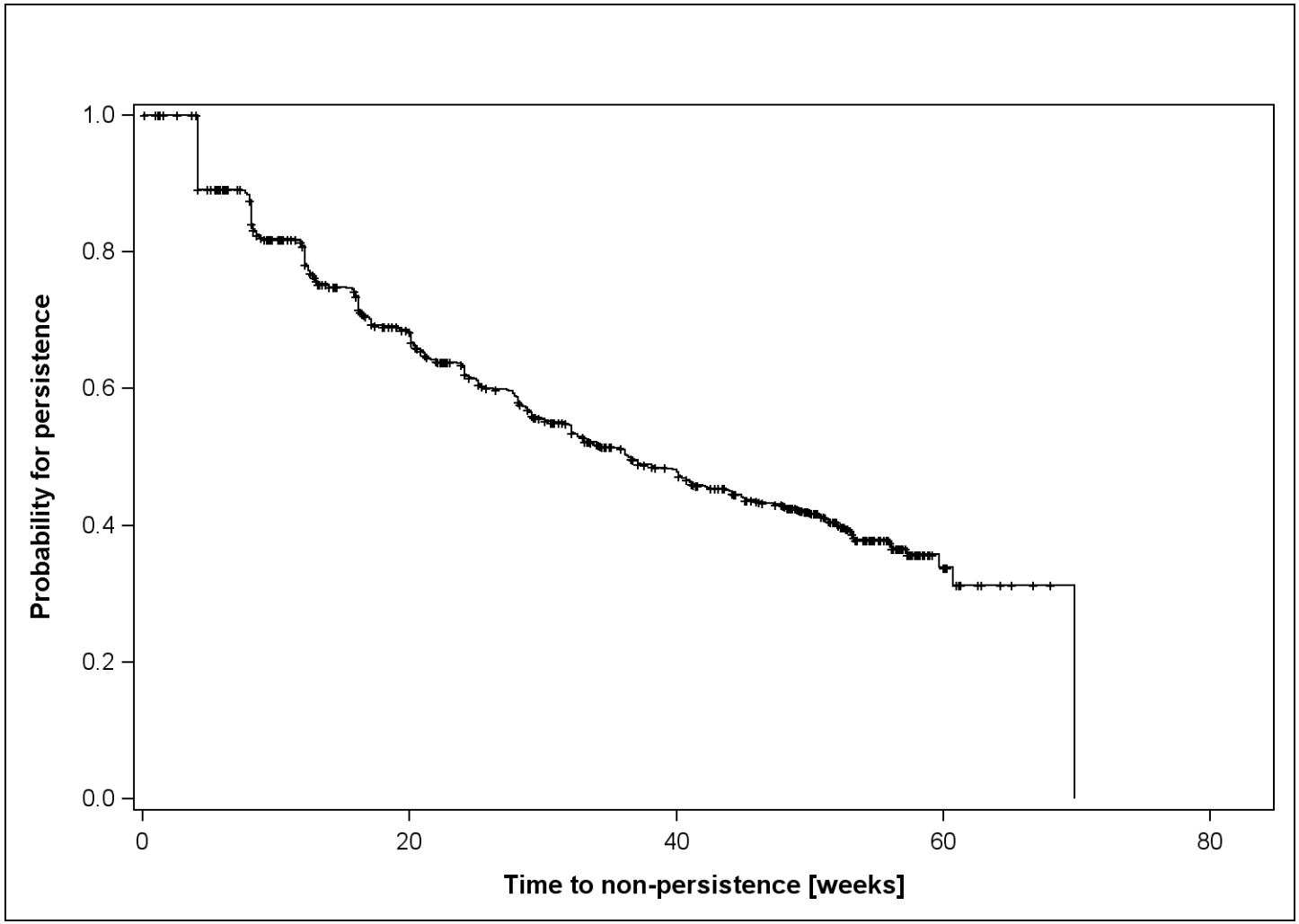
The explanatory variable 'previous antineoplastic therapy' contains information on previous surgery, previous chemotherapy, previous radiotherapy and previous antihormonal therapy. If a patient had at least one of these four therapies, the explanatory variable 'previous antineoplastic therapy' is defined as 'yes'.

Explanatory variable 'Bone metastases yes/no' was not included in the model because reference category 'no' does not exist.

The number of events for 'time to non-persistence' differs from the number of 'persistence at 48 weeks' because for 'persistence at 48 weeks' subjects who died, withdrew consent or lost to follow-up before persistence assessment are excluded.

* Hazard Ratios are adjusted for all covariates in the model.

15.3.7.1.1 Time to non-persistence [weeks] – sensitivity analysis – censoring lost to follow-up subjects - overall analysis Kaplan-Meier curve - FAS



15.3.7.1.2 Time to non-persistence [weeks] – sensitivity analysis – censoring lost to follow-up subjects - overall analysis Kaplan-Meier estimates - FAS

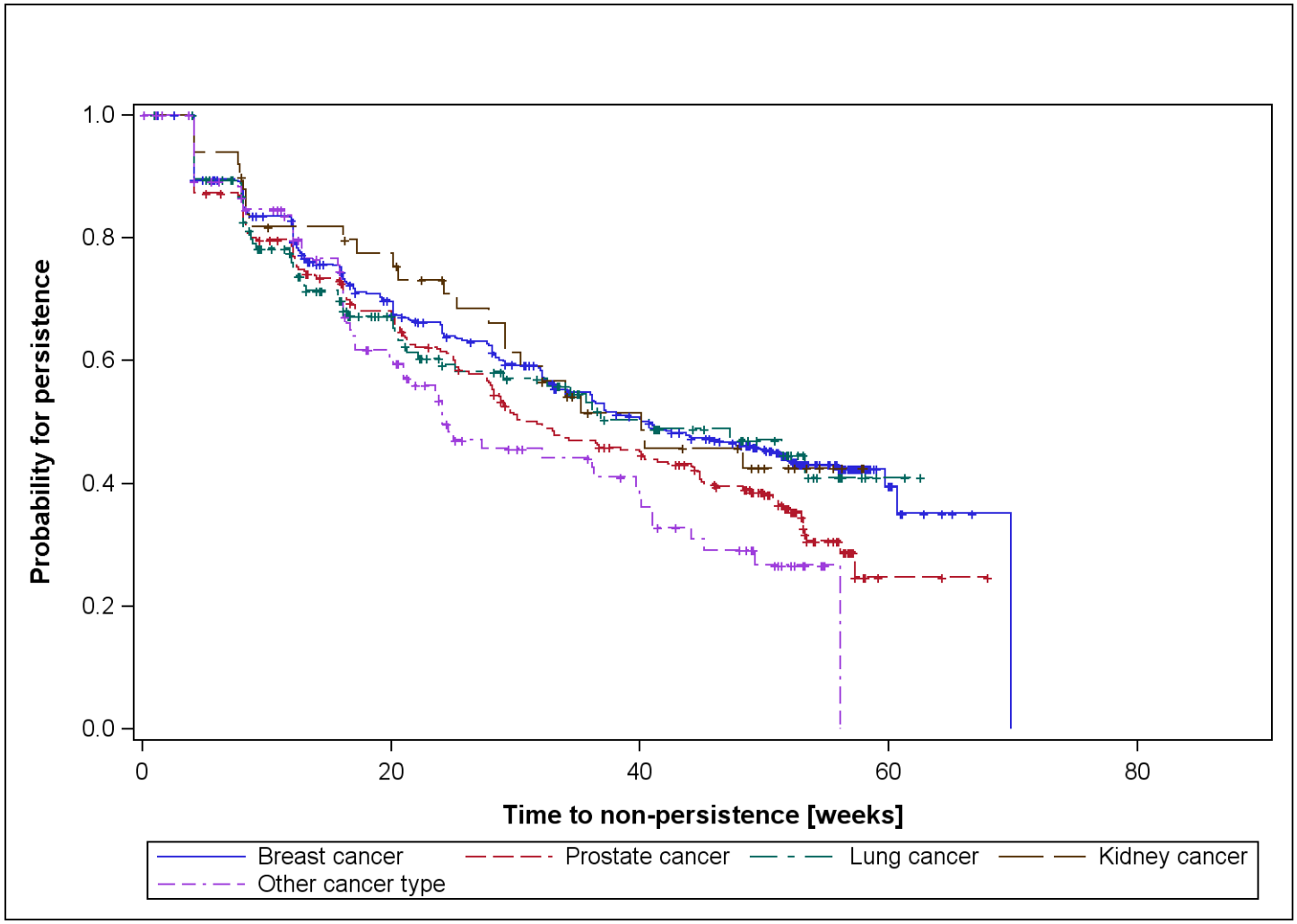
	Kaplan-Meier Quartiles [weeks]			
			95% CI	
	Quartile	Point Estimate	Lower Limit	Upper Limit
Overall (N=1128)	1st Quartile	14.00	12.43	16.14
	Median	36.43	32.57	40.71
	3rd Quartile	69.86	60.71	69.86

Probability for persistence at 24 weeks [%]
63.1

15.3.7.1.2 Time to non-persistence [weeks] – sensitivity analysis – censoring lost to follow-up subjects - overall analysis Kaplan-Meier estimates - FAS

Weeks	Number of patients at risk
0.00	1128
4.00	1116
8.00	968
12.00	867
16.00	764
20.00	680
24.00	610
28.00	558
32.00	502
36.00	454
40.00	417
44.00	376
48.00	346
52.00	243
56.00	94
60.00	18
64.00	6
68.00	2
72.00	1

15.3.7.2.1 Time to non-persistence [weeks] – sensitivity analysis – censoring lost to follow-up subjects - analysis by cancer type Kaplan-Meier curve - FAS



15.3.7.2.2 Time to non-persistence [weeks] – sensitivity analysis – censoring lost to follow-up subjects - analysis by cancer type Kaplan-Meier estimates - FAS

	Kaplan-Meier Quartiles [weeks]			
			95% CI	
Cancer type	Quartile	Point Estimate	Lower Limit	Upper Limit
Breast cancer (N=509)	1st Quartile	16.00	12.43	17.14
	Median	40.71	36.00	50.14
	3rd Quartile	69.86	not estimable	not estimable
Kidney cancer (N=50)	1st Quartile	20.57	8.29	29.14
	Median	40.14	29.14	not estimable
	3rd Quartile	not estimable	not estimable	not estimable
Lung cancer (N=159)	1st Quartile	12.14	8.29	16.57
	Median	40.71	25.14	not estimable
	3rd Quartile	not estimable	not estimable	not estimable
Other cancer type (N=116)	1st Quartile	15.86	12.00	16.43
	Median	24.14	20.14	39.71
	3rd Quartile	56.14	41.00	56.14
Prostate cancer (N=294)	1st Quartile	12.57	9.14	16.43
	Median	31.71	28.00	40.43
	3rd Quartile	57.29	53.43	not estimable

15.3.7.2.2 Time to non-persistence [weeks] – sensitivity analysis – censoring lost to follow-up subjects - analysis by cancer type Kaplan-Meier estimates - FAS

Cancer type	Probability for persistence at 24 weeks [%]
Breast cancer (N=509)	65.9
Kidney cancer (N=50)	73.2
Lung cancer (N=159)	59.3
Other cancer type (N=116)	53.5
Prostate cancer (N=294)	61.5

15.3.7.2.2 Time to non-persistence [weeks] – sensitivity analysis – censoring lost to follow-up subjects - analysis by cancer type Kaplan-Meier estimates - FAS

Cancer type	Weeks	Number of patients at risk
Breast cancer	0.00	509
	4.00	507
	8.00	447
	12.00	415
	16.00	365
	20.00	332
	24.00	311
	28.00	291
	32.00	267
	36.00	245
	40.00	224
	44.00	207
	48.00	195
	52.00	147
	56.00	62
	60.00	14
	64.00	4
	68.00	1
	72.00	1

15.3.7.2.2 Time to non-persistence [weeks] – sensitivity analysis – censoring lost to follow-up subjects - analysis by cancer type Kaplan-Meier estimates - FAS

Cancer type	Weeks	Number of patients at risk
Prostate cancer	0.00	294
	4.00	292
	8.00	251
	12.00	227
	16.00	204
	20.00	188
	24.00	169
	28.00	153
	32.00	132
	36.00	125
	40.00	117
	44.00	107
	48.00	95
	52.00	62
	56.00	19
	60.00	2
	64.00	2
	68.00	1
	72.00	1

15.3.7.2.2 Time to non-persistence [weeks] – sensitivity analysis – censoring lost to follow-up subjects - analysis by cancer type Kaplan-Meier estimates - FAS

Cancer type	Weeks	Number of patients at risk
Lung cancer	0.00	159
	4.00	155
	8.00	129
	12.00	102
	16.00	85
	20.00	70
	24.00	56
	28.00	53
	32.00	48
	36.00	38
	40.00	34
	44.00	29
	48.00	26
	52.00	17
	56.00	8
	60.00	2
	64.00	1
	68.00	1
	72.00	1

15.3.7.2.2 Time to non-persistence [weeks] – sensitivity analysis – censoring lost to follow-up subjects - analysis by cancer type Kaplan-Meier estimates - FAS

Cancer type	Weeks	Number of patients at risk
Kidney cancer	0.00	50
	4.00	50
	8.00	45
	12.00	39
	16.00	39
	20.00	36
	24.00	32
	28.00	28
	32.00	25
	36.00	18
	40.00	18
	44.00	15
	48.00	14
	52.00	9
	56.00	4
	60.00	1
	64.00	1
	68.00	1
	72.00	1

15.3.7.2.2 Time to non-persistence [weeks] – sensitivity analysis – censoring lost to follow-up subjects - analysis by cancer type Kaplan-Meier estimates - FAS

Cancer type	Weeks	Number of patients at risk
Other cancer type	0.00	116
	4.00	112
	8.00	96
	12.00	84
	16.00	71
	20.00	54
	24.00	42
	28.00	33
	32.00	30
	36.00	28
	40.00	24
	44.00	18
	48.00	16
	52.00	8
	56.00	1
	60.00	1
	64.00	1
	68.00	1
	72.00	1

15.3.8 Time to non-persistence [days] – sensitivity analysis – censoring lost to follow-up subjects - analysis using a proportional hazards model - FAS

Summary of Event and Censored Observations			
N total	N event	N censored	Percent censored
1099	593	506	46.04

Type 3 Analysis			
Variable	Degrees of freedom	Wald Statistic	p-value for Wald test
Age	1	1.0757	0.2997
Gender	1	0.4339	0.5101
	4	5.9950	0.1995
Visceral metastases	1	9.0123	0.0027
Previous antineoplastic therapy	1	0.0687	0.7933
SREs and/or tumor induced hypercalcemias	1	0.8820	0.3477
ECOG score	2	7.0447	0.0295
Previous antiresorptive therapy	1	1.2125	0.2708

Hazard Ratio Estimates		
Variable	Hazard Ratio*	95% CI for Hazard Ratio
Age: Unit=1 y	1.004	[0.996, 1.013]

Patients with missing information on previous SREs and/or tumor induced hypercalcemias or missing ECOG status were deleted from analysis.

The explanatory variable 'previous antineoplastic therapy' contains information on previous surgery, previous chemotherapy, previous radiotherapy and previous antihormonal therapy. If a patient had at least one of these four therapies, the explanatory variable 'previous antineoplastic therapy' is defined as 'yes'.

Explanatory variable 'Bone metastases yes/no' was not included in the model because reference category 'no' does not exist.

The number of events for 'time to non-persistence' differs from the number of 'persistence at 48 weeks' because for 'persistence at 48 weeks' subjects who died, withdrew consent or lost to follow-up before persistence assessment are excluded.

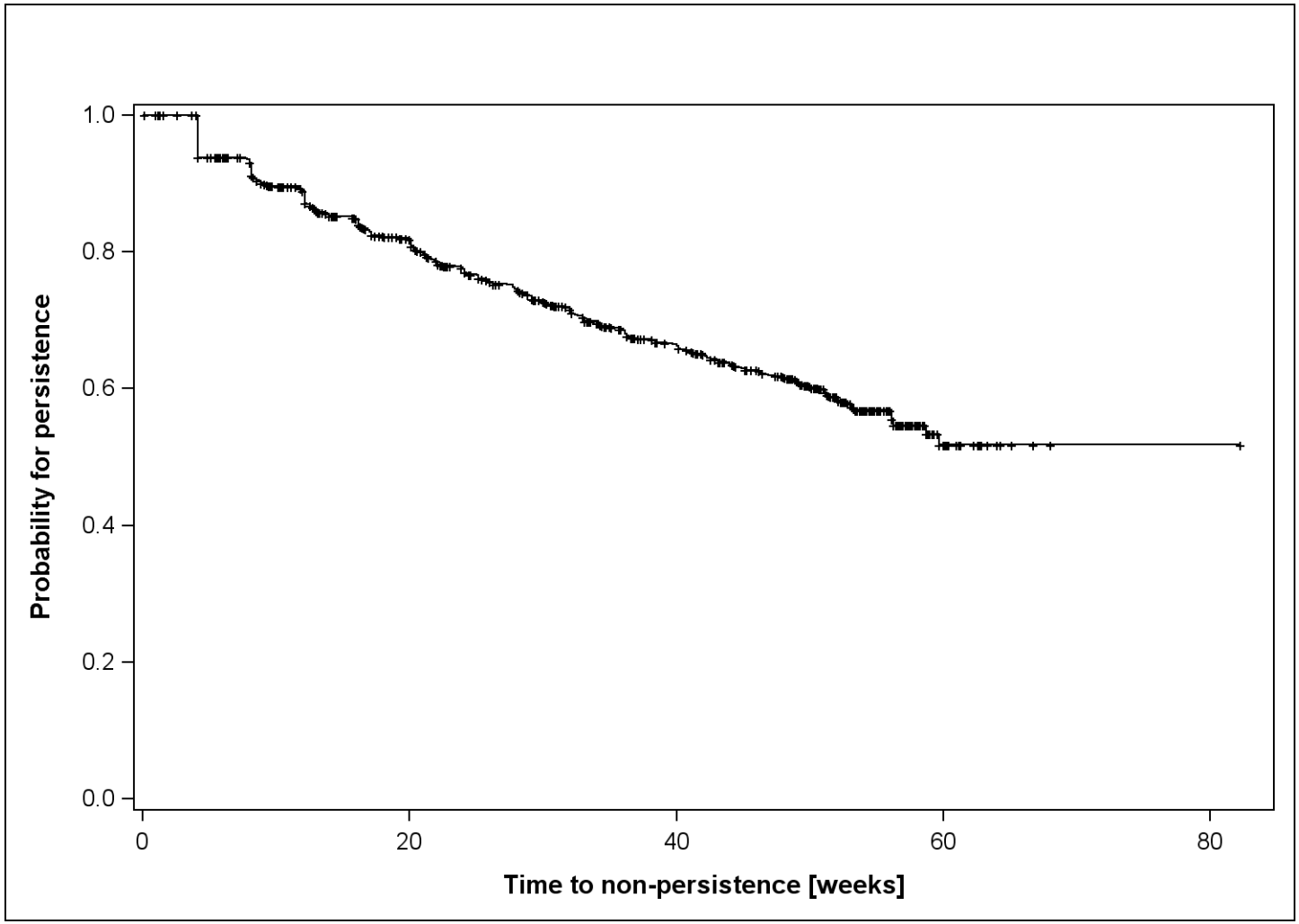
* Hazard Ratios are adjusted for all covariates in the model.

15.3.8 Time to non-persistence [days] – sensitivity analysis – censoring lost to follow-up subjects - analysis using a proportional hazards model - FAS

Hazard Ratio Estimates		
Variable	**Hazard Ratio***	**95% CI for Hazard Ratio**
Gender: Male vs Female	1.112	[0.811, 1.525]
Cancer type: Breast cancer vs Other	0.763	[0.549, 1.059]
Cancer type: Kidney cancer vs Other	0.634	[0.391, 1.028]
Cancer type: Lung cancer vs Other	0.733	[0.517, 1.039]
Cancer type: Prostate cancer vs Other	0.914	[0.652, 1.282]
Visceral metastases: Yes vs No	1.319	[1.101, 1.581]
Previous antineoplastic therapy: Yes vs No	1.027	[0.839, 1.258]
SREs and/or tumor induced hypercalcemias: Yes vs No	0.883	[0.680, 1.145]
ECOG status: 0 vs 2	0.697	[0.533, 0.911]
ECOG status: 1 vs 2	0.804	[0.630, 1.027]
Previous antiresorptive therapy: Yes vs No	1.209	[0.863, 1.694]

Patients with missing information on previous SREs and/or tumor induced hypercalcemias or missing ECOG status were deleted from analysis.
The explanatory variable 'previous antineoplastic therapy' contains information on previous surgery, previous chemotherapy, previous radiotherapy and previous antihormonal therapy. If a patient had at least one of these four therapies, the explanatory variable 'previous antineoplastic therapy' is defined as 'yes'.
Explanatory variable 'Bone metastases yes/no' was not included in the model because reference category 'no' does not exist.
The number of events for 'time to non-persistence' differs from the number of 'persistence at 48 weeks' because for 'persistence at 48 weeks' subjects who died, withdrew consent or lost to follow-up before persistence assessment are excluded.
* Hazard Ratios are adjusted for all covariates in the model.

15.3.9.1.1 Time to non-persistence [weeks] – sens. analysis – time window of ± 14 days between inj. and censoring lost to follow-up subjects - overall analysis Kaplan-Meier curve - FAS



15.3.9.1.2 Time to non-persistence [weeks] – sens. analysis – time window of ± 14 days between inj. and censoring lost to follow-up subjects - overall analysis Kaplan-Meier estimates - FAS

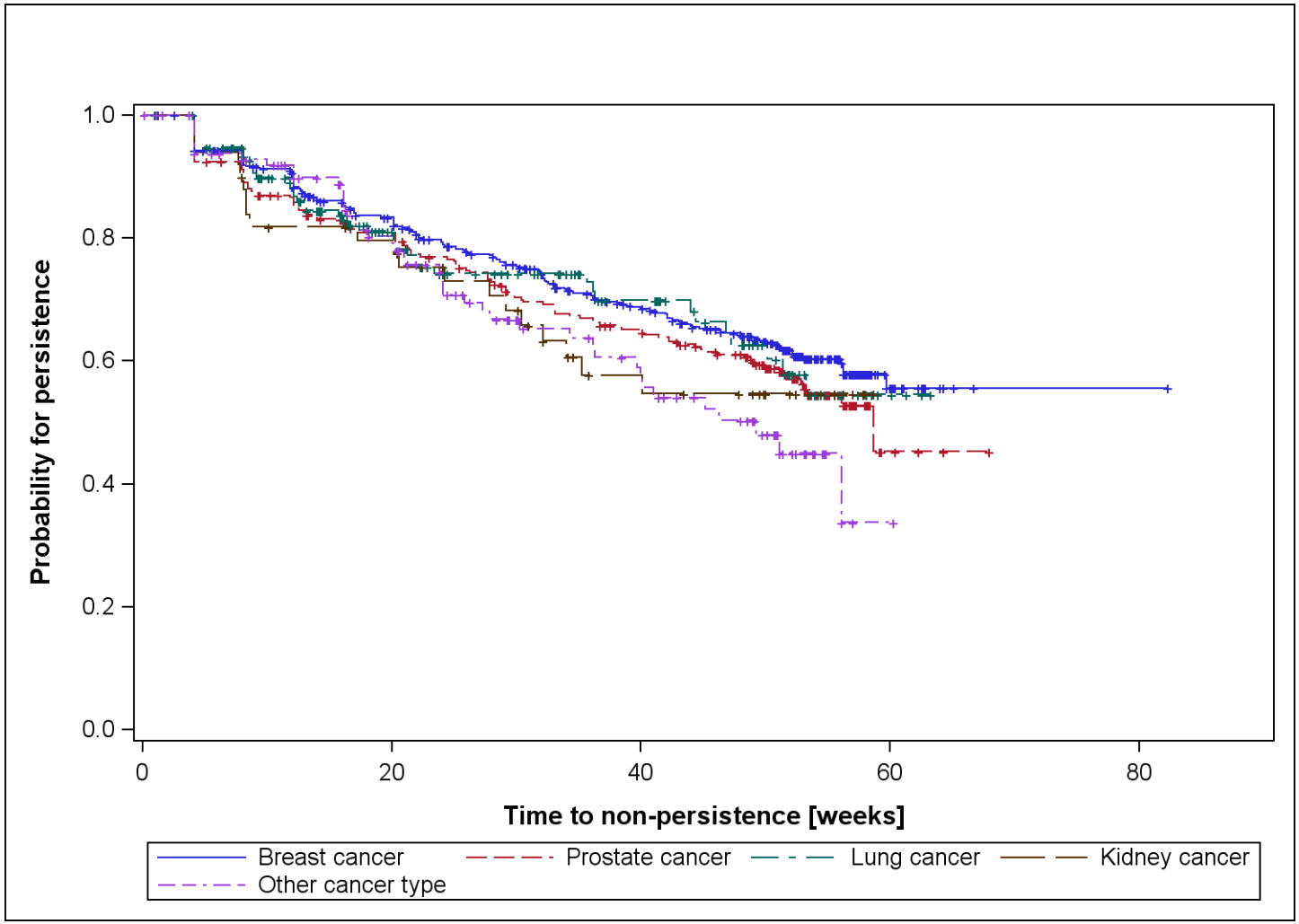
Kaplan-Meier Quartiles [weeks]				
			95% CI	
	Quartile	Point Estimate	Lower Limit	Upper Limit
Overall (N=1128)	1st Quartile	27.71	24.00	30.43
	Median	not estimable	58.71	not estimable
	3rd Quartile	not estimable	not estimable	not estimable

Probability for persistence at 24 weeks [%]
77.5

15.3.9.1.2 Time to non-persistence [weeks] – sens. analysis – time window of ± 14 days between inj. and censoring lost to follow-up subjects - overall analysis Kaplan-Meier estimates - FAS

Weeks	Number of patients at risk
0.00	1128
4.00	1116
8.00	1024
12.00	949
16.00	875
20.00	815
24.00	748
28.00	703
32.00	650
36.00	602
40.00	568
44.00	524
48.00	493
52.00	339
56.00	145
60.00	32
64.00	8
68.00	2
72.00	1

15.3.9.2.1 Time to non-persistence [weeks] – sens. analysis – time window of ± 14 days between inj. and censoring lost to follow-up subjects - analysis by cancer type Kaplan-Meier curve - FAS



15.3.9.2.2 Time to non-persistence [weeks] – sens. analysis – time window of ± 14 days between inj. and censoring lost to follow-up subjects - analysis by cancer type Kaplan-Meier estimates - FAS

	Kaplan-Meier Quartiles [weeks]			
			95% CI	
Cancer type	Quartile	Point Estimate	Lower Limit	Upper Limit
Breast cancer (N=509)	1st Quartile	31.71	24.29	34.57
	Median	not estimable	59.71	not estimable
	3rd Quartile	not estimable	not estimable	not estimable
Kidney cancer (N=50)	1st Quartile	24.29	8.29	34.00
	Median	not estimable	32.14	not estimable
	3rd Quartile	not estimable	not estimable	not estimable
Lung cancer (N=159)	1st Quartile	23.43	16.57	44.43
	Median	not estimable	50.14	not estimable
	3rd Quartile	not estimable	not estimable	not estimable
Other cancer type (N=116)	1st Quartile	23.86	16.43	30.29
	Median	49.29	36.29	not estimable
	3rd Quartile	not estimable	56.14	not estimable
Prostate cancer (N=294)	1st Quartile	26.00	20.29	30.43
	Median	58.71	52.86	not estimable
	3rd Quartile	not estimable	not estimable	not estimable

15.3.9.2.2 Time to non-persistence [weeks] – sens. analysis – time window of ± 14 days between inj. and censoring lost to follow-up subjects - analysis by cancer type Kaplan-Meier estimates - FAS

Cancer type	Probability for persistence at 24 weeks [%]
Breast cancer (N=509)	79.3
Kidney cancer (N=50)	75.3
Lung cancer (N=159)	74.3
Other cancer type (N=116)	74.5
Prostate cancer (N=294)	76.9

15.3.9.2.2 Time to non-persistence [weeks] – sens. analysis – time window of ± 14 days between inj. and censoring lost to follow-up subjects - analysis by cancer type Kaplan-Meier estimates - FAS

Cancer type	Weeks	Number of patients at risk
Breast cancer	0.00	509
	4.00	507
	8.00	473
	12.00	453
	16.00	417
	20.00	398
	24.00	374
	28.00	358
	32.00	338
	36.00	314
	40.00	298
	44.00	280
	48.00	267
	52.00	200
	56.00	88
	60.00	23
	64.00	6
	68.00	1
	72.00	1

15.3.9.2.2 Time to non-persistence [weeks] – sens. analysis – time window of ± 14 days between inj. and censoring lost to follow-up subjects - analysis by cancer type Kaplan-Meier estimates - FAS

Cancer type	Weeks	Number of patients at risk
Prostate cancer	0.00	294
	4.00	292
	8.00	267
	12.00	247
	16.00	232
	20.00	224
	24.00	211
	28.00	200
	32.00	186
	36.00	179
	40.00	170
	44.00	157
	48.00	149
	52.00	93
	56.00	35
	60.00	4
	64.00	2
	68.00	1
	72.00	1

15.3.9.2.2 Time to non-persistence [weeks] – sens. analysis – time window of ± 14 days between inj. and censoring lost to follow-up subjects - analysis by cancer type Kaplan-Meier estimates - FAS

Cancer type	Weeks	Number of patients at risk
Lung cancer	0.00	159
	4.00	155
	8.00	138
	12.00	118
	16.00	103
	20.00	85
	24.00	70
	28.00	65
	32.00	58
	36.00	50
	40.00	45
	44.00	40
	48.00	34
	52.00	22
	56.00	12
	60.00	4
	64.00	1
	68.00	1
	72.00	1

15.3.9.2.2 Time to non-persistence [weeks] – sens. analysis – time window of ± 14 days between inj. and censoring lost to follow-up subjects - analysis by cancer type Kaplan-Meier estimates - FAS

Cancer type	Weeks	Number of patients at risk
Kidney cancer	0.00	50
	4.00	50
	8.00	45
	12.00	39
	16.00	39
	20.00	37
	24.00	33
	28.00	30
	32.00	26
	36.00	19
	40.00	19
	44.00	17
	48.00	16
	52.00	11
	56.00	6
	60.00	1
	64.00	1
	68.00	1
	72.00	1

15.3.9.2.2 Time to non-persistence [weeks] – sens. analysis – time window of ± 14 days between inj. and censoring lost to follow-up subjects - analysis by cancer type Kaplan-Meier estimates - FAS

Cancer type	Weeks	Number of patients at risk
Other cancer type	0.00	116
	4.00	112
	8.00	101
	12.00	92
	16.00	84
	20.00	71
	24.00	60
	28.00	50
	32.00	42
	36.00	40
	40.00	36
	44.00	30
	48.00	27
	52.00	13
	56.00	4
	60.00	1
	64.00	1
	68.00	1
	72.00	1

15.3.10 Time to non-persistence [days] – sens. analysis – time window of ± 14 days between inj. and censoring lost to follow-up subjects - analysis using a proportional hazards model - FAS

Summary of Event and Censored Observations			
N total	N event	N censored	Percent censored
1099	404	695	63.24

Type 3 Analysis			
Variable	Degrees of freedom	Wald Statistic	p-value for Wald test
Age	1	10.5701	0.0011
Gender	1	0.1174	0.7318
	4	3.0214	0.5542
Visceral metastases	1	5.1671	0.0230
Previous antineoplastic therapy	1	0.0721	0.7883
SREs and/or tumor induced hypercalcemias	1	0.1340	0.7143
ECOG score	2	2.9224	0.2320
Previous antiresorptive therapy	1	1.3159	0.2513

Patients with missing information on previous SREs and/or tumor induced hypercalcemias or missing ECOG status were deleted from analysis.

The explanatory variable 'previous antineoplastic therapy' contains information on previous surgery, previous chemotherapy, previous radiotherapy and previous antihormonal therapy. If a patient had at least one of these four therapies, the explanatory variable 'previous antineoplastic therapy' is defined as 'yes'.

Explanatory variable 'Bone metastases yes/no' was not included in the model because reference category 'no' does not exist.

The number of events for 'time to non-persistence' differs from the number of 'persistence at 48 weeks' because for 'persistence at 48 weeks' subjects who died, withdrew consent or lost to follow-up before persistence assessment are excluded.

* Hazard Ratios are adjusted for all covariates in the model.

15.3.10 Time to non-persistence [days] – sens. analysis – time window of ± 14 days between inj. and censoring lost to follow-up subjects - analysis using a proportional hazards model - FAS

Hazard Ratio Estimates		
Variable	**Hazard Ratio***	**95% CI for Hazard Ratio**
Age: Unit=1 y	1.017	[1.007, 1.027]
Gender: Male vs Female	1.069	[0.731, 1.563]
Cancer type: Breast cancer vs Other	0.757	[0.509, 1.124]
Cancer type: Kidney cancer vs Other	0.910	[0.527, 1.572]
Cancer type: Lung cancer vs Other	0.744	[0.486, 1.138]
Cancer type: Prostate cancer vs Other	0.781	[0.519, 1.175]
Visceral metastases: Yes vs No	1.286	[1.035, 1.597]
Previous antineoplastic therapy: Yes vs No	1.034	[0.810, 1.321]
SREs and/or tumor induced hypercalcemias: Yes vs No	0.944	[0.693, 1.285]
ECOG status: 0 vs 2	0.769	[0.558, 1.059]
ECOG status: 1 vs 2	0.790	[0.589, 1.059]
Previous antiresorptive therapy: Yes vs No	1.258	[0.850, 1.863]

Patients with missing information on previous SREs and/or tumor induced hypercalcemias or missing ECOG status were deleted from analysis.

The explanatory variable 'previous antineoplastic therapy' contains information on previous surgery, previous chemotherapy, previous radiotherapy and previous antihormonal therapy. If a patient had at least one of these four therapies, the explanatory variable 'previous antineoplastic therapy' is defined as 'yes'.

Explanatory variable 'Bone metastases yes/no' was not included in the model because reference category 'no' does not exist.

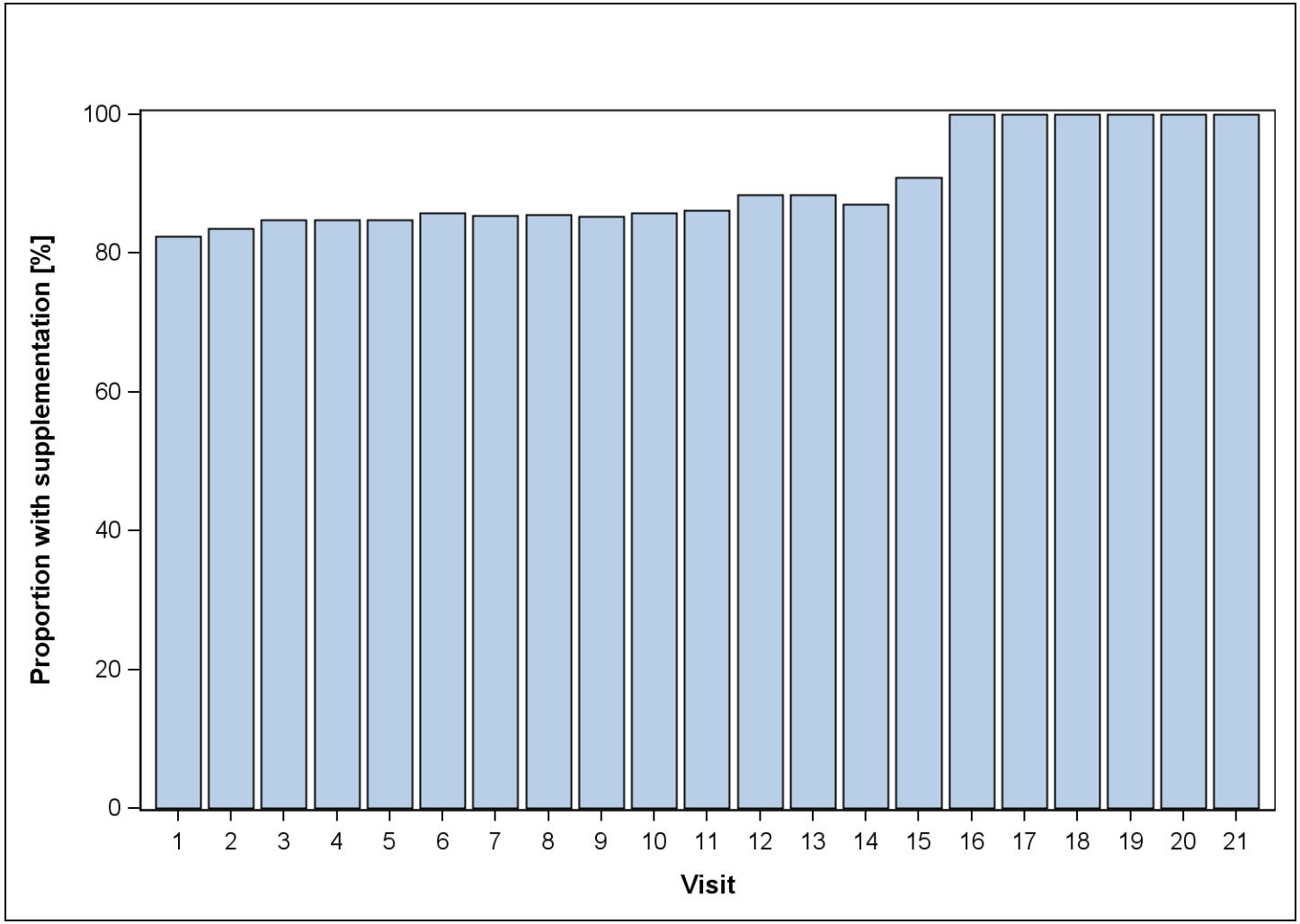
The number of events for 'time to non-persistence' differs from the number of 'persistence at 48 weeks' because for 'persistence at 48 weeks' subjects who died, withdrew consent or lost to follow-up before persistence assessment are excluded.

* Hazard Ratios are adjusted for all covariates in the model.

15.4.1.1 Frequency of Vitamin D supplementation by visit - FAS

Visit	Missing	N Evaluable	Yes n (%)	No n (%)
Visit 1	4	1080	890 (82.4%)	190 (17.6%)
Visit 2	3	1040	869 (83.6%)	171 (16.4%)
Visit 3	3	999	847 (84.8%)	152 (15.2%)
Visit 4	8	942	799 (84.8%)	143 (15.2%)
Visit 5	3	904	766 (84.7%)	138 (15.3%)
Visit 6	1	850	729 (85.8%)	121 (14.2%)
Visit 7	2	817	698 (85.4%)	119 (14.6%)
Visit 8	1	775	663 (85.5%)	112 (14.5%)
Visit 9	2	737	629 (85.3%)	108 (14.7%)
Visit 10	1	697	598 (85.8%)	99 (14.2%)
Visit 11	5	635	547 (86.1%)	88 (13.9%)
Visit 12	3	546	483 (88.5%)	63 (11.5%)
Visit 13	4	370	327 (88.4%)	43 (11.6%)
Visit 14	1	100	87 (87.0%)	13 (13.0%)
Visit 15	0	22	20 (90.9%)	2 (9.1%)
Visit 16	0	10	10 (100.0%)	0 (0.0%)
Visit 17	0	5	5 (100.0%)	0 (0.0%)
Visit 18	0	3	3 (100.0%)	0 (0.0%)
Visit 19	0	3	3 (100.0%)	0 (0.0%)
Visit 20	0	3	3 (100.0%)	0 (0.0%)
Visit 21	0	1	1 (100.0%)	0 (0.0%)

15.4.1.2 Frequency of Vitamin D supplementation by visit graph - FAS



15.4.1.3 Summary of daily dose of Vitamin D supplementation by visit - FAS

Cancer type	Visit	Unit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Breast cancer	Visit 1	Pill	9	2.0	1.5	1	1	1	4	4
		µg	8	13.0	7.7	0	10	10	21	22
		IU	381	705.3	2140.1	400	400	400	800	41600
	Visit 2	Pill	10	2.2	1.5	1	1	1	4	4
		µg	9	14.2	8.0	0	10	10	22	22
		mg	2	700.0	424.3	400	400	700	1000	1000
		IU	375	585.0	405.4	126	400	400	800	2857
	Visit 3	Pill	9	2.0	1.5	1	1	1	4	4
		µg	9	14.2	8.0	0	10	10	22	22
		mg	1	1000.0		1000	1000	1000	1000	1000
		IU	377	590.5	405.7	286	400	400	800	2857
	Visit 4	Pill	11	1.8	1.4	1	1	1	4	4
		µg	9	67.4	162.4	0	10	10	22	500
		IU	357	603.3	496.3	120	400	400	800	5714
	Visit 5	Pill	16	1.6	1.2	1	1	1	1	4
		µg	8	13.3	8.0	0	10	10	22	22
		IU	351	606.3	513.7	33	400	400	800	5714
	Visit 6	Pill	15	1.4	1.1	1	1	1	1	4
		µg	7	15.5	8.8	0	10	22	22	22
		IU	344	609.0	517.2	200	400	400	800	5714
	Visit 7	Pill	14	1.2	0.8	1	1	1	1	4
		µg	7	13.0	9.0	0	5	10	22	22
		IU	331	610.5	510.8	200	400	400	800	5714
	Visit 8	Pill	15	1.2	0.8	1	1	1	1	4

Records with frequency 'other' were not included

15.4.1.3 Summary of daily dose of Vitamin D supplementation by visit - FAS

Cancer type	Visit	Unit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
		µg	7	13.0	9.0	0	5	10	22	22
		mg	1	1000.0		1000	1000	1000	1000	1000
		IU	317	617.6	537.6	200	400	400	800	5714
	Visit 9	Pill	13	1.2	0.8	1	1	1	1	4
		µg	7	68.7	146.3	0	5	22	22	400
		IU	310	626.4	574.1	200	400	400	800	5714
	Visit 10	Pill	14	1.2	0.8	1	1	1	1	4
		µg	6	13.5	9.8	0	5	16	22	22
		IU	297	625.5	610.3	200	400	400	800	5714
	Visit 11	Pill	12	1.0	0.0	1	1	1	1	1
		µg	7	13.0	9.0	0	5	10	22	22
		IU	279	620.5	610.5	400	400	400	800	5714
	Visit 12	Pill	12	1.0	0.0	1	1	1	1	1
		µg	5	15.2	9.9	0	10	22	22	22
		IU	245	606.4	561.8	200	400	400	500	5714
	Visit 13	Pill	6	1.0	0.0	1	1	1	1	1
		µg	5	15.2	9.9	0	10	22	22	22
		mg	1	400.0		400	400	400	400	400
		IU	174	667.1	664.2	200	400	400	800	5714
	Visit 14	Pill	3	1.0	0.0	1	1	1	1	1
		µg	1	0.4		0	0	0	0	0
		IU	52	568.7	415.9	400	400	400	450	2857
	Visit 15	µg	1	0.7		1	1	1	1	1
		mg	1	400.0		400	400	400	400	400

Records with frequency 'other' were not included

15.4.1.3 Summary of daily dose of Vitamin D supplementation by visit - FAS

Cancer type	Visit	Unit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
		IU	13	656.7	681.4	400	400	400	400	2857
	Visit 16	IU	7	751.0	928.7	400	400	400	400	2857
	Visit 17	IU	3	400.0	0.0	400	400	400	400	400
	Visit 18	IU	2	400.0	0.0	400	400	400	400	400
	Visit 19	IU	2	400.0	0.0	400	400	400	400	400
	Visit 20	IU	2	400.0	0.0	400	400	400	400	400
	Visit 21	IU	1	400.0		400	400	400	400	400
Prostate cancer	Visit 1	Pill	1	1.0		1	1	1	1	1
		µg	27	9.8	3.8	0	10	10	10	25
		IU	208	779.8	1523.7	13	400	800	800	20000
	Visit 2	Pill	2	1.0	0.0	1	1	1	1	1
		µg	31	11.7	9.0	0	10	10	10	55
		IU	202	741.5	1395.3	143	400	800	800	20000
	Visit 3	Pill	2	1.0	0.0	1	1	1	1	1
		µg	28	10.2	4.2	0	10	10	10	25
		IU	202	673.9	335.0	143	400	800	800	2857
	Visit 4	Pill	1	1.0		1	1	1	1	1
		Powder	1	880.0		880	880	880	880	880
		µg	28	13.4	17.5	0	10	10	10	100
		IU	194	671.0	334.8	143	400	800	800	2857
	Visit 5	Pill	1	1.0		1	1	1	1	1
		µg	28	9.8	3.7	0	10	10	10	25
		IU	194	679.6	372.4	143	400	800	800	2857

Records with frequency 'other' were not included

15.4.1.3 Summary of daily dose of Vitamin D supplementation by visit - FAS

Cancer type	Visit	Unit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
	Visit 6	Pill	1	1.0		1	1	1	1	1
		µg	26	11.2	4.1	5	10	10	10	25
		IU	188	679.8	372.3	143	400	800	800	2857
	Visit 7	Pill	1	1.0		1	1	1	1	1
		µg	27	10.7	3.8	5	10	10	10	25
		IU	185	679.6	361.9	143	400	800	800	2857
	Visit 8	Pill	1	1.0		1	1	1	1	1
		µg	25	10.6	3.3	5	10	10	10	25
		IU	174	681.9	378.4	13	400	800	800	2857
	Visit 9	Pill	1	1.0		1	1	1	1	1
		µg	25	11.0	3.8	5	10	10	10	25
		IU	167	682.0	379.2	143	400	800	800	2857
	Visit 10	Pill	1	2.0		2	2	2	2	2
		µg	23	10.7	3.5	5	10	10	10	25
		IU	160	687.2	383.5	143	400	800	800	2857
	Visit 11	Pill	1	2.0		2	2	2	2	2
		µg	22	10.7	3.6	5	10	10	10	25
		IU	145	771.0	804.8	143	400	800	800	8880
	Visit 12	Pill	1	2.0		2	2	2	2	2
		µg	20	10.8	3.7	5	10	10	10	25
		mg	1	2500.0		2500	2500	2500	2500	2500
		IU	125	716.6	433.1	143	400	800	800	2857
	Visit 13	µg	10	10.0	0.0	10	10	10	10	10
		mg	1	1000.0		1000	1000	1000	1000	1000

Records with frequency 'other' were not included

15.4.1.3 Summary of daily dose of Vitamin D supplementation by visit - FAS

Cancer type	Visit	Unit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
		IU	82	735.3	418.5	400	400	800	800	2857
	Visit 14	IU	19	677.9	302.1	400	400	800	800	1600
	Visit 15	IU	4	820.0	40.0	800	800	800	840	880
	Visit 16	IU	3	826.7	46.2	800	800	800	880	880
	Visit 17	IU	2	840.0	56.6	800	800	840	880	880
	Visit 18	IU	1	800.0		800	800	800	800	800
	Visit 19	IU	1	800.0		800	800	800	800	800
	Visit 20	IU	1	800.0		800	800	800	800	800
Lung cancer	Visit 1	Pill	5	1.0	0.0	1	1	1	1	1
		µg	2	10.0	0.0	10	10	10	10	10
		IU	122	565.6	216.5	200	400	400	800	1000
	Visit 2	Pill	3	1.0	0.0	1	1	1	1	1
		µg	2	10.0	0.0	10	10	10	10	10
		IU	106	590.2	259.9	200	400	400	800	1600
	Visit 3	Pill	4	1.0	0.0	1	1	1	1	1
		µg	2	10.0	0.0	10	10	10	10	10
		IU	94	574.9	215.5	400	400	400	800	1000
	Visit 4	Pill	4	1.3	0.5	1	1	1	2	2
		µg	2	16.0	8.5	10	10	16	22	22
		IU	81	589.6	217.1	400	400	400	800	1000
	Visit 5	Pill	4	1.3	0.5	1	1	1	2	2
		µg	1	10.0		10	10	10	10	10
		IU	70	584.6	217.0	400	400	400	800	1000

Records with frequency 'other' were not included

15.4.1.3 Summary of daily dose of Vitamin D supplementation by visit - FAS

Cancer type	Visit	Unit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
	Visit 6	Pill	2	1.0	0.0	1	1	1	1	1
		µg	1	10.0		10	10	10	10	10
		g	1	880.0		880	880	880	880	880
		IU	57	595.8	218.3	400	400	400	800	1000
	Visit 7	Pill	2	1.0	0.0	1	1	1	1	1
		µg	1	10.0		10	10	10	10	10
		IU	54	575.6	216.2	400	400	400	800	1000
	Visit 8	Pill	1	1.0		1	1	1	1	1
		µg	1	10.0		10	10	10	10	10
		IU	51	558.4	208.9	400	400	400	800	880
	Visit 9	Pill	1	1.0		1	1	1	1	1
		µg	1	10.0		10	10	10	10	10
		IU	43	653.0	563.8	400	400	400	800	4000
	Visit 10	Pill	1	1.0		1	1	1	1	1
		µg	1	10.0		10	10	10	10	10
		IU	41	544.4	204.1	400	400	400	800	880
	Visit 11	Pill	1	1.0		1	1	1	1	1
		IU	32	519.7	186.2	400	400	400	800	880
	Visit 12	Pill	1	1.0		1	1	1	1	1
		IU	27	542.2	206.2	400	400	400	800	880
	Visit 13	IU	19	509.5	189.0	400	400	400	800	880
	Visit 14	IU	5	576.0	242.7	400	400	400	800	880
	Visit 15	IU	1	880.0		880	880	880	880	880

Records with frequency 'other' were not included

15.4.1.3 Summary of daily dose of Vitamin D supplementation by visit - FAS

Cancer type	Visit	Unit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Kidney cancer	Visit 1	Pill	1	1.0		1	1	1	1	1
		µg	3	14.0	6.9	10	10	10	22	22
		IU	32	653.9	483.4	200	400	400	800	2857
	Visit 2	Pill	2	1.0	0.0	1	1	1	1	1
		µg	3	14.0	6.9	10	10	10	22	22
		IU	32	653.9	483.4	200	400	400	800	2857
	Visit 3	Pill	1	1.0		1	1	1	1	1
		µg	3	14.0	6.9	10	10	10	22	22
		IU	33	679.0	509.8	400	400	400	800	2857
	Visit 4	µg	3	14.0	6.9	10	10	10	22	22
		IU	31	703.4	523.8	400	400	400	800	2857
	Visit 5	µg	2	16.0	8.5	10	10	16	22	22
		IU	30	631.6	344.4	400	400	400	800	1760
	Visit 6	µg	3	18.0	6.9	10	10	22	22	22
		IU	26	664.2	355.7	400	400	400	800	1760
	Visit 7	µg	3	18.0	6.9	10	10	22	22	22
		IU	24	612.9	303.0	40	400	400	800	1429
	Visit 8	µg	3	18.0	6.9	10	10	22	22	22
		IU	21	711.8	377.2	400	400	800	880	1760
	Visit 9	µg	3	18.0	6.9	10	10	22	22	22
		IU	20	678.9	404.7	29	400	600	840	1760
	Visit 10	µg	3	18.0	6.9	10	10	22	22	22
		IU	18	695.6	347.9	400	400	800	800	1760
	Visit 11	µg	2	16.0	8.5	10	10	16	22	22

Records with frequency 'other' were not included

15.4.1.3 Summary of daily dose of Vitamin D supplementation by visit - FAS

Cancer type	Visit	Unit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
		IU	16	707.5	361.2	400	400	800	840	1760
	Visit 12	µg	3	18.0	6.9	10	10	22	22	22
		IU	16	682.5	368.2	400	400	600	840	1760
	Visit 13	µg	3	18.0	6.9	10	10	22	22	22
		IU	10	664.0	229.6	400	400	800	880	880
	Visit 14	µg	1	22.0		22	22	22	22	22
		IU	3	666.7	230.9	400	400	800	800	800
Other cancer type	Visit 1	Pill	1	1.0		1	1	1	1	1
		µg	3	13.3	10.4	5	5	10	25	25
		IU	81	585.9	358.9	400	400	400	800	2857
	Visit 2	Pill	1	1.0		1	1	1	1	1
		µg	3	13.3	10.4	5	5	10	25	25
		IU	80	589.7	395.4	400	400	400	800	2857
	Visit 3	Pill	1	1.0		1	1	1	1	1
		µg	2	15.0	14.1	5	5	15	25	25
		IU	74	610.5	407.3	400	400	400	800	2857
	Visit 4	Pill	1	1.0		1	1	1	1	1
		µg	2	15.0	14.1	5	5	15	25	25
		IU	68	599.7	359.9	400	400	400	800	2857
	Visit 5	µg	2	15.0	14.1	5	5	15	25	25
		IU	54	604.4	342.7	400	400	400	800	2400
	Visit 6	µg	2	15.0	14.1	5	5	15	25	25
		IU	49	645.2	467.8	400	400	400	800	2857

Records with frequency 'other' were not included

15.4.1.3 Summary of daily dose of Vitamin D supplementation by visit - FAS

Cancer type	Visit	Unit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
	Visit 7	µg	2	15.0	14.1	5	5	15	25	25
		IU	43	656.2	490.6	400	400	400	800	2857
	Visit 8	µg	2	15.0	14.1	5	5	15	25	25
		IU	40	675.4	503.7	400	400	400	800	2857
	Visit 9	µg	2	15.0	14.1	5	5	15	25	25
		IU	34	688.7	539.8	400	400	400	880	2857
	Visit 10	µg	2	15.0	14.1	5	5	15	25	25
		IU	29	691.6	578.3	400	400	400	800	2857
	Visit 11	µg	2	15.0	14.1	5	5	15	25	25
		IU	26	648.4	499.0	400	400	400	800	2857
	Visit 12	µg	1	25.0		25	25	25	25	25
		IU	25	658.3	506.7	400	400	400	800	2857
	Visit 13	IU	16	698.6	616.1	400	400	400	880	2857
	Visit 14	mg	1	600.0		600	600	600	600	600
		IU	2	640.0	339.4	400	400	640	880	880
Total	Visit 1	Pill	17	1.5	1.2	1	1	1	1	4
		µg	43	11.0	5.4	0	10	10	10	25
		IU	824	689.7	1653.0	13	400	400	800	41600
	Visit 2	Pill	18	1.7	1.3	1	1	1	1	4
		µg	48	12.3	8.4	0	10	10	10	55
		mg	2	700.0	424.3	400	400	700	1000	1000
		IU	795	628.7	780.0	126	400	400	800	20000
	Visit 3	Pill	17	1.5	1.2	1	1	1	1	4

Records with frequency 'other' were not included

15.4.1.3 Summary of daily dose of Vitamin D supplementation by visit - FAS

Cancer type	Visit	Unit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
		µg	44	11.5	5.8	0	10	10	10	25
		mg	1	1000.0		1000	1000	1000	1000	1000
		IU	780	615.8	376.5	143	400	400	800	2857
	Visit 4	Pill	17	1.6	1.2	1	1	1	1	4
		Powder	1	880.0		880	880	880	880	880
		µg	44	24.7	74.8	0	10	10	10	500
		IU	731	623.6	423.5	120	400	400	800	5714
	Visit 5	Pill	21	1.5	1.1	1	1	1	1	4
		µg	41	11.1	5.6	0	10	10	10	25
		IU	699	625.4	436.3	33	400	400	800	5714
	Visit 6	Pill	18	1.3	1.0	1	1	1	1	4
		µg	39	12.6	6.1	0	10	10	20	25
		g	1	880.0		880	880	880	880	880
		IU	664	632.7	450.8	143	400	400	800	5714
	Visit 7	Pill	17	1.2	0.7	1	1	1	1	4
		µg	40	11.9	5.9	0	10	10	10	25
		IU	637	630.8	444.5	40	400	400	800	5714
	Visit 8	Pill	17	1.2	0.7	1	1	1	1	4
		µg	38	11.8	5.8	0	10	10	10	25
		mg	1	1000.0		1000	1000	1000	1000	1000
		IU	603	638.2	468.2	13	400	400	800	5714
	Visit 9	Pill	15	1.2	0.8	1	1	1	1	4
		µg	38	22.4	63.2	0	10	10	15	400
		IU	574	650.1	515.4	29	400	400	800	5714

Records with frequency 'other' were not included

15.4.1.3 Summary of daily dose of Vitamin D supplementation by visit - FAS

Cancer type	Visit	Unit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
	Visit 10	Pill	16	1.3	0.8	1	1	1	1	4
		µg	35	12.0	6.0	0	10	10	10	25
		IU	545	643.4	520.9	143	400	400	800	5714
	Visit 11	Pill	14	1.1	0.3	1	1	1	1	2
		µg	33	11.8	5.9	0	10	10	10	25
		IU	498	662.1	648.5	143	400	400	800	8880
	Visit 12	Pill	14	1.1	0.3	1	1	1	1	2
		µg	29	12.8	6.3	0	10	10	15	25
		mg	1	2500.0		2500	2500	2500	2500	2500
		IU	438	639.6	503.7	143	400	400	800	5714
	Visit 13	Pill	6	1.0	0.0	1	1	1	1	1
		µg	18	12.8	6.3	0	10	10	22	22
		mg	2	700.0	424.3	400	400	700	1000	1000
		IU	301	677.3	572.0	200	400	400	800	5714
	Visit 14	Pill	3	1.0	0.0	1	1	1	1	1
		µg	2	11.2	15.3	0	0	11	22	22
		mg	1	600.0		600	600	600	600	600
		IU	81	600.2	372.7	400	400	400	800	2857
	Visit 15	µg	1	0.7		1	1	1	1	1
		mg	1	400.0		400	400	400	400	400
		IU	18	705.4	578.5	400	400	400	800	2857
	Visit 16	IU	10	773.7	759.5	400	400	400	800	2857
	Visit 17	IU	5	576.0	242.7	400	400	400	800	880
	Visit 18	IU	3	533.3	230.9	400	400	400	800	800

Records with frequency 'other' were not included

15.4.1.3 Summary of daily dose of Vitamin D supplementation by visit - FAS

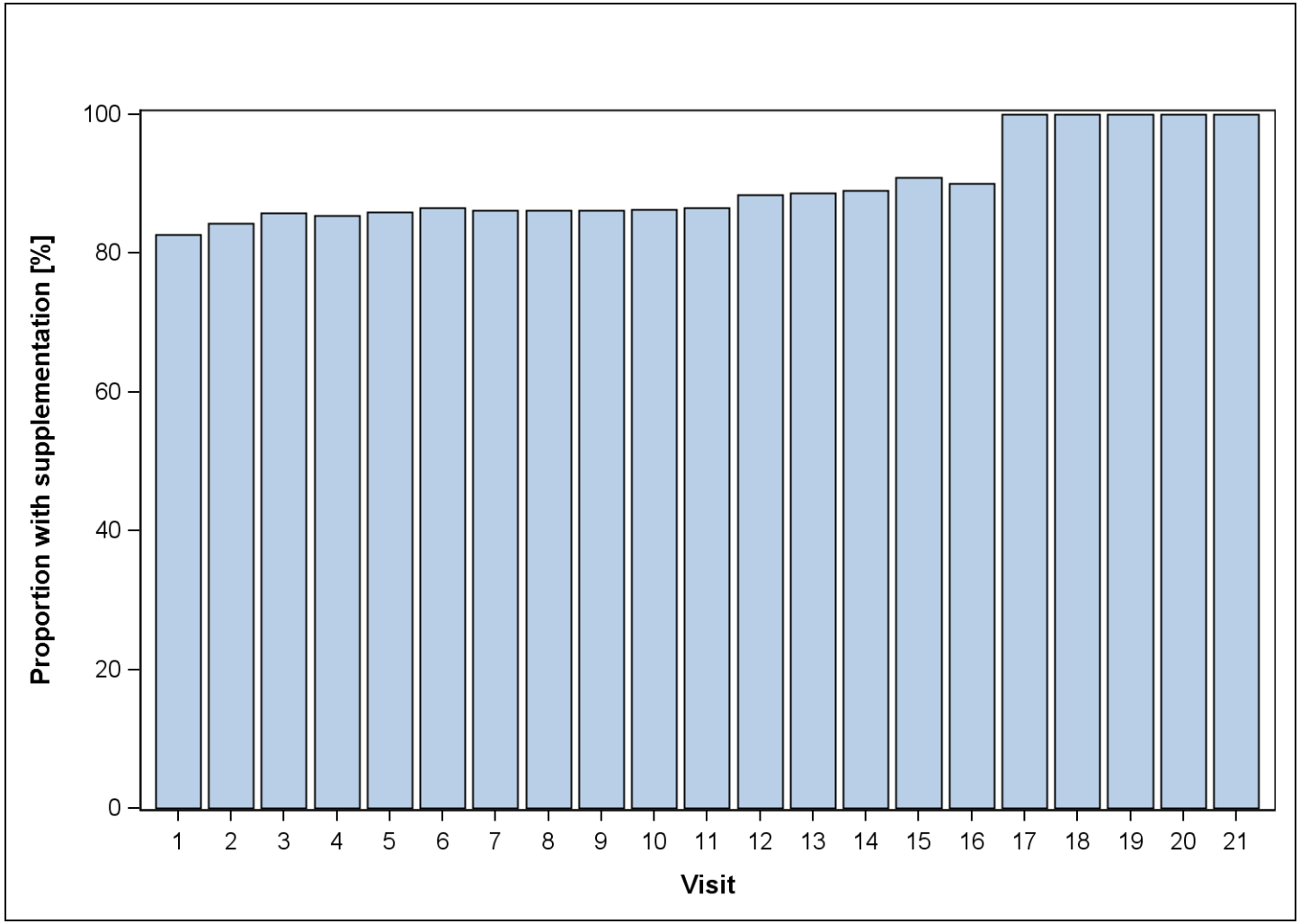
Cancer type	Visit	Unit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
	Visit 19	IU	3	533.3	230.9	400	400	400	800	800
	Visit 20	IU	3	533.3	230.9	400	400	400	800	800
	Visit 21	IU	1	400.0		400	400	400	400	400

Records with frequency 'other' were not included

15.4.2.1 Frequency of Calcium supplementation by visit - FAS

Visit	Missing	N Evaluable	Yes n (%)	No n (%)
Visit 1	3	1081	893 (82.6%)	188 (17.4%)
Visit 2	2	1041	878 (84.3%)	163 (15.7%)
Visit 3	3	999	857 (85.8%)	142 (14.2%)
Visit 4	6	944	806 (85.4%)	138 (14.6%)
Visit 5	3	904	777 (86.0%)	127 (14.0%)
Visit 6	1	850	736 (86.6%)	114 (13.4%)
Visit 7	2	817	704 (86.2%)	113 (13.8%)
Visit 8	1	775	668 (86.2%)	107 (13.8%)
Visit 9	2	737	635 (86.2%)	102 (13.8%)
Visit 10	1	697	601 (86.2%)	96 (13.8%)
Visit 11	4	636	550 (86.5%)	86 (13.5%)
Visit 12	3	546	483 (88.5%)	63 (11.5%)
Visit 13	4	370	328 (88.6%)	42 (11.4%)
Visit 14	1	100	89 (89.0%)	11 (11.0%)
Visit 15	0	22	20 (90.9%)	2 (9.1%)
Visit 16	0	10	9 (90.0%)	1 (10.0%)
Visit 17	0	5	5 (100.0%)	0 (0.0%)
Visit 18	0	3	3 (100.0%)	0 (0.0%)
Visit 19	0	3	3 (100.0%)	0 (0.0%)
Visit 20	0	3	3 (100.0%)	0 (0.0%)
Visit 21	0	1	1 (100.0%)	0 (0.0%)

15.4.2.2 Frequency of Calcium supplementation by visit graph - FAS



15.4.2.3 Summary of daily dose of Calcium supplementation by visit - FAS

Cancer type	Visit	Unit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Breast cancer	Visit 1	Pill	11	1.4	0.9	1	1	1	1	4
		mg	386	697.7	299.7	31	500	600	1000	3000
		IU	1	1000.0		1000	1000	1000	1000	1000
	Visit 2	Pill	15	1.3	0.8	1	1	1	1	4
		mg	383	683.9	265.6	34	500	600	1000	2400
	Visit 3	Pill	14	1.3	0.8	1	1	1	1	4
		Powder	0							
		mg	386	689.5	275.5	14	500	600	1000	2400
	Visit 4	Pill	16	1.2	0.8	1	1	1	1	4
		Ampul	1	1200.0		1200	1200	1200	1200	1200
		mg	363	681.7	273.2	34	500	600	1000	2400
	Visit 5	Pill	21	1.1	0.7	1	1	1	1	4
		Ampul	1	14.3		14	14	14	14	14
		mg	355	680.8	279.2	33	500	600	600	2400
	Visit 6	Pill	20	1.2	0.7	1	1	1	1	4
		mg	346	678.7	280.3	34	500	600	600	2400
	Visit 7	Pill	19	1.0	0.0	1	1	1	1	1
		Ampul	1	1200.0		1200	1200	1200	1200	1200
		mg	331	676.8	266.1	34	500	600	600	2000
	Visit 8	Pill	20	1.0	0.0	1	1	1	1	1
		mg	319	680.2	264.3	34	500	600	600	2000
		IU	1	400.0		400	400	400	400	400
	Visit 9	Pill	18	1.1	0.3	1	1	1	1	2
		mg	313	676.0	275.9	34	500	600	600	2400

Records with frequency 'other' were not included

15.4.2.3 Summary of daily dose of Calcium supplementation by visit - FAS

Cancer type	Visit	Unit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
	Visit 10	Pill	16	1.1	0.3	1	1	1	1	2
		µg	1	600.0		600	600	600	600	600
		mg	297	679.2	282.7	34	500	600	600	2400
	Visit 11	Pill	15	1.0	0.0	1	1	1	1	1
		mg	283	671.8	273.4	34	500	600	600	2400
	Visit 12	Pill	16	1.0	0.0	1	1	1	1	1
		mg	248	669.0	275.9	34	500	600	600	2400
	Visit 13	Pill	10	1.0	0.0	1	1	1	1	1
		mg	177	690.6	336.0	34	500	600	600	3000
	Visit 14	Pill	6	1.0	0.0	1	1	1	1	1
		mg	52	611.2	261.5	34	500	500	600	1500
	Visit 15	mg	15	605.6	314.3	34	500	500	600	1200
	Visit 16	mg	6	550.0	54.8	500	500	550	600	600
	Visit 17	mg	3	533.3	57.7	500	500	500	600	600
	Visit 18	mg	2	550.0	70.7	500	500	550	600	600
	Visit 19	mg	2	550.0	70.7	500	500	550	600	600
	Visit 20	mg	2	550.0	70.7	500	500	550	600	600
	Visit 21	mg	1	600.0		600	600	600	600	600
Prostate cancer	Visit 1	Pill	1	1.0		1	1	1	1	1
		mg	234	792.3	326.1	16	500	600	1000	2500
	Visit 2	Pill	2	1.0	0.0	1	1	1	1	1
		mg	234	798.2	327.5	31	500	600	1000	2500
	Visit 3	Pill	1	1.0		1	1	1	1	1

Records with frequency 'other' were not included

15.4.2.3 Summary of daily dose of Calcium supplementation by visit - FAS

Cancer type	Visit	Unit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
		mg	233	817.5	333.6	31	500	600	1000	2500
	Visit 4	Pill	1	1.0		1	1	1	1	1
		Powder	1	1000.0		1000	1000	1000	1000	1000
		mg	225	804.1	323.1	31	500	600	1000	2500
		IU	1	1000.0		1000	1000	1000	1000	1000
	Visit 5	Pill	2	1.0	0.0	1	1	1	1	1
		mg	225	806.4	324.2	31	500	600	1000	2500
	Visit 6	Pill	2	1.0	0.0	1	1	1	1	1
		mg	218	814.1	324.6	120	500	700	1000	3000
	Visit 7	Pill	2	1.0	0.0	1	1	1	1	1
		mg	216	824.1	345.5	100	500	880	1000	3000
	Visit 8	Pill	2	1.0	0.0	1	1	1	1	1
		mg	202	815.3	341.4	120	500	600	1000	3000
	Visit 9	Pill	2	1.0	0.0	1	1	1	1	1
		mg	195	828.2	355.9	500	500	800	1000	3000
	Visit 10	Pill	2	1.5	0.7	1	1	2	2	2
		mg	185	834.6	371.7	500	500	600	1000	3000
	Visit 11	Pill	2	1.5	0.7	1	1	2	2	2
		mg	168	844.7	427.3	343	500	600	1000	3600
	Visit 12	Pill	2	1.5	0.7	1	1	2	2	2
		mg	144	859.3	462.7	500	500	600	1000	3600
	Visit 13	mg	92	877.0	457.9	500	500	1000	1000	3600
		IU	1	880.0		880	880	880	880	880
	Visit 14	mg	19	878.9	435.4	500	500	1000	1000	2400

Records with frequency 'other' were not included

15.4.2.3 Summary of daily dose of Calcium supplementation by visit - FAS

Cancer type	Visit	Unit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
	Visit 15	mg	4	1000.0	0.0	1000	1000	1000	1000	1000
	Visit 16	mg	3	1000.0	0.0	1000	1000	1000	1000	1000
	Visit 17	mg	2	1000.0	0.0	1000	1000	1000	1000	1000
	Visit 18	mg	1	1000.0		1000	1000	1000	1000	1000
	Visit 19	mg	1	1000.0		1000	1000	1000	1000	1000
	Visit 20	mg	1	1000.0		1000	1000	1000	1000	1000
Lung cancer	Visit 1	Pill	5	1.0	0.0	1	1	1	1	1
		mg	126	805.2	367.4	200	600	600	1000	2500
	Visit 2	Pill	3	1.0	0.0	1	1	1	1	1
		mg	110	825.5	406.6	200	600	600	1000	2500
	Visit 3	Pill	4	1.0	0.0	1	1	1	1	1
		mg	97	804.1	349.9	500	600	600	1000	2500
	Visit 4	Pill	4	1.3	0.5	1	1	1	2	2
		mg	84	828.6	365.5	400	600	600	1000	2500
	Visit 5	Pill	4	1.3	0.5	1	1	1	2	2
		mg	71	838.0	382.5	500	600	600	1000	2500
	Visit 6	Pill	2	1.0	0.0	1	1	1	1	1
		mg	59	844.1	336.8	500	600	1000	1000	2500
	Visit 7	Pill	2	1.0	0.0	1	1	1	1	1
		mg	55	794.5	256.9	500	600	600	1000	1500
		IU	1	880.0		880	880	880	880	880
	Visit 8	Pill	1	1.0		1	1	1	1	1
		mg	52	778.8	254.4	500	600	600	1000	1500

Records with frequency 'other' were not included

15.4.2.3 Summary of daily dose of Calcium supplementation by visit - FAS

Cancer type	Visit	Unit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
	Visit 9	Pill	1	1.0		1	1	1	1	1
		mg	44	783.0	252.0	500	600	600	1000	1500
	Visit 10	Pill	1	1.0		1	1	1	1	1
		mg	42	772.6	253.3	500	600	600	1000	1500
	Visit 11	Pill	1	1.0		1	1	1	1	1
		mg	33	774.2	264.0	500	600	600	1000	1500
	Visit 12	Pill	1	1.0		1	1	1	1	1
		mg	27	750.0	239.8	500	600	600	1000	1250
	Visit 13	mg	19	700.0	216.0	500	600	600	1000	1200
	Visit 14	mg	5	800.0	282.8	600	600	600	1000	1200
	Visit 15	mg	1	1000.0		1000	1000	1000	1000	1000
Kidney cancer	Visit 1	Pill	1	1.0		1	1	1	1	1
		mg	34	739.7	271.3	250	500	600	1000	1200
	Visit 2	Pill	2	1.0	0.0	1	1	1	1	1
		mg	35	735.7	268.3	250	500	600	1000	1200
	Visit 3	Pill	1	1.0		1	1	1	1	1
		mg	35	794.3	426.3	500	500	600	1000	2400
	Visit 4	mg	33	815.2	452.2	500	500	600	1000	2500
	Visit 5	mg	31	835.5	459.4	500	500	600	1000	2500
	Visit 6	mg	28	864.3	474.7	500	550	600	1000	2500
	Visit 7	mg	26	788.5	273.3	500	500	600	1000	1200
	Visit 8	mg	22	845.5	371.3	500	500	800	1000	2000
	Visit 9	mg	22	820.1	406.2	43	500	800	1000	2000

Records with frequency 'other' were not included

15.4.2.3 Summary of daily dose of Calcium supplementation by visit - FAS

Cancer type	Visit	Unit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
	Visit 10	mg	21	928.6	441.7	500	600	1000	1000	2000
	Visit 11	mg	18	872.2	390.8	500	500	900	1000	2000
	Visit 12	mg	19	884.2	370.1	500	600	1000	1000	2000
	Visit 13	mg	13	846.2	278.7	500	500	1000	1000	1200
	Visit 14	mg	4	925.0	298.6	500	750	1000	1100	1200
Other cancer type	Visit 1	Pill	4	1.0	0.0	1	1	1	1	1
		mg	84	716.7	282.8	400	600	600	1000	2400
	Visit 2	Pill	2	1.0	0.0	1	1	1	1	1
		mg	81	766.7	505.7	100	600	600	1000	3600
		g	1	2.0		2	2	2	2	2
		IU	1	600.0		600	600	600	600	600
	Visit 3	Pill	2	1.0	0.0	1	1	1	1	1
		mg	75	786.7	477.1	500	600	600	1000	3600
		g	1	2.0		2	2	2	2	2
	Visit 4	Pill	1	1.0		1	1	1	1	1
		mg	68	758.8	362.1	500	600	600	1000	3000
		g	1	2.0		2	2	2	2	2
	Visit 5	Pill	1	1.0		1	1	1	1	1
		mg	57	814.0	531.0	500	600	600	1000	3600
		g	1	2.0		2	2	2	2	2
	Visit 6	Pill	1	1.0		1	1	1	1	1
		mg	51	829.4	519.7	500	600	600	1000	3600
	Visit 7	mg	43	807.0	493.5	500	600	600	1000	3600

Records with frequency 'other' were not included

15.4.2.3 Summary of daily dose of Calcium supplementation by visit - FAS

Cancer type	Visit	Unit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
		g	1	2.0		2	2	2	2	2
	Visit 8	Pill	1	1.0		1	1	1	1	1
		mg	41	856.1	566.1	500	600	600	1000	3600
	Visit 9	Pill	1	1.0		1	1	1	1	1
		mg	34	814.7	540.6	500	600	600	1000	3600
		g	1	2.0		2	2	2	2	2
	Visit 10	Pill	1	2.0		2	2	2	2	2
		mg	29	834.5	582.0	500	600	600	1000	3600
		g	1	2.0		2	2	2	2	2
	Visit 11	Pill	1	1.0		1	1	1	1	1
		mg	26	723.1	230.3	500	600	600	1000	1200
		g	1	2.0		2	2	2	2	2
	Visit 12	mg	24	737.5	233.7	500	600	600	1000	1200
		g	1	2.0		2	2	2	2	2
	Visit 13	Pill	1	1.0		1	1	1	1	1
		mg	14	714.3	228.2	500	600	600	1000	1200
		g	1	2.0		2	2	2	2	2
	Visit 14	mg	1	600.0		600	600	600	600	600
		g	1	2.0		2	2	2	2	2
		IU	1	400.0		400	400	400	400	400
Total	Visit 1	Pill	22	1.2	0.7	1	1	1	1	4
		mg	864	742.5	317.9	16	500	600	1000	3000
		IU	1	1000.0		1000	1000	1000	1000	1000

Records with frequency 'other' were not included

15.4.2.3 Summary of daily dose of Calcium supplementation by visit - FAS

Cancer type	Visit	Unit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
	Visit 2	Pill	24	1.2	0.6	1	1	1	1	4
		mg	843	744.2	337.2	31	500	600	1000	3600
		g	1	2.0		2	2	2	2	2
		IU	1	600.0		600	600	600	600	600
	Visit 3	Pill	22	1.2	0.7	1	1	1	1	4
		Powder	0							
		mg	826	752.3	335.3	14	500	600	1000	3600
		g	1	2.0		2	2	2	2	2
	Visit 4	Pill	22	1.2	0.7	1	1	1	1	4
		Ampul	1	1200.0		1200	1200	1200	1200	1200
		Powder	1	1000.0		1000	1000	1000	1000	1000
		mg	773	745.8	321.5	31	500	600	1000	3000
		g	1	2.0		2	2	2	2	2
		IU	1	1000.0		1000	1000	1000	1000	1000
	Visit 5	Pill	28	1.1	0.6	1	1	1	1	4
		Ampul	1	14.3		14	14	14	14	14
		mg	739	750.9	343.2	31	500	600	1000	3600
		g	1	2.0		2	2	2	2	2
	Visit 6	Pill	25	1.1	0.6	1	1	1	1	4
		mg	702	753.0	337.8	34	500	600	1000	3600
	Visit 7	Pill	23	1.0	0.0	1	1	1	1	1
		Ampul	1	1200.0		1200	1200	1200	1200	1200
		mg	671	746.6	318.4	34	500	600	1000	3600
		g	1	2.0		2	2	2	2	2

Records with frequency 'other' were not included

15.4.2.3 Summary of daily dose of Calcium supplementation by visit - FAS

Cancer type	Visit	Unit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
		IU	1	880.0		880	880	880	880	880
	Visit 8	Pill	24	1.0	0.0	1	1	1	1	1
		mg	636	748.2	326.7	34	500	600	1000	3600
		IU	1	400.0		400	400	400	400	400
	Visit 9	Pill	22	1.1	0.3	1	1	1	1	2
		mg	608	745.5	333.1	34	500	600	1000	3600
		g	1	2.0		2	2	2	2	2
	Visit 10	Pill	20	1.2	0.4	1	1	1	1	2
		µg	1	600.0		600	600	600	600	600
		mg	574	753.1	346.5	34	500	600	1000	3600
		g	1	2.0		2	2	2	2	2
	Visit 11	Pill	19	1.1	0.2	1	1	1	1	2
		mg	528	742.6	340.9	34	500	600	1000	3600
		g	1	2.0		2	2	2	2	2
	Visit 12	Pill	19	1.1	0.2	1	1	1	1	2
		mg	462	745.5	355.6	34	500	600	1000	3600
		g	1	2.0		2	2	2	2	2
	Visit 13	Pill	11	1.0	0.0	1	1	1	1	1
		mg	315	753.1	373.0	34	500	600	1000	3600
		g	1	2.0		2	2	2	2	2
		IU	1	880.0		880	880	880	880	880
	Visit 14	Pill	6	1.0	0.0	1	1	1	1	1
		mg	81	701.0	331.0	34	500	600	1000	2400
		g	1	2.0		2	2	2	2	2

Records with frequency 'other' were not included

15.4.2.3 Summary of daily dose of Calcium supplementation by visit - FAS

Cancer type	Visit	Unit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
		IU	1	400.0		400	400	400	400	400
	Visit 15	mg	20	704.2	321.7	34	500	600	1000	1200
	Visit 16	mg	9	700.0	229.1	500	500	600	1000	1000
	Visit 17	mg	5	720.0	258.8	500	500	600	1000	1000
	Visit 18	mg	3	700.0	264.6	500	500	600	1000	1000
	Visit 19	mg	3	700.0	264.6	500	500	600	1000	1000
	Visit 20	mg	3	700.0	264.6	500	500	600	1000	1000
	Visit 21	mg	1	600.0		600	600	600	600	600

Records with frequency 'other' were not included

15.5.1 VAS* pain score by cancer type and visit - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Breast cancer	Visit 1	380	26.16	23.46	0.00	5.00	20.00	40.00	95.00
	Visit 2	335	25.24	22.53	0.00	5.00	23.00	40.00	95.00
	Visit 3	327	25.27	22.71	0.00	5.00	20.00	40.00	100.00
	Visit 4	318	25.27	22.65	0.00	5.00	20.00	40.00	100.00
	Visit 5	291	26.31	23.03	0.00	5.00	22.00	40.00	90.00
	Visit 6	272	25.24	21.69	0.00	5.00	20.00	40.00	95.00
	Visit 7	228	25.57	21.95	0.00	7.00	20.00	40.00	92.00
Prostate cancer	Visit 1	240	21.93	22.58	0.00	1.00	15.00	35.00	92.00
	Visit 2	211	18.89	20.36	0.00	2.00	10.00	30.00	100.00
	Visit 3	217	18.84	20.11	0.00	0.00	10.00	30.00	87.00
	Visit 4	205	22.44	22.68	0.00	5.00	15.00	37.00	100.00
	Visit 5	187	20.56	21.27	0.00	4.00	10.00	30.00	85.00
	Visit 6	180	21.44	23.37	0.00	3.50	10.00	36.00	100.00
	Visit 7	127	21.36	23.25	0.00	0.00	10.00	40.00	94.00
Lung cancer	Visit 1	107	29.48	24.43	0.00	5.00	25.00	50.00	85.00
	Visit 2	88	30.76	25.05	0.00	8.50	30.00	50.00	90.00
	Visit 3	82	29.10	24.93	0.00	5.00	25.00	50.00	90.00
	Visit 4	67	32.99	27.12	0.00	7.00	30.00	58.00	85.00
	Visit 5	53	36.49	28.82	0.00	6.00	35.00	65.00	95.00
	Visit 6	42	25.55	23.09	0.00	5.00	23.50	35.00	80.00
	Visit 7	37	22.03	21.04	0.00	5.00	15.00	37.00	80.00

* Visual Analogue Scale (records the patient's self-rated sensation of pain) ranges from 0 (lowest pain) to 100 (highest pain).
Only planned visits according to protocol were included into the analysis (at each XGEVA application until a maximum of 24 weeks after the first XGEVA application, that means from visit 1 to visit 7 as a maximum).
If for a patient two different values were documented at the same visit the minimum value was included in the analysis.

15.5.1 VAS* pain score by cancer type and visit - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Kidney cancer	Visit 1	42	27.81	21.00	0.00	8.00	25.00	48.00	77.00
	Visit 2	35	25.86	24.62	0.00	4.00	20.00	45.00	85.00
	Visit 3	31	29.74	23.68	0.00	6.00	25.00	50.00	75.00
	Visit 4	29	27.10	19.82	0.00	15.00	25.00	40.00	75.00
	Visit 5	28	29.93	21.49	0.00	10.00	24.00	50.00	75.00
	Visit 6	19	34.05	22.67	0.00	12.00	35.00	50.00	70.00
	Visit 7	17	28.59	17.73	0.00	15.00	30.00	38.00	70.00
Other cancer type	Visit 1	83	30.34	22.12	0.00	10.00	30.00	45.00	85.00
	Visit 2	65	31.29	23.64	0.00	10.00	30.00	48.00	85.00
	Visit 3	57	30.35	24.45	0.00	10.00	25.00	50.00	85.00
	Visit 4	53	34.58	22.00	0.00	15.00	38.00	50.00	76.00
	Visit 5	46	31.70	21.16	0.00	11.00	32.50	45.00	85.00
	Visit 6	39	27.10	24.00	0.00	4.00	25.00	45.00	85.00
	Visit 7	31	26.39	20.45	0.00	8.00	25.00	40.00	75.00
Total	Visit 1	852	25.87	23.22	0.00	5.00	20.00	40.00	95.00
	Visit 2	734	24.64	22.79	0.00	5.00	20.00	40.00	100.00
	Visit 3	714	24.36	22.71	0.00	5.00	20.00	40.00	100.00
	Visit 4	672	25.99	23.24	0.00	5.00	20.00	40.00	100.00
	Visit 5	605	26.00	23.27	0.00	5.00	20.00	40.00	95.00
	Visit 6	552	24.46	22.63	0.00	5.00	20.00	40.00	100.00
	Visit 7	440	24.23	22.03	0.00	5.00	20.00	40.00	94.00

* Visual Analogue Scale (records the patient's self-rated sensation of pain) ranges from 0 (lowest pain) to 100 (highest pain).
Only planned visits according to protocol were included into the analysis (at each XGEVA application until a maximum of 24 weeks after the first XGEVA application, that means from visit 1 to visit 7 as a maximum).
If for a patient two different values were documented at the same visit the minimum value was included in the analysis.

15.5.2 Absolute changes from Visit 1 in VAS* pain score by cancer type and visit - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Breast cancer	Visit 2	292	-0.58	19.92	-85.00	-5.00	0.00	5.00	93.00
	Visit 3	286	1.04	23.01	-85.00	-9.00	0.00	8.00	100.00
	Visit 4	275	-0.28	22.09	-85.00	-10.00	0.00	10.00	100.00
	Visit 5	251	1.15	23.98	-85.00	-10.00	0.00	10.00	90.00
	Visit 6	236	0.83	23.30	-85.00	-10.00	0.00	12.00	80.00
	Visit 7	204	1.28	23.23	-55.00	-10.00	0.00	13.50	80.00
Prostate cancer	Visit 2	192	-3.46	18.59	-70.00	-6.00	0.00	3.00	100.00
	Visit 3	198	-3.25	17.74	-77.00	-8.00	0.00	2.00	65.00
	Visit 4	185	0.33	21.17	-78.00	-6.00	0.00	5.00	83.00
	Visit 5	171	0.06	19.82	-60.00	-5.00	0.00	8.00	70.00
	Visit 6	166	-0.40	21.77	-82.00	-6.00	0.00	6.00	85.00
	Visit 7	115	0.77	23.44	-65.00	-5.00	0.00	8.00	81.00
Lung cancer	Visit 2	78	0.83	16.55	-45.00	-5.00	0.00	5.00	61.00
	Visit 3	69	0.65	18.08	-50.00	-5.00	0.00	5.00	60.00
	Visit 4	55	3.96	19.49	-45.00	-5.00	1.00	10.00	75.00
	Visit 5	46	7.96	22.53	-40.00	-5.00	3.00	20.00	78.00
	Visit 6	37	1.78	23.93	-65.00	-10.00	0.00	10.00	50.00
	Visit 7	33	-1.91	22.47	-70.00	-14.00	0.00	10.00	40.00
Kidney cancer	Visit 2	31	-0.94	23.08	-77.00	-10.00	0.00	6.00	70.00
	Visit 3	27	5.89	22.28	-35.00	-8.00	0.00	10.00	65.00
	Visit 4	25	1.16	21.68	-67.00	-10.00	0.00	13.00	36.00
	Visit 5	25	2.52	22.30	-77.00	-2.00	2.00	15.00	45.00

* Visual Analogue Scale (records the patient's self-rated sensation of pain) ranges from 0 (lowest pain) to 100 (highest pain).
Only planned visits according to protocol were included into the analysis (at each XGEVA application until a maximum of 24 weeks after the first XGEVA application, that means from visit 1 to visit 7 as a maximum).
If for a patient two different values were documented at the same visit the minimum value was included in the analysis.

15.5.2 Absolute changes from Visit 1 in VAS* pain score by cancer type and visit - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
	Visit 6	17	6.47	26.35	-38.00	-3.00	7.00	20.00	58.00
	Visit 7	13	0.69	12.33	-15.00	-3.00	0.00	5.00	26.00

* Visual Analogue Scale (records the patient's self-rated sensation of pain) ranges from 0 (lowest pain) to 100 (highest pain).
Only planned visits according to protocol were included into the analysis (at each XGEVA application until a maximum of 24 weeks after the first XGEVA application, that means from visit 1 to visit 7 as a maximum).
If for a patient two different values were documented at the same visit the minimum value was included in the analysis.

15.5.2 Absolute changes from Visit 1 in VAS* pain score by cancer type and visit - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Other cancer type	Visit 2	56	-0.75	24.91	-50.00	-15.00	-1.00	8.00	85.00
	Visit 3	50	-2.82	25.46	-55.00	-20.00	0.00	10.00	85.00
	Visit 4	46	0.87	22.57	-40.00	-10.00	0.00	10.00	52.00
	Visit 5	40	1.05	20.45	-38.00	-10.00	-1.00	10.00	60.00
	Visit 6	34	-2.62	21.70	-44.00	-22.00	0.00	10.00	45.00
	Visit 7	27	-5.85	19.79	-45.00	-20.00	-3.00	7.00	41.00
Total	Visit 2	649	-1.29	19.80	-85.00	-5.00	0.00	5.00	100.00
	Visit 3	630	-0.45	21.23	-85.00	-8.00	0.00	5.00	100.00
	Visit 4	586	0.46	21.56	-85.00	-10.00	0.00	10.00	100.00
	Visit 5	533	1.44	22.27	-85.00	-8.00	0.00	10.00	90.00
	Visit 6	490	0.44	22.80	-85.00	-10.00	0.00	10.00	85.00
	Visit 7	392	0.35	22.72	-70.00	-10.00	0.00	10.00	81.00

* Visual Analogue Scale (records the patient's self-rated sensation of pain) ranges from 0 (lowest pain) to 100 (highest pain).
Only planned visits according to protocol were included into the analysis (at each XGEVA application until a maximum of 24 weeks after the first XGEVA application, that means from visit 1 to visit 7 as a maximum).
If for a patient two different values were documented at the same visit the minimum value was included in the analysis.

15.5.3 EQ-5D item: mobility and visit - FAS

	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Visit 1	363			224			107			40			76			810		
I have no problems in walking about		197	(54.3%)		129	(57.6%)		59	(55.1%)		20	(50.0%)		41	(53.9%)		446	(55.1%)
I have some problems in walking about		162	(44.6%)		93	(41.5%)		47	(43.9%)		20	(50.0%)		32	(42.1%)		354	(43.7%)
I am confined to bed		4	(1.1%)		2	(0.9%)		1	(0.9%)		0	(0.0%)		3	(3.9%)		10	(1.2%)
Visit 4	285			193			61			26			53			618		
I have no problems in walking about		161	(56.5%)		110	(57.0%)		25	(41.0%)		11	(42.3%)		26	(49.1%)		333	(53.9%)
I have some problems in walking about		119	(41.8%)		81	(42.0%)		35	(57.4%)		15	(57.7%)		25	(47.2%)		275	(44.5%)
I am confined to bed		5	(1.8%)		2	(1.0%)		1	(1.6%)		0	(0.0%)		2	(3.8%)		10	(1.6%)
Visit 7	248			166			35			19			30			498		
I have no problems in walking about		140	(56.5%)		86	(51.8%)		22	(62.9%)		9	(47.4%)		12	(40.0%)		269	(54.0%)
I have some problems in walking about		104	(41.9%)		79	(47.6%)		12	(34.3%)		10	(52.6%)		15	(50.0%)		220	(44.2%)
I am confined to bed		4	(1.6%)		1	(0.6%)		1	(2.9%)		0	(0.0%)		3	(10.0%)		9	(1.8%)
Visit 10	218			148			22			12			22			422		
I have no problems in walking about		125	(57.3%)		84	(56.8%)		13	(59.1%)		6	(50.0%)		8	(36.4%)		236	(55.9%)
I have some problems in walking about		92	(42.2%)		64	(43.2%)		9	(40.9%)		6	(50.0%)		13	(59.1%)		184	(43.6%)
I am confined to bed		1	(0.5%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(4.5%)		2	(0.5%)

Only planned visits according to protocol were included into the analysis (visit 1, visit 4, visit 7, visit 10 and study end). The numbering of visits as documented in the paper questionnaire was used. This could be different from eCRF.

15.5.3 EQ-5D item: mobility and visit - FAS

	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Study end	144			92			9			11			16			272		
I have no problems in walking about		81	(56.3%)		52	(56.5%)		7	(77.8%)		6	(54.5%)		10	(62.5%)		156	(57.4%)
I have some problems in walking about		63	(43.8%)		40	(43.5%)		2	(22.2%)		5	(45.5%)		5	(31.3%)		115	(42.3%)
I am confined to bed		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(6.3%)		1	(0.4%)

Only planned visits according to protocol were included into the analysis (visit 1, visit 4, visit 7, visit 10 and study end). The numbering of visits as documented in the paper questionnaire was used. This could be different from eCRF.

15.5.4 EQ-5D item: self care by cancer type and visit - FAS

	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Visit 1	364			223			107			40			76			810		
I have no problems with self-care		271	(74.5%)		166	(74.4%)		74	(69.2%)		30	(75.0%)		53	(69.7%)		594	(73.3%)
I have some problem washing or dressing myself		80	(22.0%)		52	(23.3%)		27	(25.2%)		9	(22.5%)		19	(25.0%)		187	(23.1%)
I am unable to wash or dress myself		13	(3.6%)		5	(2.2%)		6	(5.6%)		1	(2.5%)		4	(5.3%)		29	(3.6%)
Visit 4	287			193			62			25			53			620		
I have no problems with self-care		222	(77.4%)		143	(74.1%)		36	(58.1%)		19	(76.0%)		37	(69.8%)		457	(73.7%)
I have some problem washing or dressing myself		55	(19.2%)		44	(22.8%)		24	(38.7%)		5	(20.0%)		13	(24.5%)		141	(22.7%)
I am unable to wash or dress myself		10	(3.5%)		6	(3.1%)		2	(3.2%)		1	(4.0%)		3	(5.7%)		22	(3.5%)
Visit 7	248			164			35			19			31			497		
I have no problems with self-care		189	(76.2%)		116	(70.7%)		24	(68.6%)		14	(73.7%)		20	(64.5%)		363	(73.0%)
I have some problem washing or dressing myself		51	(20.6%)		43	(26.2%)		11	(31.4%)		5	(26.3%)		9	(29.0%)		119	(23.9%)
I am unable to wash or dress myself		8	(3.2%)		5	(3.0%)		0	(0.0%)		0	(0.0%)		2	(6.5%)		15	(3.0%)

Only planned visits according to protocol were included into the analysis (visit 1, visit 4, visit 7, visit 10 and study end). The numbering of visits as documented in the paper questionnaire was used. This could be different from eCRF.

15.5.4 EQ-5D item: self care by cancer type and visit - FAS

	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Visit 10	219			148			22			12			22			423		
I have no problems with self-care		163	(74.4%)		106	(71.6%)		15	(68.2%)		9	(75.0%)		14	(63.6%)		307	(72.6%)
I have some problem washing or dressing myself		48	(21.9%)		37	(25.0%)		5	(22.7%)		2	(16.7%)		6	(27.3%)		98	(23.2%)
I am unable to wash or dress myself		8	(3.7%)		5	(3.4%)		2	(9.1%)		1	(8.3%)		2	(9.1%)		18	(4.3%)
Study end	145			92			9			11			16			273		
I have no problems with self-care		105	(72.4%)		62	(67.4%)		8	(88.9%)		9	(81.8%)		10	(62.5%)		194	(71.1%)
I have some problem washing or dressing myself		38	(26.2%)		27	(29.3%)		1	(11.1%)		1	(9.1%)		4	(25.0%)		71	(26.0%)
I am unable to wash or dress myself		2	(1.4%)		3	(3.3%)		0	(0.0%)		1	(9.1%)		2	(12.5%)		8	(2.9%)

Only planned visits according to protocol were included into the analysis (visit 1, visit 4, visit 7, visit 10 and study end). The numbering of visits as documented in the paper questionnaire was used. This could be different from eCRF.

15.5.5 EQ-5D item: usual activities by cancer type and visit - FAS

	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Visit 1	364			224			107			40			76			811		
I have no problems with performing my usual activities		155	(42.6%)		126	(56.3%)		40	(37.4%)		16	(40.0%)		23	(30.3%)		360	(44.4%)
I have some problems with performing my usual activities		178	(48.9%)		91	(40.6%)		48	(44.9%)		23	(57.5%)		44	(57.9%)		384	(47.3%)
I am unable to perform my usual activities		31	(8.5%)		7	(3.1%)		19	(17.8%)		1	(2.5%)		9	(11.8%)		67	(8.3%)
Visit 4	286			192			62			26			52			618		
I have no problems with performing my usual activities		135	(47.2%)		114	(59.4%)		16	(25.8%)		7	(26.9%)		14	(26.9%)		286	(46.3%)
I have some problems with performing my usual activities		126	(44.1%)		69	(35.9%)		33	(53.2%)		16	(61.5%)		34	(65.4%)		278	(45.0%)
I am unable to perform my usual activities		25	(8.7%)		9	(4.7%)		13	(21.0%)		3	(11.5%)		4	(7.7%)		54	(8.7%)
Visit 7	247			164			35			19			31			496		
I have no problems with performing my usual activities		115	(46.6%)		94	(57.3%)		12	(34.3%)		5	(26.3%)		11	(35.5%)		237	(47.8%)

Only planned visits according to protocol were included into the analysis (visit 1, visit 4, visit 7, visit 10 and study end). The numbering of visits as documented in the paper questionnaire was used. This could be different from eCRF.

15.5.5 EQ-5D item: usual activities by cancer type and visit - FAS

	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
I have some problems with performing my usual activities		115	(46.6%)		64	(39.0%)		20	(57.1%)		11	(57.9%)		16	(51.6%)		226	(45.6%)
I am unable to perform my usual activities		17	(6.9%)		6	(3.7%)		3	(8.6%)		3	(15.8%)		4	(12.9%)		33	(6.7%)

Only planned visits according to protocol were included into the analysis (visit 1, visit 4, visit 7, visit 10 and study end). The numbering of visits as documented in the paper questionnaire was used. This could be different from eCRF.

15.5.5 EQ-5D item: usual activities by cancer type and visit - FAS

	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Visit 10	218			147			22			11			22			420		
I have no problems with performing my usual activities		110	(50.5%)		85	(57.8%)		9	(40.9%)		4	(36.4%)		7	(31.8%)		215	(51.2%)
I have some problems with performing my usual activities		90	(41.3%)		54	(36.7%)		10	(45.5%)		6	(54.5%)		13	(59.1%)		173	(41.2%)
I am unable to perform my usual activities		18	(8.3%)		8	(5.4%)		3	(13.6%)		1	(9.1%)		2	(9.1%)		32	(7.6%)
Study end	145			92			9			11			16			273		
I have no problems with performing my usual activities		70	(48.3%)		54	(58.7%)		5	(55.6%)		6	(54.5%)		8	(50.0%)		143	(52.4%)
I have some problems with performing my usual activities		67	(46.2%)		34	(37.0%)		4	(44.4%)		4	(36.4%)		6	(37.5%)		115	(42.1%)
I am unable to perform my usual activities		8	(5.5%)		4	(4.3%)		0	(0.0%)		1	(9.1%)		2	(12.5%)		15	(5.5%)

Only planned visits according to protocol were included into the analysis (visit 1, visit 4, visit 7, visit 10 and study end). The numbering of visits as documented in the paper questionnaire was used. This could be different from eCRF.

15.5.6 EQ-5D item: pain/discomfort by cancer type and visit - FAS

	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Visit 1	364			222			107			40			76			809		
I have no pain or discomfort		100	(27.5%)		94	(42.3%)		23	(21.5%)		5	(12.5%)		13	(17.1%)		235	(29.0%)
I have moderate pain or discomfort		234	(64.3%)		119	(53.6%)		74	(69.2%)		34	(85.0%)		59	(77.6%)		520	(64.3%)
I have extreme pain or discomfort		30	(8.2%)		9	(4.1%)		10	(9.3%)		1	(2.5%)		4	(5.3%)		54	(6.7%)
Visit 4	285			191			62			26			53			617		
I have no pain or discomfort		91	(31.9%)		79	(41.4%)		9	(14.5%)		3	(11.5%)		9	(17.0%)		191	(31.0%)
I have moderate pain or discomfort		184	(64.6%)		99	(51.8%)		43	(69.4%)		22	(84.6%)		41	(77.4%)		389	(63.0%)
I have extreme pain or discomfort		10	(3.5%)		13	(6.8%)		10	(16.1%)		1	(3.8%)		3	(5.7%)		37	(6.0%)
Visit 7	249			167			35			19			32			502		
I have no pain or discomfort		84	(33.7%)		59	(35.3%)		9	(25.7%)		5	(26.3%)		9	(28.1%)		166	(33.1%)
I have moderate pain or discomfort		153	(61.4%)		103	(61.7%)		24	(68.6%)		14	(73.7%)		23	(71.9%)		317	(63.1%)
I have extreme pain or discomfort		12	(4.8%)		5	(3.0%)		2	(5.7%)		0	(0.0%)		0	(0.0%)		19	(3.8%)
Visit 10	219			148			22			12			22			423		
I have no pain or discomfort		67	(30.6%)		50	(33.8%)		7	(31.8%)		2	(16.7%)		5	(22.7%)		131	(31.0%)

Only planned visits according to protocol were included into the analysis (visit 1, visit 4, visit 7, visit 10 and study end). The numbering of visits as documented in the paper questionnaire was used. This could be different from eCRF.

15.5.6 EQ-5D item: pain/discomfort by cancer type and visit - FAS

	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
I have moderate pain or discomfort		137	(62.6%)		92	(62.2%)		15	(68.2%)		8	(66.7%)		16	(72.7%)		268	(63.4%)
I have extreme pain or discomfort		15	(6.8%)		6	(4.1%)		0	(0.0%)		2	(16.7%)		1	(4.5%)		24	(5.7%)

Only planned visits according to protocol were included into the analysis (visit 1, visit 4, visit 7, visit 10 and study end). The numbering of visits as documented in the paper questionnaire was used. This could be different from eCRF.

15.5.6 EQ-5D item: pain/discomfort by cancer type and visit - FAS

	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Study end	145			92			9			11			16			273		
I have no pain or discomfort		47	(32.4%)		32	(34.8%)		4	(44.4%)		2	(18.2%)		6	(37.5%)		91	(33.3%)
I have moderate pain or discomfort		91	(62.8%)		57	(62.0%)		5	(55.6%)		8	(72.7%)		9	(56.3%)		170	(62.3%)
I have extreme pain or discomfort		7	(4.8%)		3	(3.3%)		0	(0.0%)		1	(9.1%)		1	(6.3%)		12	(4.4%)

Only planned visits according to protocol were included into the analysis (visit 1, visit 4, visit 7, visit 10 and study end). The numbering of visits as documented in the paper questionnaire was used. This could be different from eCRF.

15.5.7 EQ-5D item: anxiety/depression by cancer type and visit - FAS

	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Visit 1	363			222			104			40			76			805		
I am not anxious or depressed		188	(51.8%)		137	(61.7%)		70	(67.3%)		24	(60.0%)		45	(59.2%)		464	(57.6%)
I am moderately anxious or depressed		160	(44.1%)		82	(36.9%)		33	(31.7%)		15	(37.5%)		27	(35.5%)		317	(39.4%)
I am extremely anxious or depressed		15	(4.1%)		3	(1.4%)		1	(1.0%)		1	(2.5%)		4	(5.3%)		24	(3.0%)
Visit 4	287			188			62			26			53			616		
I am not anxious or depressed		167	(58.2%)		124	(66.0%)		39	(62.9%)		9	(34.6%)		36	(67.9%)		375	(60.9%)
I am moderately anxious or depressed		108	(37.6%)		59	(31.4%)		21	(33.9%)		16	(61.5%)		16	(30.2%)		220	(35.7%)
I am extremely anxious or depressed		12	(4.2%)		5	(2.7%)		2	(3.2%)		1	(3.8%)		1	(1.9%)		21	(3.4%)
Visit 7	245			165			35			19			32			496		
I am not anxious or depressed		138	(56.3%)		107	(64.8%)		25	(71.4%)		9	(47.4%)		18	(56.3%)		297	(59.9%)
I am moderately anxious or depressed		99	(40.4%)		56	(33.9%)		9	(25.7%)		10	(52.6%)		12	(37.5%)		186	(37.5%)
I am extremely anxious or depressed		8	(3.3%)		2	(1.2%)		1	(2.9%)		0	(0.0%)		2	(6.3%)		13	(2.6%)

Only planned visits according to protocol were included into the analysis (visit 1, visit 4, visit 7, visit 10 and study end). The numbering of visits as documented in the paper questionnaire was used. This could be different from eCRF.

15.5.7 EQ-5D item: anxiety/depression by cancer type and visit - FAS

	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Visit 10	219			148			22			12			22			423		
I am not anxious or depressed		117	(53.4%)		89	(60.1%)		15	(68.2%)		5	(41.7%)		8	(36.4%)		234	(55.3%)
I am moderately anxious or depressed		89	(40.6%)		55	(37.2%)		7	(31.8%)		6	(50.0%)		14	(63.6%)		171	(40.4%)
I am extremely anxious or depressed		13	(5.9%)		4	(2.7%)		0	(0.0%)		1	(8.3%)		0	(0.0%)		18	(4.3%)
Study end	143			91			9			11			16			270		
I am not anxious or depressed		90	(62.9%)		53	(58.2%)		8	(88.9%)		6	(54.5%)		10	(62.5%)		167	(61.9%)
I am moderately anxious or depressed		48	(33.6%)		35	(38.5%)		1	(11.1%)		4	(36.4%)		6	(37.5%)		94	(34.8%)
I am extremely anxious or depressed		5	(3.5%)		3	(3.3%)		0	(0.0%)		1	(9.1%)		0	(0.0%)		9	(3.3%)

Only planned visits according to protocol were included into the analysis (visit 1, visit 4, visit 7, visit 10 and study end). The numbering of visits as documented in the paper questionnaire was used. This could be different from eCRF.

15.5.8 EQ VAS* scale by cancer type and visit - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Breast cancer	Visit 1	359	64.71	21.19	0.00	50.00	70.00	80.00	100.00
	Visit 4	280	66.10	22.50	0.00	50.00	70.00	85.00	100.00
	Visit 7	245	65.22	22.31	0.00	50.00	70.00	80.00	100.00
	Visit 10	211	65.89	22.19	0.00	50.00	70.00	80.00	100.00
	Study end	143	67.16	20.85	0.00	50.00	70.00	85.00	100.00
Prostate cancer	Visit 1	223	66.58	21.37	0.00	50.00	70.00	80.00	100.00
	Visit 4	196	67.15	21.47	0.00	55.00	70.00	80.00	100.00
	Visit 7	167	68.08	22.04	0.00	50.00	74.00	85.00	100.00
	Visit 10	144	67.76	21.96	15.00	51.00	74.00	83.50	100.00
	Study end	90	69.31	21.74	4.00	60.00	73.00	85.00	100.00
Lung cancer	Visit 1	108	58.99	20.01	10.00	46.00	60.00	72.50	100.00
	Visit 4	61	58.89	23.08	0.00	40.00	60.00	75.00	100.00
	Visit 7	35	66.66	18.32	40.00	50.00	65.00	80.00	100.00
	Visit 10	20	70.00	20.87	20.00	57.50	75.00	90.00	98.00
	Study end	9	72.56	25.22	15.00	60.00	80.00	88.00	95.00
Kidney cancer	Visit 1	40	62.25	17.83	10.00	50.00	60.00	75.00	90.00
	Visit 4	26	64.27	20.29	25.00	50.00	70.00	75.00	95.00
	Visit 7	19	60.95	20.45	23.00	50.00	60.00	75.00	100.00
	Visit 10	12	65.42	18.88	25.00	55.00	70.00	79.00	90.00
	Study end	11	68.00	19.03	30.00	55.00	70.00	80.00	100.00
Other cancer type	Visit 1	74	59.97	20.44	10.00	48.00	65.00	75.00	100.00

* EQ Visual Analogue Scale (records the patient's self-rated health on a vertical visual analogue scale) ranges from 0 (worst health) to 100 (best health).
Only planned visits according to protocol were included into the analysis (visit 1, visit 4, visit 7, visit 10 and study end). The numbering of visits as documented in the paper questionnaire was used. This could be different from eCRF.
If for a patient two different values were documented at the same visit the minimum value was included in the analysis.

15.5.8 EQ VAS* scale by cancer type and visit - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
	Visit 4	52	53.58	17.81	3.00	45.00	50.00	65.00	90.00
	Visit 7	32	56.88	21.92	5.00	44.00	57.50	70.00	100.00
	Visit 10	21	58.14	22.48	10.00	45.00	60.00	70.00	90.00
	Study end	15	65.13	23.60	15.00	50.00	70.00	80.00	95.00

* EQ Visual Analogue Scale (records the patient's self-rated health on a vertical visual analogue scale) ranges from 0 (worst health) to 100 (best health).
Only planned visits according to protocol were included into the analysis (visit 1, visit 4, visit 7, visit 10 and study end). The numbering of visits as documented in the paper questionnaire was used. This could be different from eCRF.
If for a patient two different values were documented at the same visit the minimum value was included in the analysis.

15.5.8 EQ VAS* scale by cancer type and visit - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Total	Visit 1	804	63.90	20.98	0.00	50.00	69.00	80.00	100.00
	Visit 4	615	64.58	22.10	0.00	50.00	68.00	80.00	100.00
	Visit 7	498	65.58	21.97	0.00	50.00	70.00	80.00	100.00
	Visit 10	408	66.34	21.99	0.00	50.00	70.00	82.00	100.00
	Study end	268	67.99	21.28	0.00	52.50	70.00	85.00	100.00

* EQ Visual Analogue Scale (records the patient's self-rated health on a vertical visual analogue scale) ranges from 0 (worst health) to 100 (best health).
Only planned visits according to protocol were included into the analysis (visit 1, visit 4, visit 7, visit 10 and study end). The numbering of visits as documented in the paper questionnaire was used. This could be different from eCRF.
If for a patient two different values were documented at the same visit the minimum value was included in the analysis.

15.5.9 Absolute changes from Visit 1 in EQ VAS* scale by cancer type and visit - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Breast cancer	Visit 4	229	-1.68	22.02	-100.00	-10.00	0.00	7.00	75.00
	Visit 7	210	0.98	20.85	-90.00	-10.00	0.00	10.00	85.00
	Visit 10	173	0.02	25.10	-95.00	-10.00	0.00	10.00	85.00
	Study end	116	1.16	25.67	-90.00	-10.00	0.00	15.00	83.00
Prostate cancer	Visit 4	169	0.52	23.00	-80.00	-7.00	0.00	10.00	96.00
	Visit 7	146	-0.85	22.90	-88.00	-10.00	0.00	10.00	81.00
	Visit 10	126	0.10	24.81	-70.00	-10.00	0.00	12.00	91.00
	Study end	76	-2.72	24.10	-86.00	-10.00	0.00	10.00	65.00
Lung cancer	Visit 4	54	-2.19	22.82	-70.00	-10.00	0.00	10.00	45.00
	Visit 7	33	7.94	19.56	-35.00	0.00	8.00	20.00	55.00
	Visit 10	19	8.16	19.28	-25.00	-5.00	8.00	20.00	50.00
	Study end	7	6.14	17.63	-25.00	-2.00	10.00	20.00	30.00
Kidney cancer	Visit 4	22	-3.14	24.13	-60.00	-20.00	-4.50	5.00	60.00
	Visit 7	16	-7.31	13.07	-30.00	-15.00	-5.00	0.00	20.00
	Visit 10	10	-4.50	11.97	-25.00	-10.00	-5.00	5.00	12.00
	Study end	9	5.89	15.24	-5.00	-5.00	-5.00	10.00	38.00
Other cancer type	Visit 4	43	-6.98	21.53	-48.00	-20.00	-5.00	5.00	50.00
	Visit 7	27	-4.78	26.28	-80.00	-18.00	-2.00	10.00	55.00
	Visit 10	17	-0.88	15.93	-25.00	-15.00	0.00	5.00	25.00
	Study end	12	-3.17	16.26	-25.00	-15.50	-3.50	7.50	30.00
Total	Visit 4	517	-1.51	22.48	-100.00	-10.00	0.00	9.00	96.00

* EQ Visual Analogue Scale (records the patient's self-rated health on a vertical visual analogue scale) ranges from 0 (worst health) to 100 (best health).
Only planned visits according to protocol were included into the analysis (visit 1, visit 4, visit 7, visit 10 and study end). The numbering of visits as documented in the paper questionnaire was used. This could be different from eCRF.
If for a patient two different values were documented at the same visit the minimum value was included in the analysis.

15.5.9 Absolute changes from Visit 1 in EQ VAS* scale by cancer type and visit - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
	Visit 7	432	0.23	21.73	-90.00	-10.00	0.00	10.00	85.00
	Visit 10	345	0.32	24.04	-95.00	-10.00	0.00	10.00	91.00
	Study end	220	-0.06	24.11	-90.00	-10.00	0.00	10.00	83.00

* EQ Visual Analogue Scale (records the patient's self-rated health on a vertical visual analogue scale) ranges from 0 (worst health) to 100 (best health).
Only planned visits according to protocol were included into the analysis (visit 1, visit 4, visit 7, visit 10 and study end). The numbering of visits as documented in the paper questionnaire was used. This could be different from eCRF.
If for a patient two different values were documented at the same visit the minimum value was included in the analysis.

15.6.1 Patients with at least one dose modification by cancer type - FAS

	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
Patients with at least one dose modification	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
No	508	(99.8%)	294	(100.0%)	158	(99.4%)	49	(98.0%)	116	(100.0%)	1125	(99.7%)
Yes	1	(0.2%)	0	(0.0%)	1	(0.6%)	1	(2.0%)	0	(0.0%)	3	(0.3%)

15.6.2 Dose application during study by cancer type and visit - FAS

	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Baseline 1st application	509			294			159			50			116			1128		
120 mg		509	(100.0%)		294	(100.0%)		159	(100.0%)		49	(98.0%)		116	(100.0%)		1127	(99.9%)
Other dose		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(2.0%)		0	(0.0%)		1	(0.1%)
Baseline 2nd application	143			53			38			9			25			268		
120 mg		143	(100.0%)		53	(100.0%)		38	(100.0%)		9	(100.0%)		25	(100.0%)		268	(100.0%)
Other dose		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Visit 1	491			290			147			48			108			1084		
120 mg		491	(100.0%)		290	(100.0%)		146	(99.3%)		48	(100.0%)		108	(100.0%)		1083	(99.9%)
Other dose		0	(0.0%)		0	(0.0%)		1	(0.7%)		0	(0.0%)		0	(0.0%)		1	(0.1%)
Visit 2	485			284			128			47			98			1042		
120 mg		485	(100.0%)		284	(100.0%)		127	(99.2%)		47	(100.0%)		98	(100.0%)		1041	(99.9%)
Other dose		0	(0.0%)		0	(0.0%)		1	(0.8%)		0	(0.0%)		0	(0.0%)		1	(0.1%)
Visit 3	473			277			117			45			89			1001		
120 mg		473	(100.0%)		277	(100.0%)		116	(99.1%)		45	(100.0%)		89	(100.0%)		1000	(99.9%)
Other dose		0	(0.0%)		0	(0.0%)		1	(0.9%)		0	(0.0%)		0	(0.0%)		1	(0.1%)
Visit 4	458			264			101			42			80			945		
120 mg		457	(99.8%)		264	(100.0%)		100	(99.0%)		42	(100.0%)		80	(100.0%)		943	(99.8%)
Other dose		1	(0.2%)		0	(0.0%)		1	(1.0%)		0	(0.0%)		0	(0.0%)		2	(0.2%)
Visit 5	449			262			86			40			68			905		
120 mg		449	(100.0%)		262	(100.0%)		85	(98.8%)		40	(100.0%)		68	(100.0%)		904	(99.9%)
Other dose		0	(0.0%)		0	(0.0%)		1	(1.2%)		0	(0.0%)		0	(0.0%)		1	(0.1%)
Visit 6	429			253			70			35			62			849		

15.6.2 Dose application during study by cancer type and visit - FAS

	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
120 mg		429	(100.0%)		253	(100.0%)		70	(100.0%)		35	(100.0%)		62	(100.0%)		849	(100.0%)
Other dose		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

15.6.2 Dose application during study by cancer type and visit - FAS

	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Visit 7	418			247			66			32			54			817		
120 mg		418	(100.0%)		247	(100.0%)		66	(100.0%)		32	(100.0%)		54	(100.0%)		817	(100.0%)
Other dose		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Visit 8	401			234			61			28			51			775		
120 mg		401	(100.0%)		234	(100.0%)		61	(100.0%)		28	(100.0%)		51	(100.0%)		775	(100.0%)
Other dose		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Visit 9	392			222			53			27			43			737		
120 mg		392	(100.0%)		222	(100.0%)		53	(100.0%)		27	(100.0%)		43	(100.0%)		737	(100.0%)
Other dose		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Visit 10	372			212			50			26			37			697		
120 mg		372	(100.0%)		212	(100.0%)		50	(100.0%)		26	(100.0%)		37	(100.0%)		697	(100.0%)
Other dose		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Visit 11	352			189			39			23			32			635		
120 mg		352	(100.0%)		189	(100.0%)		39	(100.0%)		23	(100.0%)		32	(100.0%)		635	(100.0%)
Other dose		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Visit 12	305			161			31			22			28			547		
120 mg		305	(100.0%)		161	(100.0%)		31	(100.0%)		22	(100.0%)		28	(100.0%)		547	(100.0%)
Other dose		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Visit 13	219			98			22			14			17			370		
120 mg		219	(100.0%)		98	(100.0%)		22	(100.0%)		14	(100.0%)		17	(100.0%)		370	(100.0%)
Other dose		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Visit 14	65			21			6			5			3			100		
120 mg		65	(100.0%)		21	(100.0%)		6	(100.0%)		5	(100.0%)		3	(100.0%)		100	(100.0%)
Other dose		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

15.6.2 Dose application during study by cancer type and visit - FAS

	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Visit 15	17			4			1			0			0			22		
120 mg		17	(100.0%)		4	(100.0%)		1	(100.0%)		0	(0.0%)		0	(0.0%)		22	(100.0%)
Other dose		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Visit 16	7			3			0			0			0			10		
120 mg		7	(100.0%)		3	(100.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		10	(100.0%)
Other dose		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Visit 17	3			2			0			0			0			5		
120 mg		3	(100.0%)		2	(100.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		5	(100.0%)
Other dose		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Visit 18	2			1			0			0			0			3		
120 mg		2	(100.0%)		1	(100.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		3	(100.0%)
Other dose		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Visit 19	2			1			0			0			0			3		
120 mg		2	(100.0%)		1	(100.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		3	(100.0%)
Other dose		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Visit 20	2			1			0			0			0			3		
120 mg		2	(100.0%)		1	(100.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		3	(100.0%)
Other dose		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Visit 21	1			0			0			0			0			1		
120 mg		1	(100.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(100.0%)
Other dose		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

15.6.3 Number of XGEVA injections during study by cancer type and visit - FAS

Cancer type	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Breast cancer	509	11.8	3.9	1	10	13.0	14	21
Prostate cancer	294	11.5	3.6	1	10	13.0	14	22
Lung cancer	159	7.4	4.6	1	3	6.0	12	16
Kidney cancer	50	9.9	4.3	2	6	11.0	14	15
Other cancer type	116	7.8	4.5	1	4	7.0	13	15
Total	1128	10.6	4.4	1	7	13.0	14	22

15.7.1 Concomitant antineoplastic therapy by cancer type - FAS

	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Concomitant surgery												
No	490	(96.3%)	291	(99.0%)	156	(98.1%)	49	(98.0%)	112	(96.6%)	1098	(97.3%)
Yes	19	(3.7%)	3	(1.0%)	3	(1.9%)	1	(2.0%)	4	(3.4%)	30	(2.7%)
Concomitant radiotherapy												
No	362	(71.1%)	252	(85.7%)	119	(74.8%)	30	(60.0%)	80	(69.0%)	843	(74.7%)
Yes	147	(28.9%)	42	(14.3%)	40	(25.2%)	20	(40.0%)	36	(31.0%)	285	(25.3%)
Concomitant chemotherapy												
No	221	(43.4%)	171	(58.2%)	29	(18.2%)	6	(12.0%)	20	(17.2%)	447	(39.6%)
Yes	288	(56.6%)	123	(41.8%)	130	(81.8%)	44	(88.0%)	96	(82.8%)	681	(60.4%)
Concomitant antihormonal therapy												
No	187	(36.7%)	51	(17.3%)	159	(100.0%)	49	(98.0%)	110	(94.8%)	556	(49.3%)
Yes	322	(63.3%)	243	(82.7%)	0	(0.0%)	1	(2.0%)	6	(5.2%)	572	(50.7%)

Surgeries are counted as concomitant surgeries if the date of the surgery is on or after day 1 or if the date of the surgery is missing and the tick box for previous surgery of the eCRF is not ticked.
Therapies are counted as concomitant therapies if the stop date of the therapy is on or after day 1 or missing.

15.7.2 Concomitant surgeries by MedDRA system organ class and preferred term and by cancer type and overall - FAS

MedDRA System Organ Class Preferred Term	Breast cancer (N=19)		Prostate cancer (N=3)		Lung cancer (N=3)		Kidney cancer (N=1)		Other cancer type (N=4)		Total (N=30)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Total	19	(100.0%)	3	(100.0%)	3	(100.0%)	1	(100.0%)	4	(100.0%)	30	(100.0%)
Surgical and medical procedures												
Total	18	(94.7%)	3	(100.0%)	3	(100.0%)	1	(100.0%)	4	(100.0%)	29	(96.7%)
Mastectomy	7	(36.8%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	7	(23.3%)
Internal fixation of spine	3	(15.8%)	0	(0.0%)	1	(33.3%)	0	(0.0%)	0	(0.0%)	4	(13.3%)
Lymphadenectomy	2	(10.5%)	0	(0.0%)	1	(33.3%)	0	(0.0%)	0	(0.0%)	3	(10.0%)
Malignant tumour excision	3	(15.8%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	3	(10.0%)
Salpingo-oophorectomy bilateral	3	(15.8%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	3	(10.0%)
Laparoscopic surgery	1	(5.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(25.0%)	2	(6.7%)
Spinal decompression	2	(10.5%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(6.7%)
Spinal fusion surgery	2	(10.5%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(6.7%)
Spinal laminectomy	1	(5.3%)	0	(0.0%)	1	(33.3%)	0	(0.0%)	0	(0.0%)	2	(6.7%)
Breast lump removal	1	(5.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(3.3%)
Central venous catheterisation	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(25.0%)	1	(3.3%)
Colectomy	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(25.0%)	1	(3.3%)
Colostomy closure	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(25.0%)	1	(3.3%)
Foot amputation	0	(0.0%)	1	(33.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(3.3%)
Gastrectomy	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(25.0%)	1	(3.3%)
Gastroenterostomy	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(100.0%)	0	(0.0%)	1	(3.3%)
Hip arthroplasty	1	(5.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(3.3%)

Surgeries are counted as concomitant surgeries if the date of the surgery is on or after day 1 or if the date of the surgery is missing and the tick box for previous surgery of the eCRF is not ticked.
MedDRA version 15.1.

15.7.2 Concomitant surgeries by MedDRA system organ class and preferred term and by cancer type and overall - FAS

MedDRA System Organ Class Preferred Term	Breast cancer (N=19)		Prostate cancer (N=3)		Lung cancer (N=3)		Kidney cancer (N=1)		Other cancer type (N=4)		Total (N=30)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Laparotomy	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(100.0%)	0	(0.0%)	1	(3.3%)
Lung lobectomy	0	(0.0%)	0	(0.0%)	1	(33.3%)	0	(0.0%)	0	(0.0%)	1	(3.3%)
Malignant breast lump removal	1	(5.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(3.3%)
Muscle flap operation	1	(5.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(3.3%)
Omentectomy	1	(5.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(3.3%)
Open reduction of fracture	0	(0.0%)	1	(33.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(3.3%)
Osteosynthesis	0	(0.0%)	0	(0.0%)	1	(33.3%)	0	(0.0%)	0	(0.0%)	1	(3.3%)
Prosthesis implantation	0	(0.0%)	1	(33.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(3.3%)
Radical hysterectomy	1	(5.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(3.3%)
Radical mastectomy	1	(5.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(3.3%)
Resection of rectum	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(25.0%)	1	(3.3%)
Sigmoidectomy	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(25.0%)	1	(3.3%)
Transurethral prostatectomy	0	(0.0%)	1	(33.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(3.3%)
Vertebroplasty	1	(5.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(3.3%)
Investigations												
Total	3	(15.8%)	0	(0.0%)	0	(0.0%)	1	(100.0%)	0	(0.0%)	4	(13.3%)
Biopsy liver	1	(5.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(3.3%)
Biopsy small intestine	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(100.0%)	0	(0.0%)	1	(3.3%)
Biopsy spinal cord	1	(5.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(3.3%)
Biopsy vulva	1	(5.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(3.3%)

Surgeries are counted as concomitant surgeries if the date of the surgery is on or after day 1 or if the date of the surgery is missing and the tick box for previous surgery of the eCRF is not ticked.
MedDRA version 15.1.

15.7.2 Concomitant surgeries by MedDRA system organ class and preferred term and by cancer type and overall - FAS

	Breast cancer (N=19)		Prostate cancer (N=3)		Lung cancer (N=3)		Kidney cancer (N=1)		Other cancer type (N=4)		Total (N=30)	
MedDRA System Organ Class Preferred Term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)												
Total	1	(5.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(3.3%)
Breast cancer recurrent	1	(5.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(3.3%)
Metastases to skin	1	(5.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(3.3%)

Surgeries are counted as concomitant surgeries if the date of the surgery is on or after day 1 or if the date of the surgery is missing and the tick box for previous surgery of the eCRF is not ticked.
MedDRA version 15.1.

15.7.3 Concomitant chemotherapy by preferred term - by cancer type - FAS

	Breast cancer (N=288)		Prostate cancer (N=123)		Lung cancer (N=130)		Kidney cancer (N=44)		Other cancer type (N=96)		Total (N=681)	
Preferred term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Total	288	(100.0%)	123	(100.0%)	130	(100.0%)	44	(100.0%)	96	(100.0%)	681	(100.0%)
Docetaxel	39	(13.5%)	91	(74.0%)	17	(13.1%)	0	(0.0%)	5	(5.2%)	152	(22.3%)
Paclitaxel	96	(33.3%)	0	(0.0%)	30	(23.1%)	1	(2.3%)	18	(18.8%)	145	(21.3%)
Bevacizumab	87	(30.2%)	0	(0.0%)	24	(18.5%)	2	(4.5%)	15	(15.6%)	128	(18.8%)
Carboplatin	18	(6.3%)	3	(2.4%)	58	(44.6%)	0	(0.0%)	16	(16.7%)	95	(14.0%)
Trastuzumab	68	(23.6%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	4	(4.2%)	72	(10.6%)
Cisplatin	4	(1.4%)	1	(0.8%)	43	(33.1%)	1	(2.3%)	22	(22.9%)	71	(10.4%)
Capecitabine	52	(18.1%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	10	(10.4%)	62	(9.1%)
Vinorelbine	23	(8.0%)	0	(0.0%)	22	(16.9%)	0	(0.0%)	0	(0.0%)	45	(6.6%)
Gemcitabine	12	(4.2%)	2	(1.6%)	12	(9.2%)	2	(4.5%)	16	(16.7%)	44	(6.5%)
Everolimus	26	(9.0%)	0	(0.0%)	0	(0.0%)	12	(27.3%)	1	(1.0%)	39	(5.7%)
Cyclophosphamide	25	(8.7%)	0	(0.0%)	9	(6.9%)	0	(0.0%)	0	(0.0%)	34	(5.0%)
Pertuzumab	29	(10.1%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	29	(4.3%)
Fluorouracil	8	(2.8%)	0	(0.0%)	1	(0.8%)	0	(0.0%)	19	(19.8%)	28	(4.1%)
Pemetrexed disodium	0	(0.0%)	0	(0.0%)	27	(20.8%)	0	(0.0%)	1	(1.0%)	28	(4.1%)
Doxorubicin	15	(5.2%)	0	(0.0%)	4	(3.1%)	0	(0.0%)	6	(6.3%)	25	(3.7%)
Abiraterone acetate	0	(0.0%)	21	(17.1%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	21	(3.1%)
Cabazitaxel	0	(0.0%)	21	(17.1%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	21	(3.1%)
Etoposide	0	(0.0%)	1	(0.8%)	19	(14.6%)	0	(0.0%)	1	(1.0%)	21	(3.1%)

Chemotherapies with missing chemotheray name (N=1) were not included in the analysis.
Some of these chemotherapies may have been given in combination, but have been presented separately in this table.
Therapies are counted as concomitant therapies if the stop date of the therapy is on or after day 1 or missing.
WHO Drug Dictionary version 2012 June.

15.7.3 Concomitant chemotherapy by preferred term - by cancer type - FAS

	Breast cancer (N=288)		Prostate cancer (N=123)		Lung cancer (N=130)		Kidney cancer (N=44)		Other cancer type (N=96)		Total (N=681)	
Preferred term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Pemetrexed	0	(0.0%)	0	(0.0%)	20	(15.4%)	0	(0.0%)	1	(1.0%)	21	(3.1%)
Eribulin	20	(6.9%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	20	(2.9%)
Gemcitabine hydrochloride	3	(1.0%)	0	(0.0%)	5	(3.8%)	1	(2.3%)	8	(8.3%)	17	(2.5%)
Prednisolone	0	(0.0%)	17	(13.8%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	17	(2.5%)
Epirubicin	13	(4.5%)	0	(0.0%)	1	(0.8%)	0	(0.0%)	2	(2.1%)	16	(2.3%)
Paclitaxel albumin	15	(5.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(1.0%)	16	(2.3%)
Topotecan	0	(0.0%)	0	(0.0%)	13	(10.0%)	1	(2.3%)	2	(2.1%)	16	(2.3%)
Combinations of antineoplastic agents	1	(0.3%)	1	(0.8%)	0	(0.0%)	0	(0.0%)	12	(12.5%)	14	(2.1%)
Vinorelbine tartrate	10	(3.5%)	0	(0.0%)	4	(3.1%)	0	(0.0%)	0	(0.0%)	14	(2.1%)
Erlotinib hydrochloride	0	(0.0%)	0	(0.0%)	13	(10.0%)	0	(0.0%)	0	(0.0%)	13	(1.9%)
Pegylated liposomal doxorubicin hydrochloride	11	(3.8%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(2.1%)	13	(1.9%)
Temsirolimus	0	(0.0%)	0	(0.0%)	0	(0.0%)	11	(25.0%)	0	(0.0%)	11	(1.6%)
Irinotecan	0	(0.0%)	1	(0.8%)	1	(0.8%)	0	(0.0%)	8	(8.3%)	10	(1.5%)
Methotrexate	10	(3.5%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	10	(1.5%)
Sunitinib malate	0	(0.0%)	0	(0.0%)	0	(0.0%)	10	(22.7%)	0	(0.0%)	10	(1.5%)
Liposomal doxorubicin hydrochloride	9	(3.1%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	9	(1.3%)
Trastuzumab emtansine	9	(3.1%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	9	(1.3%)
Eribulin mesilate	8	(2.8%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	8	(1.2%)
Fluorouracil w/folinic acid/irinotecan	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	8	(8.3%)	8	(1.2%)
Pazopanib hydrochloride	0	(0.0%)	0	(0.0%)	0	(0.0%)	8	(18.2%)	0	(0.0%)	8	(1.2%)

Chemotherapies with missing chemotheray name (N=1) were not included in the analysis.
Some of these chemotherapies may have been given in combination, but have been presented separately in this table.
Therapies are counted as concomitant therapies if the stop date of the therapy is on or after day 1 or missing.
WHO Drug Dictionary version 2012 June.

15.7.3 Concomitant chemotherapy by preferred term - by cancer type - FAS

	Breast cancer (N=288)		Prostate cancer (N=123)		Lung cancer (N=130)		Kidney cancer (N=44)		Other cancer type (N=96)		Total (N=681)	
Preferred term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Cetuximab	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	7	(7.3%)	7	(1.0%)
Folinic acid	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	7	(7.3%)	7	(1.0%)
Other antineoplastic agents	3	(1.0%)	4	(3.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	7	(1.0%)
Oxaliplatin	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	7	(7.3%)	7	(1.0%)
Afatinib	0	(0.0%)	0	(0.0%)	6	(4.6%)	0	(0.0%)	0	(0.0%)	6	(0.9%)
Carboplatin w/gemcitabine	3	(1.0%)	0	(0.0%)	2	(1.5%)	0	(0.0%)	1	(1.0%)	6	(0.9%)
Axitinib	0	(0.0%)	0	(0.0%)	0	(0.0%)	5	(11.4%)	0	(0.0%)	5	(0.7%)
Cisplatin w/etoposide	0	(0.0%)	0	(0.0%)	5	(3.8%)	0	(0.0%)	0	(0.0%)	5	(0.7%)
Exemestane	5	(1.7%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	5	(0.7%)
Panitumumab	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	5	(5.2%)	5	(0.7%)
Pazopanib	0	(0.0%)	0	(0.0%)	0	(0.0%)	5	(11.4%)	0	(0.0%)	5	(0.7%)
Sorafenib tosilate	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(4.5%)	3	(3.1%)	5	(0.7%)
Calcium folinate	1	(0.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	3	(3.1%)	4	(0.6%)
Monoclonal antibodies	1	(0.3%)	0	(0.0%)	2	(1.5%)	0	(0.0%)	1	(1.0%)	4	(0.6%)
Buparlisib	3	(1.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	3	(0.4%)
Erlotinib	0	(0.0%)	0	(0.0%)	3	(2.3%)	0	(0.0%)	0	(0.0%)	3	(0.4%)
Lapatinib	3	(1.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	3	(0.4%)
Mitomycin	2	(0.7%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(1.0%)	3	(0.4%)
Topotecan hydrochloride	0	(0.0%)	0	(0.0%)	3	(2.3%)	0	(0.0%)	0	(0.0%)	3	(0.4%)
Trofosfamide	1	(0.3%)	0	(0.0%)	2	(1.5%)	0	(0.0%)	0	(0.0%)	3	(0.4%)

Chemotherapies with missing chemotheray name (N=1) were not included in the analysis.
Some of these chemotherapies may have been given in combination, but have been presented separately in this table.
Therapies are counted as concomitant therapies if the stop date of the therapy is on or after day 1 or missing.
WHO Drug Dictionary version 2012 June.

15.7.3 Concomitant chemotherapy by preferred term - by cancer type - FAS

	Breast cancer (N=288)		Prostate cancer (N=123)		Lung cancer (N=130)		Kidney cancer (N=44)		Other cancer type (N=96)		Total (N=681)	
Preferred term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Vincristine	0	(0.0%)	0	(0.0%)	3	(2.3%)	0	(0.0%)	0	(0.0%)	3	(0.4%)
Anastrozole	2	(0.7%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.3%)
Crizotinib	0	(0.0%)	0	(0.0%)	2	(1.5%)	0	(0.0%)	0	(0.0%)	2	(0.3%)
Doxorubicin hydrochloride	1	(0.3%)	0	(0.0%)	1	(0.8%)	0	(0.0%)	0	(0.0%)	2	(0.3%)
Methotrexate sodium	0	(0.0%)	1	(0.8%)	0	(0.0%)	0	(0.0%)	1	(1.0%)	2	(0.3%)
Placebo	2	(0.7%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.3%)
Ramucirumab	1	(0.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(1.0%)	2	(0.3%)
Sorafenib	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(2.3%)	1	(1.0%)	2	(0.3%)
Sunitinib	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(4.5%)	0	(0.0%)	2	(0.3%)
Taxol w/carboplatin	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(2.1%)	2	(0.3%)
Vinflunine ditartrate	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(2.1%)	2	(0.3%)
Xelox	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(2.1%)	2	(0.3%)
Abiraterone	0	(0.0%)	1	(0.8%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Abiraterone acetate w/prednisolone	0	(0.0%)	1	(0.8%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Bendamustine	1	(0.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Catumaxomab	1	(0.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Dacarbazine citrate	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(1.0%)	1	(0.1%)
Folate sodium	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(1.0%)	1	(0.1%)
Folic acid	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(1.0%)	1	(0.1%)
Gefitinib	0	(0.0%)	0	(0.0%)	1	(0.8%)	0	(0.0%)	0	(0.0%)	1	(0.1%)

Chemotherapies with missing chemotheray name (N=1) were not included in the analysis.
Some of these chemotherapies may have been given in combination, but have been presented separately in this table.
Therapies are counted as concomitant therapies if the stop date of the therapy is on or after day 1 or missing.
WHO Drug Dictionary version 2012 June.

15.7.3 Concomitant chemotherapy by preferred term - by cancer type - FAS

	Breast cancer (N=288)		Prostate cancer (N=123)		Lung cancer (N=130)		Kidney cancer (N=44)		Other cancer type (N=96)		Total (N=681)	
Preferred term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Hydroxycarbamide	0	(0.0%)	0	(0.0%)	1	(0.8%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Ifosfamide	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(1.0%)	1	(0.1%)
Ipilimumab	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(1.0%)	1	(0.1%)
Lapatinib ditosylate monohydrate	1	(0.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Letrozole	1	(0.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Mesna	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(1.0%)	1	(0.1%)
Mitoxantrone	1	(0.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Prednisone	0	(0.0%)	1	(0.8%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Regorafenib	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(1.0%)	1	(0.1%)
Temozolomide	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(1.0%)	1	(0.1%)
Trabectedin	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(1.0%)	1	(0.1%)
Vandetanib	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(1.0%)	1	(0.1%)
Vinblastine	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(1.0%)	1	(0.1%)
Vincristine sulfate	0	(0.0%)	0	(0.0%)	1	(0.8%)	0	(0.0%)	0	(0.0%)	1	(0.1%)

Chemotherapies with missing chemotheray name (N=1) were not included in the analysis.
Some of these chemotherapies may have been given in combination, but have been presented separately in this table.
Therapies are counted as concomitant therapies if the stop date of the therapy is on or after day 1 or missing.
WHO Drug Dictionary version 2012 June.

15.7.4 Concomitant antihormonal therapy (incl. antibodies and small molecules) by preferred term - by cancer type - FAS

	Breast cancer (N=322)		Prostate cancer (N=243)		Kidney cancer (N=1)		Other cancer type (N=6)		Total (N=572)	
Preferred term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Total	322	(100.0%)	243	(100.0%)	1	(100.0%)	6	(100.0%)	572	(100.0%)
Leuprorelin acetate	1	(0.3%)	137	(56.4%)	0	(0.0%)	1	(16.7%)	139	(24.3%)
Letrozole	118	(36.6%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	118	(20.6%)
Anastrozole	116	(36.0%)	0	(0.0%)	0	(0.0%)	1	(16.7%)	117	(20.5%)
Bicalutamide	0	(0.0%)	82	(33.7%)	0	(0.0%)	1	(16.7%)	83	(14.5%)
Exemestane	70	(21.7%)	0	(0.0%)	0	(0.0%)	2	(33.3%)	72	(12.6%)
Tamoxifen	57	(17.7%)	1	(0.4%)	0	(0.0%)	0	(0.0%)	58	(10.1%)
Abiraterone acetate	0	(0.0%)	37	(15.2%)	0	(0.0%)	0	(0.0%)	37	(6.5%)
Buserelin acetate	0	(0.0%)	34	(14.0%)	0	(0.0%)	0	(0.0%)	34	(5.9%)
Other antineoplastic agents	0	(0.0%)	24	(9.9%)	0	(0.0%)	0	(0.0%)	24	(4.2%)
Degarelix	0	(0.0%)	18	(7.4%)	0	(0.0%)	0	(0.0%)	18	(3.1%)
Fulvestrant	17	(5.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	17	(3.0%)
Triptorelin embonate	0	(0.0%)	17	(7.0%)	0	(0.0%)	0	(0.0%)	17	(3.0%)
Goserelin	4	(1.2%)	7	(2.9%)	0	(0.0%)	0	(0.0%)	11	(1.9%)
Leuprorelin	1	(0.3%)	9	(3.7%)	0	(0.0%)	0	(0.0%)	10	(1.7%)
Abiraterone	0	(0.0%)	8	(3.3%)	0	(0.0%)	0	(0.0%)	8	(1.4%)
Everolimus	5	(1.6%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	5	(0.9%)
Flutamide	0	(0.0%)	5	(2.1%)	0	(0.0%)	0	(0.0%)	5	(0.9%)
Gonadotropin releasing hormone analogues	1	(0.3%)	3	(1.2%)	0	(0.0%)	0	(0.0%)	4	(0.7%)
Aromatase inhibitors	3	(0.9%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	3	(0.5%)
Cyproterone acetate	0	(0.0%)	3	(1.2%)	0	(0.0%)	0	(0.0%)	3	(0.5%)

Therapies are counted as concomitant therapies if the stop date of the therapy is on or after day 1 or missing.
WHO Drug Dictionary version 2012 June.

15.7.4 Concomitant antihormonal therapy (incl. antibodies and small molecules) by preferred term - by cancer type - FAS

	Breast cancer (N=322)		Prostate cancer (N=243)		Kidney cancer (N=1)		Other cancer type (N=6)		Total (N=572)	
Preferred term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Abiraterone acetate w/prednisolone	0	(0.0%)	2	(0.8%)	0	(0.0%)	0	(0.0%)	2	(0.3%)
Histrelin acetate	0	(0.0%)	2	(0.8%)	0	(0.0%)	0	(0.0%)	2	(0.3%)
Triptorelin	0	(0.0%)	2	(0.8%)	0	(0.0%)	0	(0.0%)	2	(0.3%)
Abarelix	0	(0.0%)	1	(0.4%)	0	(0.0%)	0	(0.0%)	1	(0.2%)
Alfuzosin	0	(0.0%)	1	(0.4%)	0	(0.0%)	0	(0.0%)	1	(0.2%)
Bucricaine hydrochloride	1	(0.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.2%)
Combinations of antineoplastic agents	1	(0.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.2%)
Cyproterone	0	(0.0%)	1	(0.4%)	0	(0.0%)	0	(0.0%)	1	(0.2%)
Gonadorelin	0	(0.0%)	1	(0.4%)	0	(0.0%)	0	(0.0%)	1	(0.2%)
Goserelin acetate	0	(0.0%)	1	(0.4%)	0	(0.0%)	0	(0.0%)	1	(0.2%)
Medroxyprogesterone acetate	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(16.7%)	1	(0.2%)
Octreotide acetate	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(16.7%)	1	(0.2%)
Pazopanib hydrochloride	0	(0.0%)	0	(0.0%)	1	(100.0%)	0	(0.0%)	1	(0.2%)
Prednisolone	0	(0.0%)	1	(0.4%)	0	(0.0%)	0	(0.0%)	1	(0.2%)
Prednisone	0	(0.0%)	1	(0.4%)	0	(0.0%)	0	(0.0%)	1	(0.2%)
Trastuzumab	1	(0.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.2%)

Therapies are counted as concomitant therapies if the stop date of the therapy is on or after day 1 or missing.
WHO Drug Dictionary version 2012 June.

15.7.5 Analgesics given throughout the study by cancer type and overall - FAS

	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
Cleaned term	**Pat. n**	**Pat. %**	**Pat. n**	**Pat. %**	**Pat. n**	**Pat. %**	**Pat. n**	**Pat. %**	**Pat. n**	**Pat. %**	**Pat. n**	**Pat. %**
Total	238	(46.8%)	124	(42.2%)	100	(62.9%)	36	(72.0%)	86	(74.1%)	584	(51.8%)
Novaminsulfon	66	(13.0%)	30	(10.2%)	29	(18.2%)	16	(32.0%)	32	(27.6%)	173	(15.3%)
Ibuprofen	72	(14.1%)	34	(11.6%)	31	(19.5%)	5	(10.0%)	12	(10.3%)	154	(13.7%)
Novalgin	44	(8.6%)	22	(7.5%)	25	(15.7%)	4	(8.0%)	18	(15.5%)	113	(10.0%)
Fentanyl	34	(6.7%)	11	(3.7%)	27	(17.0%)	8	(16.0%)	21	(18.1%)	101	(9.0%)
Metamizol	28	(5.5%)	25	(8.5%)	11	(6.9%)	5	(10.0%)	11	(9.5%)	80	(7.1%)
Tilidin	28	(5.5%)	13	(4.4%)	16	(10.1%)	4	(8.0%)	13	(11.2%)	74	(6.6%)
Hydromorphon	19	(3.7%)	11	(3.7%)	19	(11.9%)	6	(12.0%)	15	(12.9%)	70	(6.2%)
Morphin	16	(3.1%)	9	(3.1%)	11	(6.9%)	3	(6.0%)	17	(14.7%)	56	(5.0%)
Palladon	7	(1.4%)	6	(2.0%)	20	(12.6%)	1	(2.0%)	11	(9.5%)	45	(4.0%)
Targin	15	(2.9%)	11	(3.7%)	10	(6.3%)	2	(4.0%)	7	(6.0%)	45	(4.0%)
Tramadol	17	(3.3%)	10	(3.4%)	4	(2.5%)	3	(6.0%)	3	(2.6%)	37	(3.3%)
Diclofenac	9	(1.8%)	15	(5.1%)	2	(1.3%)	1	(2.0%)	4	(3.4%)	31	(2.7%)
Oxycodon	5	(1.0%)	7	(2.4%)	6	(3.8%)	2	(4.0%)	6	(5.2%)	26	(2.3%)
Sevredol	3	(0.6%)	3	(1.0%)	9	(5.7%)	2	(4.0%)	2	(1.7%)	19	(1.7%)
Tramal	8	(1.6%)	5	(1.7%)	2	(1.3%)	1	(2.0%)	3	(2.6%)	19	(1.7%)
Effentora	2	(0.4%)	3	(1.0%)	5	(3.1%)	0	(0.0%)	4	(3.4%)	14	(1.2%)
Arcoxia	8	(1.6%)	1	(0.3%)	3	(1.9%)	0	(0.0%)	1	(0.9%)	13	(1.2%)
Paracetamol	7	(1.4%)	1	(0.3%)	0	(0.0%)	1	(2.0%)	4	(3.4%)	13	(1.2%)
Voltaren	4	(0.8%)	1	(0.3%)	1	(0.6%)	1	(2.0%)	5	(4.3%)	12	(1.1%)
Etoricoxib	5	(1.0%)	3	(1.0%)	1	(0.6%)	2	(4.0%)	0	(0.0%)	11	(1.0%)

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15.7.5 Analgesics given throughout the study by cancer type and overall - FAS

	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
Cleaned term	**Pat. n**	**Pat. %**	**Pat. n**	**Pat. %**	**Pat. n**	**Pat. %**	**Pat. n**	**Pat. %**	**Pat. n**	**Pat. %**	**Pat. n**	**Pat. %**
Lyrica	4	(0.8%)	2	(0.7%)	4	(2.5%)	0	(0.0%)	1	(0.9%)	11	(1.0%)
Pregabalin	3	(0.6%)	3	(1.0%)	2	(1.3%)	1	(2.0%)	2	(1.7%)	11	(1.0%)
Valoron	6	(1.2%)	3	(1.0%)	2	(1.3%)	0	(0.0%)	0	(0.0%)	11	(1.0%)
Abstral	3	(0.6%)	0	(0.0%)	3	(1.9%)	0	(0.0%)	4	(3.4%)	10	(0.9%)
Jurnista	2	(0.4%)	3	(1.0%)	3	(1.9%)	1	(2.0%)	1	(0.9%)	10	(0.9%)
Ibuflam	2	(0.4%)	3	(1.0%)	1	(0.6%)	1	(2.0%)	1	(0.9%)	8	(0.7%)
Palexia	3	(0.6%)	1	(0.3%)	3	(1.9%)	0	(0.0%)	1	(0.9%)	8	(0.7%)
Oxygesic	1	(0.2%)	1	(0.3%)	2	(1.3%)	0	(0.0%)	3	(2.6%)	7	(0.6%)
Buprenorphin	2	(0.4%)	0	(0.0%)	0	(0.0%)	2	(4.0%)	2	(1.7%)	6	(0.5%)
Naloxon/Oxycodon	2	(0.4%)	2	(0.7%)	1	(0.6%)	1	(2.0%)	0	(0.0%)	6	(0.5%)
Tilidin/Naloxon	2	(0.4%)	1	(0.3%)	2	(1.3%)	0	(0.0%)	1	(0.9%)	6	(0.5%)
Celebrex	3	(0.6%)	0	(0.0%)	1	(0.6%)	1	(2.0%)	0	(0.0%)	5	(0.4%)
Codein	1	(0.2%)	0	(0.0%)	4	(2.5%)	0	(0.0%)	0	(0.0%)	5	(0.4%)
Dexamethason	1	(0.2%)	1	(0.3%)	1	(0.6%)	0	(0.0%)	2	(1.7%)	5	(0.4%)
Norspan Pflaster	5	(1.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	5	(0.4%)
Oramorph	0	(0.0%)	2	(0.7%)	2	(1.3%)	0	(0.0%)	1	(0.9%)	5	(0.4%)
Celecoxib	2	(0.4%)	0	(0.0%)	0	(0.0%)	1	(2.0%)	1	(0.9%)	4	(0.4%)
Dexketoprofen	0	(0.0%)	3	(1.0%)	0	(0.0%)	0	(0.0%)	1	(0.9%)	4	(0.4%)
MST	2	(0.4%)	0	(0.0%)	1	(0.6%)	0	(0.0%)	1	(0.9%)	4	(0.4%)
Parecoxib	1	(0.2%)	1	(0.3%)	0	(0.0%)	0	(0.0%)	2	(1.7%)	4	(0.4%)
Transtec	1	(0.2%)	0	(0.0%)	0	(0.0%)	1	(2.0%)	2	(1.7%)	4	(0.4%)
Amitriptylin	2	(0.4%)	0	(0.0%)	0	(0.0%)	1	(2.0%)	0	(0.0%)	3	(0.3%)

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15.7.5 Analgesics given throughout the study by cancer type and overall - FAS

	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
Cleaned term	**Pat. n**	**Pat. %**	**Pat. n**	**Pat. %**	**Pat. n**	**Pat. %**	**Pat. n**	**Pat. %**	**Pat. n**	**Pat. %**	**Pat. n**	**Pat. %**
Dronabinol	2	(0.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.9%)	3	(0.3%)
MSI	1	(0.2%)	0	(0.0%)	2	(1.3%)	0	(0.0%)	0	(0.0%)	3	(0.3%)
Naproxen	2	(0.4%)	1	(0.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	3	(0.3%)
Opioid	3	(0.6%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	3	(0.3%)
Acetylsalicylsäure	0	(0.0%)	1	(0.3%)	0	(0.0%)	0	(0.0%)	1	(0.9%)	2	(0.2%)
Actic	0	(0.0%)	0	(0.0%)	1	(0.6%)	0	(0.0%)	1	(0.9%)	2	(0.2%)
Capros	1	(0.2%)	1	(0.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.2%)
Dihydrocodein	1	(0.2%)	0	(0.0%)	1	(0.6%)	0	(0.0%)	0	(0.0%)	2	(0.2%)
Durogesic Pflaster	0	(0.0%)	2	(0.7%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.2%)
Gabapentin	2	(0.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.2%)
Katadolon	1	(0.2%)	0	(0.0%)	1	(0.6%)	0	(0.0%)	0	(0.0%)	2	(0.2%)
Methadon	2	(0.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.2%)
Morphin/Sevredol	1	(0.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.9%)	2	(0.2%)
Opiumtinktur	0	(0.0%)	0	(0.0%)	1	(0.6%)	0	(0.0%)	1	(0.9%)	2	(0.2%)
Tapentadol	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(2.0%)	1	(0.9%)	2	(0.2%)
Temgesic	1	(0.2%)	0	(0.0%)	1	(0.6%)	0	(0.0%)	0	(0.0%)	2	(0.2%)
Tramadil	1	(0.2%)	1	(0.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(0.2%)
Analgin	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.9%)	1	(0.1%)
Arcoxia/Etoricoxib	0	(0.0%)	0	(0.0%)	1	(0.6%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Buscopan	1	(0.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Butylscopolamin	0	(0.0%)	1	(0.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Capros akut/Morphin	1	(0.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)

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15.7.5 Analgesics given throughout the study by cancer type and overall - FAS

	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
Cleaned term	**Pat. n**	**Pat. %**	**Pat. n**	**Pat. %**	**Pat. n**	**Pat. %**	**Pat. n**	**Pat. %**	**Pat. n**	**Pat. %**	**Pat. n**	**Pat. %**
Carbamzepin	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(2.0%)	0	(0.0%)	1	(0.1%)
Codein/Tramadoln	1	(0.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
DHC 60	1	(0.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Duloxetin hadrochlorid	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(2.0%)	0	(0.0%)	1	(0.1%)
Effentora/Fentanyl	1	(0.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Etericoxib	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(2.0%)	0	(0.0%)	1	(0.1%)
Fentadolon	0	(0.0%)	0	(0.0%)	1	(0.6%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Fentanyl Pflaster/Nasenspray	0	(0.0%)	0	(0.0%)	1	(0.6%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Fentanyl/Abstral	0	(0.0%)	0	(0.0%)	1	(0.6%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Flupirtin	0	(0.0%)	1	(0.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Flupirtin maleat	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(2.0%)	0	(0.0%)	1	(0.1%)
Haloperidol	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.9%)	1	(0.1%)
Hydromorphon/Palladon	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.9%)	1	(0.1%)
L-Polamidon	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.9%)	1	(0.1%)
M-Long	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(2.0%)	0	(0.0%)	1	(0.1%)
Naloxon	0	(0.0%)	1	(0.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Naloxon/Tilidin	0	(0.0%)	1	(0.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Novaminsulfon/Metamizol	1	(0.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Ortoton	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(2.0%)	0	(0.0%)	1	(0.1%)
Oyxcodon/Naloxon	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.9%)	1	(0.1%)
Paracodin	1	(0.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Paramorphin	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.9%)	1	(0.1%)

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15.7.5 Analgesics given throughout the study by cancer type and overall - FAS

	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
Cleaned term	**Pat. n**	**Pat. %**	**Pat. n**	**Pat. %**	**Pat. n**	**Pat. %**	**Pat. n**	**Pat. %**	**Pat. n**	**Pat. %**	**Pat. n**	**Pat. %**
PecFent	1	(0.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Piritramid	0	(0.0%)	1	(0.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Prednison	1	(0.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Sympal	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.9%)	1	(0.1%)
Tramabeta	0	(0.0%)	0	(0.0%)	1	(0.6%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Trancopal	1	(0.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)
Trevilor	1	(0.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)

Cleaned term: Verbatim was cleaned regarding capitalization and blanks and dosing specifications were removed.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.6 Consumption of analgesic drugs throughout the study - FAS

	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
Consumption of any analgesic drug?	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
No	271	(53.2%)	170	(57.8%)	59	(37.1%)	14	(28.0%)	30	(25.9%)	544	(48.2%)
Yes	238	(46.8%)	124	(42.2%)	100	(62.9%)	36	(72.0%)	86	(74.1%)	584	(51.8%)

Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.7 Analgesic score (AQA) of pain medications given throughout the study - FAS

	Breast cancer (N=509)		Prostate cancer (N=294)		Lung cancer (N=159)		Kidney cancer (N=50)		Other cancer type (N=116)		Total (N=1128)	
Analgesic score (AQA)*	**Pat. n**	**Pat. %**	**Pat. n**	**Pat. %**	**Pat. n**	**Pat. %**	**Pat. n**	**Pat. %**	**Pat. n**	**Pat. %**	**Pat. n**	**Pat. %**
No analgesic	14	(2.8%)	7	(2.4%)	7	(4.4%)	4	(8.0%)	4	(3.4%)	36	(3.2%)
Non-opioid analgesics	193	(37.9%)	105	(35.7%)	78	(49.1%)	30	(60.0%)	70	(60.3%)	476	(42.2%)
Weak opioids	60	(11.8%)	33	(11.2%)	32	(20.1%)	8	(16.0%)	20	(17.2%)	153	(13.6%)
All strong opoids	91	(17.9%)	56	(19.0%)	69	(43.4%)	22	(44.0%)	62	(53.4%)	300	(26.6%)
Strong opioids dose 1	84	(16.5%)	51	(17.3%)	63	(39.6%)	19	(38.0%)	55	(47.4%)	272	(24.1%)
Strong opioids dose 2	10	(2.0%)	5	(1.7%)	11	(6.9%)	5	(10.0%)	17	(14.7%)	48	(4.3%)
Strong opioids dose 3	6	(1.2%)	1	(0.3%)	5	(3.1%)	0	(0.0%)	11	(9.5%)	23	(2.0%)
Strong opioids dose 4	3	(0.6%)	0	(0.0%)	4	(2.5%)	0	(0.0%)	5	(4.3%)	12	(1.1%)
Strong opioids dose 5	0	(0.0%)	1	(0.3%)	1	(0.6%)	1	(2.0%)	0	(0.0%)	3	(0.3%)
Missing	5	(1.0%)	2	(0.7%)	0	(0.0%)	1	(2.0%)	3	(2.6%)	11	(1.0%)

* Number and percentages refer to patients who received at least one medication with the respective score. Some patients received more than one medication and are displayed in more than one AQA score category
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.8 Consumption of analgesic drugs throughout the study by period - FAS

Period Consumption of any analgesic drug?	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 1 (0 - 2 weeks)	509			294			159			50			116			1128		
No		382	(75.0%)		233	(79.3%)		87	(54.7%)		26	(52.0%)		53	(45.7%)		781	(69.2%)
Yes		127	(25.0%)		61	(20.7%)		72	(45.3%)		24	(48.0%)		63	(54.3%)		347	(30.8%)
Period 2 (2 - 6 weeks)	508			293			156			50			113			1120		
No		346	(68.1%)		214	(73.0%)		78	(50.0%)		22	(44.0%)		38	(33.6%)		698	(62.3%)
Yes		162	(31.9%)		79	(27.0%)		78	(50.0%)		28	(56.0%)		75	(66.4%)		422	(37.7%)
Period 3 (6 - 10 weeks)	503			290			151			50			110			1104		
No		330	(65.6%)		202	(69.7%)		70	(46.4%)		20	(40.0%)		34	(30.9%)		656	(59.4%)
Yes		173	(34.4%)		88	(30.3%)		81	(53.6%)		30	(60.0%)		76	(69.1%)		448	(40.6%)
Period 4 (10 - 14 weeks)	497			287			139			48			103			1074		
No		319	(64.2%)		199	(69.3%)		65	(46.8%)		21	(43.8%)		32	(31.1%)		636	(59.2%)
Yes		178	(35.8%)		88	(30.7%)		74	(53.2%)		27	(56.3%)		71	(68.9%)		438	(40.8%)
Period 5 (14 - 18 weeks)	481			278			129			47			93			1028		
No		309	(64.2%)		193	(69.4%)		59	(45.7%)		19	(40.4%)		29	(31.2%)		609	(59.2%)
Yes		172	(35.8%)		85	(30.6%)		70	(54.3%)		28	(59.6%)		64	(68.8%)		419	(40.8%)
Period 6 (18 - 22 weeks)	470			273			112			45			84			984		
No		297	(63.2%)		191	(70.0%)		46	(41.1%)		19	(42.2%)		24	(28.6%)		577	(58.6%)
Yes		173	(36.8%)		82	(30.0%)		66	(58.9%)		26	(57.8%)		60	(71.4%)		407	(41.4%)

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15.7.8 Consumption of analgesic drugs throughout the study by period - FAS

Period / Consumption of any analgesic drug?	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 7 (22 - 26 weeks)	455			267			98			42			76			938		
No		283	(62.2%)		188	(70.4%)		41	(41.8%)		18	(42.9%)		22	(28.9%)		552	(58.8%)
Yes		172	(37.8%)		79	(29.6%)		57	(58.2%)		24	(57.1%)		54	(71.1%)		386	(41.2%)
Period 8 (26 - 30 weeks)	444			260			84			40			68			896		
No		279	(62.8%)		186	(71.5%)		35	(41.7%)		19	(47.5%)		20	(29.4%)		539	(60.2%)
Yes		165	(37.2%)		74	(28.5%)		49	(58.3%)		21	(52.5%)		48	(70.6%)		357	(39.8%)
Period 9 (30 - 34 weeks)	433			256			78			38			59			864		
No		268	(61.9%)		185	(72.3%)		34	(43.6%)		19	(50.0%)		16	(27.1%)		522	(60.4%)
Yes		165	(38.1%)		71	(27.7%)		44	(56.4%)		19	(50.0%)		43	(72.9%)		342	(39.6%)
Period 10 (34 - 38 weeks)	416			251			70			36			53			826		
No		257	(61.8%)		183	(72.9%)		32	(45.7%)		19	(52.8%)		15	(28.3%)		506	(61.3%)
Yes		159	(38.2%)		68	(27.1%)		38	(54.3%)		17	(47.2%)		38	(71.7%)		320	(38.7%)
Period 11 (38 - 42 weeks)	408			243			59			32			50			792		
No		249	(61.0%)		180	(74.1%)		28	(47.5%)		16	(50.0%)		12	(24.0%)		485	(61.2%)
Yes		159	(39.0%)		63	(25.9%)		31	(52.5%)		16	(50.0%)		38	(76.0%)		307	(38.8%)
Period 12 (42 - 46 weeks)	399			235			51			30			44			759		
No		245	(61.4%)		172	(73.2%)		24	(47.1%)		14	(46.7%)		9	(20.5%)		464	(61.1%)
Yes		154	(38.6%)		63	(26.8%)		27	(52.9%)		16	(53.3%)		35	(79.5%)		295	(38.9%)

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15.7.8 Consumption of analgesic drugs throughout the study by period - FAS

Period Consumption of any analgesic drug?	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 13 (46 - 50 weeks)	385			228			46			28			39			726		
No		236	(61.3%)		165	(72.4%)		22	(47.8%)		14	(50.0%)		8	(20.5%)		445	(61.3%)
Yes		149	(38.7%)		63	(27.6%)		24	(52.2%)		14	(50.0%)		31	(79.5%)		281	(38.7%)
Period 14 (50 - 54 weeks)	372			211			39			26			37			685		
No		226	(60.8%)		157	(74.4%)		22	(56.4%)		14	(53.8%)		8	(21.6%)		427	(62.3%)
Yes		146	(39.2%)		54	(25.6%)		17	(43.6%)		12	(46.2%)		29	(78.4%)		258	(37.7%)
Period 15 (54 - 58 weeks)	275			150			27			19			23			494		
No		167	(60.7%)		119	(79.3%)		15	(55.6%)		10	(52.6%)		3	(13.0%)		314	(63.6%)
Yes		108	(39.3%)		31	(20.7%)		12	(44.4%)		9	(47.4%)		20	(87.0%)		180	(36.4%)
Period 16 (58 - 62 weeks)	122			56			16			13			10			217		
No		78	(63.9%)		49	(87.5%)		12	(75.0%)		8	(61.5%)		1	(10.0%)		148	(68.2%)
Yes		44	(36.1%)		7	(12.5%)		4	(25.0%)		5	(38.5%)		9	(90.0%)		69	(31.8%)
Period 17 (62 - 66 weeks)	51			22			4			4			2			83		
No		32	(62.7%)		18	(81.8%)		3	(75.0%)		2	(50.0%)		0	(0.0%)		55	(66.3%)
Yes		19	(37.3%)		4	(18.2%)		1	(25.0%)		2	(50.0%)		2	(100.0%)		28	(33.7%)
Period 18 (66 - 70 weeks)	19			8			0			0			1			28		
No		11	(57.9%)		6	(75.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		17	(60.7%)
Yes		8	(42.1%)		2	(25.0%)		0	(0.0%)		0	(0.0%)		1	(100.0%)		11	(39.3%)

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15.7.8 Consumption of analgesic drugs throughout the study by period - FAS

Period / Consumption of any analgesic drug?	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 19 (70 - 74 weeks)	11			4			0			0			0			15		
No		7	(63.6%)		2	(50.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		9	(60.0%)
Yes		4	(36.4%)		2	(50.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		6	(40.0%)
Period 20 (74 - 78 weeks)	6			4			0			0			0			10		
No		4	(66.7%)		2	(50.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		6	(60.0%)
Yes		2	(33.3%)		2	(50.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		4	(40.0%)
Period 21 (78 - 82 weeks)	5			4			0			0			0			9		
No		4	(80.0%)		2	(50.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		6	(66.7%)
Yes		1	(20.0%)		2	(50.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		3	(33.3%)
Period 22 (82 - 86 weeks)	3			3			0			0			0			6		
No		2	(66.7%)		1	(33.3%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		3	(50.0%)
Yes		1	(33.3%)		2	(66.7%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		3	(50.0%)
Period 23 (86 - 90 weeks)	2			3			0			0			0			5		
No		1	(50.0%)		1	(33.3%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		2	(40.0%)
Yes		1	(50.0%)		2	(66.7%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		3	(60.0%)
Period 24 (90 - 94 weeks)	0			1			0			0			0			1		
No		0	(0.0%)		1	(100.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(100.0%)
Yes		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

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15.7.8 Consumption of analgesic drugs throughout the study by period - FAS

Period / Consumption of any analgesic drug?	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 25 (94 - 98 weeks)	0			1			0			0			0			1		
No		0	(0.0%)		1	(100.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(100.0%)
Yes		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Period 26 (98 - 102 weeks)	0			1			0			0			0			1		
No		0	(0.0%)		1	(100.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(100.0%)
Yes		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Period 27 (102 - 106 weeks)	0			1			0			0			0			1		
No		0	(0.0%)		1	(100.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(100.0%)
Yes		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Period 28 (106 - 110 weeks)	0			1			0			0			0			1		
No		0	(0.0%)		1	(100.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(100.0%)
Yes		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Period 29 (110 - 114 weeks)	0			1			0			0			0			1		
No		0	(0.0%)		1	(100.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(100.0%)
Yes		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Period 30 (114 - 118 weeks)	0			1			0			0			0			1		
No		0	(0.0%)		1	(100.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(100.0%)
Yes		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

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15.7.8 Consumption of analgesic drugs throughout the study by period - FAS

Period / Consumption of any analgesic drug?	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 31 (118 - 122 weeks)	0			1			0			0			0			1		
No		0	(0.0%)		1	(100.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(100.0%)
Yes		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Period 32 (122 - 126 weeks)	0			1			0			0			0			1		
No		0	(0.0%)		1	(100.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(100.0%)
Yes		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Period 33 (126 - 130 weeks)	0			1			0			0			0			1		
No		0	(0.0%)		1	(100.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(100.0%)
Yes		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Period 34 (130 - 134 weeks)	0			1			0			0			0			1		
No		0	(0.0%)		1	(100.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(100.0%)
Yes		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Period 35 (134 - 138 weeks)	0			1			0			0			0			1		
No		0	(0.0%)		1	(100.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(100.0%)
Yes		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Period 36 (138 - 142 weeks)	0			1			0			0			0			1		
No		0	(0.0%)		1	(100.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(100.0%)
Yes		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

N=number of patients in respective period
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.9 Worst analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period Worst AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 1 (0 - 2 weeks)	509			294			159			50			116			1128		
No analgesic		1	(0.2%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(0.1%)
Non-opioid analgesics		59	(11.6%)		26	(8.8%)		26	(16.4%)		9	(18.0%)		21	(18.1%)		141	(12.5%)
Weak opioids		26	(5.1%)		15	(5.1%)		13	(8.2%)		4	(8.0%)		11	(9.5%)		69	(6.1%)
All strong opoids		40	(7.9%)		20	(6.8%)		33	(20.8%)		11	(22.0%)		29	(25.0%)		133	(11.8%)
Strong opioids dose 1		35	(6.9%)		18	(6.1%)		27	(17.0%)		9	(18.0%)		23	(19.8%)		112	(9.9%)
Strong opioids dose 2		3	(0.6%)		2	(0.7%)		2	(1.3%)		1	(2.0%)		2	(1.7%)		10	(0.9%)
Strong opioids dose 3		2	(0.4%)		0	(0.0%)		2	(1.3%)		0	(0.0%)		4	(3.4%)		8	(0.7%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		2	(1.3%)		0	(0.0%)		0	(0.0%)		2	(0.2%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(2.0%)		0	(0.0%)		1	(0.1%)
Missing		1	(0.2%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		2	(1.7%)		3	(0.3%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.9 Worst analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Worst AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 2 (2 - 6 weeks)	508			293			156			50			113			1120		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		74	(14.6%)		37	(12.6%)		22	(14.1%)		10	(20.0%)		24	(21.2%)		167	(14.9%)
Weak opioids		31	(6.1%)		19	(6.5%)		12	(7.7%)		3	(6.0%)		12	(10.6%)		77	(6.9%)
All strong opoids		55	(10.8%)		23	(7.8%)		44	(28.2%)		15	(30.0%)		37	(32.7%)		174	(15.5%)
Strong opioids dose 1		45	(8.9%)		21	(7.2%)		37	(23.7%)		11	(22.0%)		27	(23.9%)		141	(12.6%)
Strong opioids dose 2		6	(1.2%)		2	(0.7%)		3	(1.9%)		3	(6.0%)		5	(4.4%)		19	(1.7%)
Strong opioids dose 3		2	(0.4%)		0	(0.0%)		2	(1.3%)		0	(0.0%)		4	(3.5%)		8	(0.7%)
Strong opioids dose 4		2	(0.4%)		0	(0.0%)		2	(1.3%)		0	(0.0%)		1	(0.9%)		5	(0.4%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(2.0%)		0	(0.0%)		1	(0.1%)
Missing		2	(0.4%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		2	(1.8%)		4	(0.4%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.9 Worst analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Worst AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 3 (6 - 10 weeks)	503			290			151			50			110			1104		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		77	(15.3%)		43	(14.8%)		21	(13.9%)		12	(24.0%)		23	(20.9%)		176	(15.9%)
Weak opioids		35	(7.0%)		23	(7.9%)		13	(8.6%)		3	(6.0%)		11	(10.0%)		85	(7.7%)
All strong opoids		59	(11.7%)		22	(7.6%)		47	(31.1%)		15	(30.0%)		41	(37.3%)		184	(16.7%)
Strong opioids dose 1		51	(10.1%)		20	(6.9%)		37	(24.5%)		11	(22.0%)		29	(26.4%)		148	(13.4%)
Strong opioids dose 2		4	(0.8%)		2	(0.7%)		5	(3.3%)		3	(6.0%)		5	(4.5%)		19	(1.7%)
Strong opioids dose 3		2	(0.4%)		0	(0.0%)		2	(1.3%)		0	(0.0%)		5	(4.5%)		9	(0.8%)
Strong opioids dose 4		2	(0.4%)		0	(0.0%)		3	(2.0%)		0	(0.0%)		2	(1.8%)		7	(0.6%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(2.0%)		0	(0.0%)		1	(0.1%)
Missing		2	(0.4%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(0.9%)		3	(0.3%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.9 Worst analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Worst AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 4 (10 - 14 weeks)	497			287			139			48			103			1074		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		79	(15.9%)		42	(14.6%)		18	(12.9%)		11	(22.9%)		19	(18.4%)		169	(15.7%)
Weak opioids		34	(6.8%)		25	(8.7%)		14	(10.1%)		1	(2.1%)		9	(8.7%)		83	(7.7%)
All strong opoids		63	(12.7%)		20	(7.0%)		42	(30.2%)		15	(31.3%)		42	(40.8%)		182	(16.9%)
Strong opioids dose 1		56	(11.3%)		18	(6.3%)		31	(22.3%)		11	(22.9%)		33	(32.0%)		149	(13.9%)
Strong opioids dose 2		4	(0.8%)		2	(0.7%)		5	(3.6%)		4	(8.3%)		2	(1.9%)		17	(1.6%)
Strong opioids dose 3		2	(0.4%)		0	(0.0%)		2	(1.4%)		0	(0.0%)		3	(2.9%)		7	(0.7%)
Strong opioids dose 4		1	(0.2%)		0	(0.0%)		4	(2.9%)		0	(0.0%)		4	(3.9%)		9	(0.8%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		2	(0.4%)		1	(0.3%)		0	(0.0%)		0	(0.0%)		1	(1.0%)		4	(0.4%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.9 Worst analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Worst AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 5 (14 - 18 weeks)	481			278			129			47			93			1028		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		74	(15.4%)		42	(15.1%)		16	(12.4%)		11	(23.4%)		17	(18.3%)		160	(15.6%)
Weak opioids		33	(6.9%)		22	(7.9%)		12	(9.3%)		1	(2.1%)		8	(8.6%)		76	(7.4%)
All strong opoids		65	(13.5%)		20	(7.2%)		42	(32.6%)		16	(34.0%)		38	(40.9%)		181	(17.6%)
Strong opioids dose 1		56	(11.6%)		18	(6.5%)		32	(24.8%)		11	(23.4%)		26	(28.0%)		143	(13.9%)
Strong opioids dose 2		4	(0.8%)		2	(0.7%)		4	(3.1%)		5	(10.6%)		4	(4.3%)		19	(1.8%)
Strong opioids dose 3		3	(0.6%)		0	(0.0%)		4	(3.1%)		0	(0.0%)		5	(5.4%)		12	(1.2%)
Strong opioids dose 4		2	(0.4%)		0	(0.0%)		2	(1.6%)		0	(0.0%)		3	(3.2%)		7	(0.7%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		1	(0.4%)		0	(0.0%)		0	(0.0%)		1	(1.1%)		2	(0.2%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.9 Worst analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Worst AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 6 (18 - 22 weeks)	470			273			112			45			84			984		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		74	(15.7%)		34	(12.5%)		17	(15.2%)		10	(22.2%)		15	(17.9%)		150	(15.2%)
Weak opioids		32	(6.8%)		19	(7.0%)		12	(10.7%)		1	(2.2%)		7	(8.3%)		71	(7.2%)
All strong opoids		67	(14.3%)		29	(10.6%)		37	(33.0%)		15	(33.3%)		38	(45.2%)		186	(18.9%)
Strong opioids dose 1		58	(12.3%)		27	(9.9%)		27	(24.1%)		11	(24.4%)		25	(29.8%)		148	(15.0%)
Strong opioids dose 2		3	(0.6%)		2	(0.7%)		4	(3.6%)		4	(8.9%)		4	(4.8%)		17	(1.7%)
Strong opioids dose 3		4	(0.9%)		0	(0.0%)		4	(3.6%)		0	(0.0%)		6	(7.1%)		14	(1.4%)
Strong opioids dose 4		2	(0.4%)		0	(0.0%)		2	(1.8%)		0	(0.0%)		3	(3.6%)		7	(0.7%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.9 Worst analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Worst AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 7 (22 - 26 weeks)	455			267			98			42			76			938		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		79	(17.4%)		28	(10.5%)		14	(14.3%)		10	(23.8%)		15	(19.7%)		146	(15.6%)
Weak opioids		29	(6.4%)		19	(7.1%)		12	(12.2%)		1	(2.4%)		5	(6.6%)		66	(7.0%)
All strong opoids		64	(14.1%)		32	(12.0%)		31	(31.6%)		13	(31.0%)		34	(44.7%)		174	(18.6%)
Strong opioids dose 1		56	(12.3%)		30	(11.2%)		20	(20.4%)		10	(23.8%)		23	(30.3%)		139	(14.8%)
Strong opioids dose 2		3	(0.7%)		2	(0.7%)		6	(6.1%)		3	(7.1%)		3	(3.9%)		17	(1.8%)
Strong opioids dose 3		4	(0.9%)		0	(0.0%)		4	(4.1%)		0	(0.0%)		5	(6.6%)		13	(1.4%)
Strong opioids dose 4		1	(0.2%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		3	(3.9%)		4	(0.4%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		1	(1.0%)		0	(0.0%)		0	(0.0%)		1	(0.1%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
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15.7.9 Worst analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Worst AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 8 (26 - 30 weeks)	444			260			84			40			68			896		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		75	(16.9%)		29	(11.2%)		14	(16.7%)		9	(22.5%)		12	(17.6%)		139	(15.5%)
Weak opioids		30	(6.8%)		16	(6.2%)		9	(10.7%)		0	(0.0%)		5	(7.4%)		60	(6.7%)
All strong opoids		60	(13.5%)		29	(11.2%)		26	(31.0%)		12	(30.0%)		31	(45.6%)		158	(17.6%)
Strong opioids dose 1		53	(11.9%)		26	(10.0%)		19	(22.6%)		9	(22.5%)		24	(35.3%)		131	(14.6%)
Strong opioids dose 2		2	(0.5%)		3	(1.2%)		4	(4.8%)		3	(7.5%)		2	(2.9%)		14	(1.6%)
Strong opioids dose 3		4	(0.9%)		0	(0.0%)		2	(2.4%)		0	(0.0%)		3	(4.4%)		9	(1.0%)
Strong opioids dose 4		1	(0.2%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		2	(2.9%)		3	(0.3%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		1	(1.2%)		0	(0.0%)		0	(0.0%)		1	(0.1%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
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15.7.9 Worst analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Worst AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 9 (30 - 34 weeks)	433			256			78			38			59			864		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		77	(17.8%)		27	(10.5%)		12	(15.4%)		8	(21.1%)		13	(22.0%)		137	(15.9%)
Weak opioids		29	(6.7%)		16	(6.3%)		10	(12.8%)		0	(0.0%)		6	(10.2%)		61	(7.1%)
All strong opoids		59	(13.6%)		28	(10.9%)		22	(28.2%)		11	(28.9%)		24	(40.7%)		144	(16.7%)
Strong opioids dose 1		51	(11.8%)		26	(10.2%)		14	(17.9%)		8	(21.1%)		18	(30.5%)		117	(13.5%)
Strong opioids dose 2		4	(0.9%)		2	(0.8%)		5	(6.4%)		3	(7.9%)		2	(3.4%)		16	(1.9%)
Strong opioids dose 3		3	(0.7%)		0	(0.0%)		2	(2.6%)		0	(0.0%)		1	(1.7%)		6	(0.7%)
Strong opioids dose 4		1	(0.2%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		3	(5.1%)		4	(0.5%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		1	(1.3%)		0	(0.0%)		0	(0.0%)		1	(0.1%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.9 Worst analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Worst AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 10 (34 - 38 weeks)	416			251			70			36			53			826		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		73	(17.5%)		24	(9.6%)		9	(12.9%)		7	(19.4%)		13	(24.5%)		126	(15.3%)
Weak opioids		27	(6.5%)		17	(6.8%)		10	(14.3%)		0	(0.0%)		4	(7.5%)		58	(7.0%)
All strong opoids		59	(14.2%)		27	(10.8%)		19	(27.1%)		10	(27.8%)		21	(39.6%)		136	(16.5%)
Strong opioids dose 1		53	(12.7%)		25	(0.0%)		13	(18.6%)		7	(19.4%)		15	(28.3%)		113	(13.7%)
Strong opioids dose 2		3	(0.7%)		2	(0.8%)		4	(5.7%)		3	(8.3%)		2	(3.8%)		14	(1.7%)
Strong opioids dose 3		2	(0.5%)		0	(0.0%)		1	(1.4%)		0	(0.0%)		1	(1.9%)		4	(0.5%)
Strong opioids dose 4		1	(0.2%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		3	(5.7%)		4	(0.5%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		1	(1.4%)		0	(0.0%)		0	(0.0%)		1	(0.1%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
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15.7.9 Worst analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Worst AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 11 (38 - 42 weeks)	408			243			59			32			50			792		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		71	(17.4%)		20	(8.2%)		9	(15.3%)		6	(18.8%)		10	(20.0%)		116	(14.6%)
Weak opioids		28	(6.9%)		16	(6.6%)		8	(13.6%)		0	(0.0%)		4	(8.0%)		56	(7.1%)
All strong opoids		60	(14.7%)		27	(11.1%)		14	(23.7%)		10	(31.3%)		24	(48.0%)		135	(17.0%)
Strong opioids dose 1		55	(13.5%)		24	(9.9%)		11	(18.6%)		7	(21.9%)		18	(36.0%)		115	(14.5%)
Strong opioids dose 2		3	(0.7%)		3	(1.2%)		2	(3.4%)		3	(9.4%)		2	(4.0%)		13	(1.6%)
Strong opioids dose 3		1	(0.2%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		2	(4.0%)		3	(0.4%)
Strong opioids dose 4		1	(0.2%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		2	(4.0%)		3	(0.4%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		1	(1.7%)		0	(0.0%)		0	(0.0%)		1	(0.1%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.9 Worst analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Worst AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 12 (42 - 46 weeks)	399			235			51			30			44			759		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		69	(17.3%)		20	(8.5%)		10	(19.6%)		6	(20.0%)		8	(18.2%)		113	(14.9%)
Weak opioids		27	(6.8%)		12	(5.1%)		6	(11.8%)		0	(0.0%)		4	(9.1%)		49	(6.5%)
All strong opoids		58	(14.5%)		31	(13.2%)		11	(21.6%)		10	(33.3%)		23	(52.3%)		133	(17.5%)
Strong opioids dose 1		54	(13.5%)		27	(11.5%)		8	(15.7%)		7	(23.3%)		19	(43.2%)		115	(15.2%)
Strong opioids dose 2		3	(0.8%)		2	(0.9%)		2	(3.9%)		3	(10.0%)		2	(4.5%)		12	(1.6%)
Strong opioids dose 3		0	(0.0%)		1	(0.4%)		0	(0.0%)		0	(0.0%)		1	(2.3%)		2	(0.3%)
Strong opioids dose 4		1	(0.3%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(2.3%)		2	(0.3%)
Strong opioids dose 5		0	(0.0%)		1	(0.4%)		1	(2.0%)		0	(0.0%)		0	(0.0%)		2	(0.3%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.9 Worst analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Worst AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 13 (46 - 50 weeks)	385			228			46			28			39			726		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		67	(17.4%)		21	(9.2%)		8	(17.4%)		5	(17.9%)		6	(15.4%)		107	(14.7%)
Weak opioids		25	(6.5%)		11	(4.8%)		4	(8.7%)		2	(7.1%)		4	(10.3%)		46	(6.3%)
All strong opoids		57	(14.8%)		31	(13.6%)		12	(26.1%)		7	(25.0%)		21	(53.8%)		128	(17.6%)
Strong opioids dose 1		53	(13.8%)		27	(11.8%)		9	(19.6%)		6	(21.4%)		17	(43.6%)		112	(15.4%)
Strong opioids dose 2		3	(0.8%)		2	(0.9%)		2	(4.3%)		1	(3.6%)		2	(5.1%)		10	(1.4%)
Strong opioids dose 3		0	(0.0%)		1	(0.4%)		0	(0.0%)		0	(0.0%)		1	(2.6%)		2	(0.3%)
Strong opioids dose 4		1	(0.3%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(2.6%)		2	(0.3%)
Strong opioids dose 5		0	(0.0%)		1	(0.4%)		1	(2.2%)		0	(0.0%)		0	(0.0%)		2	(0.3%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.9 Worst analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Worst AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 14 (50 - 54 weeks)	372			211			39			26			37			685		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		65	(17.5%)		20	(9.5%)		7	(17.9%)		3	(11.5%)		5	(13.5%)		100	(14.6%)
Weak opioids		25	(6.7%)		11	(5.2%)		4	(10.3%)		1	(3.8%)		4	(10.8%)		45	(6.6%)
All strong opoids		56	(15.1%)		23	(10.9%)		6	(15.4%)		8	(30.8%)		20	(54.1%)		113	(16.5%)
Strong opioids dose 1		53	(14.2%)		20	(9.5%)		5	(12.8%)		7	(26.9%)		15	(40.5%)		100	(14.6%)
Strong opioids dose 2		3	(0.8%)		1	(0.5%)		1	(2.6%)		1	(3.8%)		3	(8.1%)		9	(1.3%)
Strong opioids dose 3		0	(0.0%)		1	(0.5%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(0.1%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		2	(5.4%)		2	(0.3%)
Strong opioids dose 5		0	(0.0%)		1	(0.5%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(0.1%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
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15.7.9 Worst analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Worst AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 15 (54 - 58 weeks)	275			150			27			19			23			494		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		47	(17.1%)		13	(8.7%)		5	(18.5%)		3	(15.8%)		2	(8.7%)		70	(14.2%)
Weak opioids		17	(6.2%)		6	(4.0%)		2	(7.4%)		0	(0.0%)		3	(13.0%)		28	(5.7%)
All strong opoids		44	(16.0%)		12	(8.0%)		5	(18.5%)		6	(31.6%)		15	(65.2%)		82	(16.6%)
Strong opioids dose 1		41	(14.9%)		12	(8.0%)		4	(14.8%)		5	(26.3%)		12	(52.2%)		74	(15.0%)
Strong opioids dose 2		3	(1.1%)		0	(0.0%)		1	(3.7%)		1	(5.3%)		1	(4.3%)		6	(1.2%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		2	(8.7%)		2	(0.4%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
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15.7.9 Worst analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Worst AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 16 (58 - 62 weeks)	122			56			16			13			10			217		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		20	(16.4%)		4	(7.1%)		1	(6.3%)		2	(15.4%)		1	(10.0%)		28	(12.9%)
Weak opioids		7	(5.7%)		2	(3.6%)		1	(6.3%)		0	(0.0%)		1	(10.0%)		11	(5.1%)
All strong opoids		17	(13.9%)		1	(1.8%)		2	(12.5%)		3	(23.1%)		7	(70.0%)		30	(13.8%)
Strong opioids dose 1		15	(12.3%)		1	(1.8%)		2	(12.5%)		2	(15.4%)		6	(60.0%)		26	(12.0%)
Strong opioids dose 2		2	(1.6%)		0	(0.0%)		0	(0.0%)		1	(7.7%)		1	(10.0%)		4	(1.8%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
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15.7.9 Worst analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Worst AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 17 (62 - 66 weeks)	51			22			4			4			2			83		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		8	(15.7%)		3	(13.6%)		0	(0.0%)		1	(25.0%)		1	(50.0%)		13	(15.7%)
Weak opioids		3	(5.9%)		1	(4.5%)		1	(25.0%)		0	(0.0%)		0	(0.0%)		5	(6.0%)
All strong opoids		8	(15.7%)		0	(0.0%)		0	(0.0%)		1	(25.0%)		1	(50.0%)		10	(12.0%)
Strong opioids dose 1		7	(13.7%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		7	(8.4%)
Strong opioids dose 2		1	(2.0%)		0	(0.0%)		0	(0.0%)		1	(25.0%)		1	(50.0%)		3	(3.6%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
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15.7.9 Worst analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Worst AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 18 (66 - 70 weeks)	19			8			0			0			1			28		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		2	(10.5%)		2	(25.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		4	(14.3%)
Weak opioids		1	(5.3%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(3.6%)
All strong opoids		5	(26.3%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(100.0%)		6	(21.4%)
Strong opioids dose 1		4	(21.1%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		4	(14.3%)
Strong opioids dose 2		1	(5.3%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(100.0%)		2	(7.1%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
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15.7.9 Worst analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Worst AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 19 (70 - 74 weeks)	11			4			0			0			0			15		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		1	(9.1%)		2	(50.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		3	(20.0%)
Weak opioids		1	(9.1%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(6.7%)
All strong opoids		2	(18.2%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		2	(13.3%)
Strong opioids dose 1		2	(18.2%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		2	(13.3%)
Strong opioids dose 2		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.9 Worst analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Worst AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 20 (74 - 78 weeks)	6			4			0			0			0			10		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		0	(0.0%)		2	(50.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		2	(20.0%)
Weak opioids		1	(16.7%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(10.0%)
All strong opoids		1	(16.7%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(10.0%)
Strong opioids dose 1		1	(16.7%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(10.0%)
Strong opioids dose 2		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.9 Worst analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Worst AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 21 (78 - 82 weeks)	5			4			0			0			0			9		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		0	(0.0%)		2	(50.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		2	(22.2%)
Weak opioids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
All strong opoids		1	(20.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(11.1%)
Strong opioids dose 1		1	(20.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(11.1%)
Strong opioids dose 2		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.9 Worst analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Worst AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 22 (82 - 86 weeks)	3			3			0			0			0			6		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		0	(0.0%)		2	(66.7%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		2	(33.3%)
Weak opioids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
All strong opoids		1	(33.3%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(16.7%)
Strong opioids dose 1		1	(33.3%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(16.7%)
Strong opioids dose 2		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.9 Worst analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Worst AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 23 (86 - 90 weeks)	2			3			0			0			0			5		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		0	(0.0%)		2	(66.7%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		2	(40.0%)
Weak opioids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
All strong opoids		1	(50.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(20.0%)
Strong opioids dose 1		1	(50.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(20.0%)
Strong opioids dose 2		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.9 Worst analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Worst AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 24 (90 - 94 weeks)	0			1			0			0			0			1		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Weak opioids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
All strong opoids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 1		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 2		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.9 Worst analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Worst AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 25 (94 - 98 weeks)	0			1			0			0			0			1		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Weak opioids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
All strong opoids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 1		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 2		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.9 Worst analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Worst AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 26 (98 - 102 weeks)	0			1			0			0			0			1		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Weak opioids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
All strong opoids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 1		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 2		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
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15.7.9 Worst analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Worst AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 27 (102 - 106 weeks)	0			1			0			0			0			1		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Weak opioids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
All strong opoids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 1		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 2		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
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15.7.9 Worst analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Worst AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 28 (106 - 110 weeks)	0			1			0			0			0			1		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Weak opioids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
All strong opoids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 1		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 2		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.9 Worst analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Worst AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 29 (110 - 114 weeks)	0			1			0			0			0			1		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Weak opioids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
All strong opoids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 1		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 2		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.9 Worst analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Worst AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 30 (114 - 118 weeks)	0			1			0			0			0			1		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Weak opioids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
All strong opoids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 1		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 2		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.9 Worst analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Worst AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 31 (118 - 122 weeks)	0			1			0			0			0			1		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Weak opioids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
All strong opoids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 1		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 2		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.9 Worst analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Worst AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 32 (122 - 126 weeks)	0			1			0			0			0			1		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Weak opioids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
All strong opoids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 1		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 2		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.9 Worst analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Worst AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 33 (126 - 130 weeks)	0			1			0			0			0			1		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Weak opioids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
All strong opoids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 1		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 2		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.9 Worst analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Worst AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 34 (130 - 134 weeks)	0			1			0			0			0			1		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Weak opioids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
All strong opoids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 1		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 2		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.9 Worst analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Worst AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 35 (134 - 138 weeks)	0			1			0			0			0			1		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Weak opioids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
All strong opoids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 1		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 2		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
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15.7.9 Worst analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Worst AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 36 (138 - 142 weeks)	0			1			0			0			0			1		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Weak opioids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
All strong opoids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 1		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 2		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.10 Best analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period Best AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 1 (0 - 2 weeks)	509			294			159			50			116			1128		
No analgesic		3	(0.6%)		3	(1.0%)		5	(3.1%)		2	(4.0%)		2	(1.7%)		15	(1.3%)
Non-opioid analgesics		94	(18.5%)		40	(13.6%)		51	(32.1%)		17	(34.0%)		44	(37.9%)		246	(21.8%)
Weak opioids		16	(3.1%)		8	(2.7%)		4	(2.5%)		2	(4.0%)		3	(2.6%)		33	(2.9%)
All strong opoids		13	(2.6%)		10	(3.4%)		12	(7.5%)		3	(6.0%)		12	(10.3%)		50	(4.4%)
Strong opioids dose 1		12	(2.4%)		9	(3.1%)		11	(6.9%)		2	(4.0%)		11	(9.5%)		45	(4.0%)
Strong opioids dose 2		1	(0.2%)		1	(0.3%)		0	(0.0%)		0	(0.0%)		1	(0.9%)		3	(0.3%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		1	(0.6%)		0	(0.0%)		0	(0.0%)		1	(0.1%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(2.0%)		0	(0.0%)		1	(0.1%)
Missing		1	(0.2%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		2	(1.7%)		3	(0.3%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients who took analgesics in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.10 Best analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Best AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 2 (2 - 6 weeks)	508			293			156			50			113			1120		
No analgesic		4	(0.8%)		4	(1.4%)		6	(3.8%)		2	(4.0%)		2	(1.8%)		18	(1.6%)
Non-opioid analgesics		120	(23.6%)		55	(18.8%)		55	(35.3%)		22	(44.0%)		54	(47.8%)		306	(27.3%)
Weak opioids		19	(3.7%)		8	(2.7%)		4	(2.6%)		1	(2.0%)		4	(3.5%)		36	(3.2%)
All strong opoids		17	(3.3%)		12	(4.1%)		13	(8.3%)		3	(6.0%)		13	(11.5%)		58	(5.2%)
Strong opioids dose 1		14	(2.8%)		11	(3.8%)		12	(7.7%)		1	(2.0%)		11	(9.7%)		49	(4.4%)
Strong opioids dose 2		3	(0.6%)		1	(0.3%)		0	(0.0%)		1	(2.0%)		2	(1.8%)		7	(0.6%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		1	(0.6%)		0	(0.0%)		0	(0.0%)		1	(0.1%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(2.0%)		0	(0.0%)		1	(0.1%)
Missing		2	(0.4%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		2	(1.8%)		4	(0.4%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients who took analgesics in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.10 Best analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Best AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 3 (6 - 10 weeks)	503			290			151			50			110			1104		
No analgesic		6	(1.2%)		4	(1.4%)		6	(4.0%)		2	(4.0%)		3	(2.7%)		21	(1.9%)
Non-opioid analgesics		125	(24.9%)		66	(22.8%)		56	(37.1%)		26	(52.0%)		55	(50.0%)		328	(29.7%)
Weak opioids		21	(4.2%)		9	(3.1%)		4	(2.6%)		1	(2.0%)		5	(4.5%)		40	(3.6%)
All strong opoids		19	(3.8%)		9	(3.1%)		15	(9.9%)		1	(2.0%)		12	(10.9%)		56	(5.1%)
Strong opioids dose 1		16	(3.2%)		8	(2.8%)		14	(9.3%)		0	(0.0%)		10	(9.1%)		48	(4.3%)
Strong opioids dose 2		3	(0.6%)		1	(0.3%)		0	(0.0%)		0	(0.0%)		2	(1.8%)		6	(0.5%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		1	(0.7%)		0	(0.0%)		0	(0.0%)		1	(0.1%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(2.0%)		0	(0.0%)		1	(0.1%)
Missing		2	(0.4%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(0.9%)		3	(0.3%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients who took analgesics in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.10 Best analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Best AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 4 (10 - 14 weeks)	497			287			139			48			103			1074		
No analgesic		8	(1.6%)		4	(1.4%)		6	(4.3%)		2	(4.2%)		3	(2.9%)		23	(2.1%)
Non-opioid analgesics		127	(25.6%)		67	(23.3%)		52	(37.4%)		24	(50.0%)		53	(51.5%)		323	(30.1%)
Weak opioids		21	(4.2%)		9	(3.1%)		5	(3.6%)		0	(0.0%)		4	(3.9%)		39	(3.6%)
All strong opoids		20	(4.0%)		7	(2.4%)		11	(7.9%)		1	(2.1%)		10	(9.7%)		49	(4.6%)
Strong opioids dose 1		18	(3.6%)		6	(2.1%)		10	(7.2%)		0	(0.0%)		9	(8.7%)		43	(4.0%)
Strong opioids dose 2		2	(0.4%)		1	(0.3%)		0	(0.0%)		1	(2.1%)		1	(1.0%)		5	(0.5%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		1	(0.7%)		0	(0.0%)		0	(0.0%)		1	(0.1%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		2	(0.4%)		1	(0.3%)		0	(0.0%)		0	(0.0%)		1	(1.0%)		4	(0.4%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients who took analgesics in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.10 Best analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Best AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 5 (14 - 18 weeks)	481			278			129			47			93			1028		
No analgesic		8	(1.7%)		4	(1.4%)		6	(4.7%)		2	(4.3%)		3	(3.2%)		23	(2.2%)
Non-opioid analgesics		124	(25.8%)		65	(23.4%)		49	(38.0%)		23	(48.9%)		48	(51.6%)		309	(30.1%)
Weak opioids		20	(4.2%)		8	(2.9%)		4	(3.1%)		0	(0.0%)		3	(3.2%)		35	(3.4%)
All strong opoids		20	(4.2%)		7	(2.5%)		11	(8.5%)		3	(6.4%)		9	(9.7%)		50	(4.9%)
Strong opioids dose 1		18	(3.7%)		6	(2.2%)		9	(7.0%)		2	(4.3%)		8	(8.6%)		43	(4.2%)
Strong opioids dose 2		2	(0.4%)		1	(0.4%)		1	(0.8%)		1	(2.1%)		1	(1.1%)		6	(0.6%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		1	(0.8%)		0	(0.0%)		0	(0.0%)		1	(0.1%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		1	(0.4%)		0	(0.0%)		0	(0.0%)		1	(1.1%)		2	(0.2%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients who took analgesics in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.10 Best analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Best AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 6 (18 - 22 weeks)	470			273			112			45			84			984		
No analgesic		8	(1.7%)		4	(1.5%)		5	(4.5%)		2	(4.4%)		3	(3.6%)		22	(2.2%)
Non-opioid analgesics		122	(26.0%)		61	(22.3%)		48	(42.9%)		22	(48.9%)		45	(53.6%)		298	(30.3%)
Weak opioids		20	(4.3%)		8	(2.9%)		5	(4.5%)		0	(0.0%)		3	(3.6%)		36	(3.7%)
All strong opoids		23	(4.9%)		9	(3.3%)		8	(7.1%)		2	(4.4%)		9	(10.7%)		51	(5.2%)
Strong opioids dose 1		20	(4.3%)		8	(2.9%)		6	(5.4%)		2	(4.4%)		8	(9.5%)		44	(4.5%)
Strong opioids dose 2		2	(0.4%)		1	(0.4%)		1	(0.9%)		0	(0.0%)		1	(1.2%)		5	(0.5%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		1	(0.9%)		0	(0.0%)		0	(0.0%)		1	(0.1%)
Strong opioids dose 4		1	(0.2%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(0.1%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients who took analgesics in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.10 Best analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Best AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 7 (22 - 26 weeks)	455			267			98			42			76			938		
No analgesic		8	(1.8%)		5	(1.9%)		5	(5.1%)		1	(2.4%)		3	(3.9%)		22	(2.3%)
Non-opioid analgesics		125	(27.5%)		58	(21.7%)		40	(40.8%)		20	(47.6%)		42	(55.3%)		285	(30.4%)
Weak opioids		17	(3.7%)		6	(2.2%)		4	(4.1%)		0	(0.0%)		2	(2.6%)		29	(3.1%)
All strong opoids		22	(4.8%)		10	(3.7%)		8	(8.2%)		3	(7.1%)		7	(9.2%)		50	(5.3%)
Strong opioids dose 1		21	(4.6%)		8	(3.0%)		6	(6.1%)		3	(7.1%)		6	(7.9%)		44	(4.7%)
Strong opioids dose 2		1	(0.2%)		2	(0.7%)		1	(1.0%)		0	(0.0%)		1	(1.3%)		5	(0.5%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		1	(1.0%)		0	(0.0%)		0	(0.0%)		1	(0.1%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients who took analgesics in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.10 Best analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Best AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 8 (26 - 30 weeks)	444			260			84			40			68			896		
No analgesic		6	(1.4%)		4	(1.5%)		3	(3.6%)		1	(2.5%)		3	(4.4%)		17	(1.9%)
Non-opioid analgesics		122	(27.5%)		57	(21.9%)		36	(42.9%)		17	(42.5%)		38	(55.9%)		270	(30.1%)
Weak opioids		15	(3.4%)		4	(1.5%)		3	(3.6%)		0	(0.0%)		2	(2.9%)		24	(2.7%)
All strong opoids		22	(5.0%)		9	(3.5%)		7	(8.3%)		3	(7.5%)		5	(7.4%)		46	(5.1%)
Strong opioids dose 1		21	(4.7%)		7	(2.7%)		6	(7.1%)		3	(7.5%)		5	(7.4%)		42	(4.7%)
Strong opioids dose 2		1	(0.2%)		2	(0.8%)		1	(1.2%)		0	(0.0%)		0	(0.0%)		4	(0.4%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients who took analgesics in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.10 Best analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Best AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 9 (30 - 34 weeks)	433			256			78			38			59			864		
No analgesic		7	(1.6%)		3	(1.2%)		4	(5.1%)		1	(2.6%)		3	(5.1%)		18	(2.1%)
Non-opioid analgesics		119	(27.5%)		54	(21.1%)		34	(43.6%)		16	(42.1%)		33	(55.9%)		256	(29.6%)
Weak opioids		15	(3.5%)		3	(1.2%)		2	(2.6%)		0	(0.0%)		3	(5.1%)		23	(2.7%)
All strong opoids		24	(5.5%)		11	(4.3%)		4	(5.1%)		2	(5.3%)		4	(6.8%)		45	(5.2%)
Strong opioids dose 1		22	(5.1%)		9	(3.5%)		3	(3.8%)		2	(5.3%)		4	(6.8%)		40	(4.6%)
Strong opioids dose 2		2	(0.5%)		2	(0.8%)		1	(1.3%)		0	(0.0%)		0	(0.0%)		5	(0.6%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients who took analgesics in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.10 Best analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Best AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 10 (34 - 38 weeks)	416			251			70			36			53			826		
No analgesic		6	(1.4%)		2	(0.8%)		3	(4.3%)		1	(2.8%)		3	(5.7%)		15	(1.8%)
Non-opioid analgesics		115	(27.6%)		54	(21.5%)		29	(41.4%)		13	(36.1%)		28	(52.8%)		239	(28.9%)
Weak opioids		14	(3.4%)		3	(1.2%)		3	(4.3%)		1	(2.8%)		3	(5.7%)		24	(2.9%)
All strong opoids		24	(5.8%)		9	(3.6%)		3	(4.3%)		2	(5.6%)		4	(7.5%)		42	(5.1%)
Strong opioids dose 1		21	(5.0%)		7	(2.8%)		2	(2.9%)		2	(5.6%)		4	(7.5%)		36	(4.4%)
Strong opioids dose 2		3	(0.7%)		2	(0.8%)		1	(1.4%)		0	(0.0%)		0	(0.0%)		6	(0.7%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients who took analgesics in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.10 Best analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Best AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 11 (38 - 42 weeks)	408			243			59			32			50			792		
No analgesic		8	(2.0%)		1	(0.4%)		2	(3.4%)		1	(3.1%)		3	(6.0%)		15	(1.9%)
Non-opioid analgesics		112	(27.5%)		52	(21.4%)		24	(40.7%)		12	(37.5%)		29	(58.0%)		229	(28.9%)
Weak opioids		15	(3.7%)		3	(1.2%)		3	(5.1%)		1	(3.1%)		2	(4.0%)		24	(3.0%)
All strong opoids		24	(5.9%)		7	(2.9%)		2	(3.4%)		2	(6.3%)		4	(8.0%)		39	(4.9%)
Strong opioids dose 1		21	(5.1%)		5	(2.1%)		1	(1.7%)		2	(6.3%)		4	(8.0%)		33	(4.2%)
Strong opioids dose 2		3	(0.7%)		2	(0.8%)		1	(1.7%)		0	(0.0%)		0	(0.0%)		6	(0.8%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients who took analgesics in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.10 Best analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Best AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 12 (42 - 46 weeks)	399			235			51			30			44			759		
No analgesic		7	(1.8%)		2	(0.9%)		1	(2.0%)		1	(3.3%)		2	(4.5%)		13	(1.7%)
Non-opioid analgesics		111	(27.8%)		52	(22.1%)		21	(41.2%)		12	(40.0%)		26	(59.1%)		222	(29.2%)
Weak opioids		14	(3.5%)		1	(0.4%)		3	(5.9%)		1	(3.3%)		2	(4.5%)		21	(2.8%)
All strong opoids		22	(5.5%)		8	(3.4%)		2	(3.9%)		2	(6.7%)		5	(11.4%)		39	(5.1%)
Strong opioids dose 1		19	(4.8%)		5	(2.1%)		1	(2.0%)		2	(6.7%)		5	(11.4%)		32	(4.2%)
Strong opioids dose 2		3	(0.8%)		3	(1.3%)		1	(2.0%)		0	(0.0%)		0	(0.0%)		7	(0.9%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients who took analgesics in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.10 Best analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Best AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 13 (46 - 50 weeks)	385			228			46			28			39			726		
No analgesic		5	(1.3%)		2	(0.9%)		1	(2.2%)		1	(3.6%)		2	(5.1%)		11	(1.5%)
Non-opioid analgesics		112	(29.1%)		50	(21.9%)		18	(39.1%)		10	(35.7%)		23	(59.0%)		213	(29.3%)
Weak opioids		11	(2.9%)		2	(0.9%)		3	(6.5%)		1	(3.6%)		2	(5.1%)		19	(2.6%)
All strong opoids		21	(5.5%)		9	(3.9%)		2	(4.3%)		2	(7.1%)		4	(10.3%)		38	(5.2%)
Strong opioids dose 1		18	(4.7%)		6	(2.6%)		1	(2.2%)		2	(7.1%)		4	(10.3%)		31	(4.3%)
Strong opioids dose 2		3	(0.8%)		3	(1.3%)		1	(2.2%)		0	(0.0%)		0	(0.0%)		7	(1.0%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients who took analgesics in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
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Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.10 Best analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Best AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 14 (50 - 54 weeks)	372			211			39			26			37			685		
No analgesic		5	(1.3%)		2	(0.9%)		1	(2.6%)		2	(7.7%)		2	(5.4%)		12	(1.8%)
Non-opioid analgesics		108	(29.0%)		42	(19.9%)		12	(30.8%)		8	(30.8%)		21	(56.8%)		191	(27.9%)
Weak opioids		12	(3.2%)		2	(0.9%)		3	(7.7%)		0	(0.0%)		2	(5.4%)		19	(2.8%)
All strong opoids		21	(5.6%)		8	(3.8%)		1	(2.6%)		2	(7.7%)		4	(10.8%)		36	(5.3%)
Strong opioids dose 1		18	(4.8%)		6	(2.8%)		0	(0.0%)		2	(7.7%)		4	(10.8%)		30	(4.4%)
Strong opioids dose 2		3	(0.8%)		2	(0.9%)		1	(2.6%)		0	(0.0%)		0	(0.0%)		6	(0.9%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients who took analgesics in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
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15.7.10 Best analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Best AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 15 (54 - 58 weeks)	275			150			27			19			23			494		
No analgesic		5	(1.8%)		2	(1.3%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		7	(1.4%)
Non-opioid analgesics		78	(28.4%)		24	(16.0%)		11	(40.7%)		7	(36.8%)		13	(56.5%)		133	(26.9%)
Weak opioids		10	(3.6%)		1	(0.7%)		0	(0.0%)		0	(0.0%)		2	(8.7%)		13	(2.6%)
All strong opoids		15	(5.5%)		4	(2.7%)		1	(3.7%)		2	(10.5%)		5	(21.7%)		27	(5.5%)
Strong opioids dose 1		13	(4.7%)		4	(2.7%)		0	(0.0%)		2	(10.5%)		5	(21.7%)		24	(4.9%)
Strong opioids dose 2		2	(0.7%)		0	(0.0%)		1	(3.7%)		0	(0.0%)		0	(0.0%)		3	(0.6%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients who took analgesics in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
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15.7.10 Best analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Best AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 16 (58 - 62 weeks)	122			56			16			13			10			217		
No analgesic		2	(1.6%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		2	(0.9%)
Non-opioid analgesics		32	(26.2%)		7	(12.5%)		4	(25.0%)		5	(38.5%)		6	(60.0%)		54	(24.9%)
Weak opioids		3	(2.5%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		3	(1.4%)
All strong opoids		7	(5.7%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		3	(30.0%)		10	(4.6%)
Strong opioids dose 1		6	(4.9%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		3	(30.0%)		9	(4.1%)
Strong opioids dose 2		1	(0.8%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(0.5%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients who took analgesics in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
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15.7.10 Best analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Best AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 17 (62 - 66 weeks)	51			22			4			4			2			83		
No analgesic		1	(2.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(1.2%)
Non-opioid analgesics		14	(27.5%)		4	(18.2%)		1	(25.0%)		2	(50.0%)		1	(50.0%)		22	(26.5%)
Weak opioids		1	(2.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(1.2%)
All strong opoids		3	(5.9%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(50.0%)		4	(4.8%)
Strong opioids dose 1		3	(5.9%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(50.0%)		4	(4.8%)
Strong opioids dose 2		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients who took analgesics in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.10 Best analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Best AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 18 (66 - 70 weeks)	19			8			0			0			1			28		
No analgesic		1	(5.3%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(3.6%)
Non-opioid analgesics		5	(26.3%)		2	(25.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		7	(25.0%)
Weak opioids		1	(5.3%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(3.6%)
All strong opoids		1	(5.3%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(100.0%)		2	(7.1%)
Strong opioids dose 1		1	(5.3%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(100.0%)		2	(7.1%)
Strong opioids dose 2		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients who took analgesics in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.10 Best analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Best AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 19 (70 - 74 weeks)	11			4			0			0			0			15		
No analgesic		1	(9.1%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(6.7%)
Non-opioid analgesics		1	(9.1%)		2	(50.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		3	(20.0%)
Weak opioids		1	(9.1%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(6.7%)
All strong opoids		1	(9.1%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(6.7%)
Strong opioids dose 1		1	(9.1%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(6.7%)
Strong opioids dose 2		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients who took analgesics in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.10 Best analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Best AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 20 (74 - 78 weeks)	6			4			0			0			0			10		
No analgesic		1	(16.7%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(10.0%)
Non-opioid analgesics		0	(0.0%)		2	(50.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		2	(20.0%)
Weak opioids		1	(16.7%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(10.0%)
All strong opoids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 1		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 2		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients who took analgesics in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.10 Best analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Best AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 21 (78 - 82 weeks)	5			4			0			0			0			9		
No analgesic		1	(20.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(11.1%)
Non-opioid analgesics		0	(0.0%)		2	(50.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		2	(22.2%)
Weak opioids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
All strong opoids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 1		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 2		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients who took analgesics in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.10 Best analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Best AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 22 (82 - 86 weeks)	3			3			0			0			0			6		
No analgesic		1	(33.3%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(16.7%)
Non-opioid analgesics		0	(0.0%)		2	(66.7%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		2	(33.3%)
Weak opioids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
All strong opoids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 1		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 2		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients who took analgesics in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
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15.7.10 Best analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Best AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 23 (86 - 90 weeks)	2			3			0			0			0			5		
No analgesic		1	(50.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		1	(20.0%)
Non-opioid analgesics		0	(0.0%)		2	(66.7%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		2	(40.0%)
Weak opioids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
All strong opoids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 1		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 2		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients who took analgesics in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
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15.7.10 Best analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Best AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 24 (90 - 94 weeks)	0			1			0			0			0			1		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Weak opioids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
All strong opoids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 1		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 2		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients who took analgesics in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
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15.7.10 Best analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Best AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 25 (94 - 98 weeks)	0			1			0			0			0			1		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Weak opioids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
All strong opoids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 1		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 2		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients who took analgesics in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
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15.7.10 Best analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Best AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 26 (98 - 102 weeks)	0			1			0			0			0			1		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Weak opioids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
All strong opoids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 1		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 2		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients who took analgesics in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.10 Best analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Best AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 27 (102 - 106 weeks)	0			1			0			0			0			1		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Weak opioids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
All strong opoids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 1		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 2		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients who took analgesics in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.10 Best analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Best AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 28 (106 - 110 weeks)	0			1			0			0			0			1		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Weak opioids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
All strong opoids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 1		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 2		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients who took analgesics in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.10 Best analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Best AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 29 (110 - 114 weeks)	0			1			0			0			0			1		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Weak opioids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
All strong opoids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 1		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 2		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients who took analgesics in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.10 Best analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period Best AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 30 (114 - 118 weeks)	0			1			0			0			0			1		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Weak opioids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
All strong opoids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 1		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 2		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients who took analgesics in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.10 Best analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Best AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 31 (118 - 122 weeks)	0			1			0			0			0			1		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Weak opioids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
All strong opoids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 1		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 2		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients who took analgesics in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.10 Best analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Best AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 32 (122 - 126 weeks)	0			1			0			0			0			1		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Weak opioids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
All strong opoids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 1		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 2		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients who took analgesics in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.10 Best analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Best AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 33 (126 - 130 weeks)	0			1			0			0			0			1		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Weak opioids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
All strong opoids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 1		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 2		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients who took analgesics in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
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15.7.10 Best analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Best AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 34 (130 - 134 weeks)	0			1			0			0			0			1		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Weak opioids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
All strong opoids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 1		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 2		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients who took analgesics in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.10 Best analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Best AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 35 (134 - 138 weeks)	0			1			0			0			0			1		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Weak opioids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
All strong opoids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 1		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 2		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients who took analgesics in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.10 Best analgesic score (AQA) of pain medications given throughout the study by period - FAS

Period / Best AQA* per patient within period	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %	N	Pat. n	Pat. %
Period 36 (138 - 142 weeks)	0			1			0			0			0			1		
No analgesic		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Non-opioid analgesics		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Weak opioids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
All strong opoids		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 1		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 2		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 3		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 4		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Strong opioids dose 5		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)
Missing		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)

* per patient within a period (each patient was only counted once in each period)
N=number of patients who took analgesics in respective period
Strong opioids dose 1: <= 75 mg OME per day, dose 2: > 75-150 mg OME per day, dose 3: > 150-300 mg OME per day, dose 4: > 300-600 mg OME per day, dose 5: > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked

15.7.11 Worst analgesic score (AQA)* of pain medications given throughout the study as numeric variable by period - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Breast cancer	Period 1 (0 - 2 weeks)	126	2.89	1.01	1.00	2.00	3.00	4.00	6.00
	Period 2 (2 - 6 weeks)	160	2.98	1.10	2.00	2.00	3.00	4.00	7.00
	Period 3 (6 - 10 weeks)	171	2.98	1.07	2.00	2.00	3.00	4.00	7.00
	Period 4 (10 - 14 weeks)	176	2.97	1.03	2.00	2.00	3.00	4.00	7.00
	Period 5 (14 - 18 weeks)	172	3.04	1.09	2.00	2.00	3.00	4.00	7.00
	Period 6 (18 - 22 weeks)	173	3.06	1.11	2.00	2.00	3.00	4.00	7.00
	Period 7 (22 - 26 weeks)	172	2.99	1.08	2.00	2.00	3.00	4.00	7.00
	Period 8 (26 - 30 weeks)	165	2.99	1.07	2.00	2.00	3.00	4.00	7.00
	Period 9 (30 - 34 weeks)	165	2.97	1.07	2.00	2.00	3.00	4.00	7.00
	Period 10 (34 - 38 weeks)	160	2.97	1.04	2.00	2.00	3.00	4.00	7.00
	Period 11 (38 - 42 weeks)	160	2.98	1.02	2.00	2.00	3.00	4.00	7.00
	Period 12 (42 - 46 weeks)	155	2.96	0.99	2.00	2.00	3.00	4.00	7.00
	Period 13 (46 - 50 weeks)	149	2.97	1.00	2.00	2.00	3.00	4.00	7.00
	Period 14 (50 - 54 weeks)	146	2.96	0.95	2.00	2.00	3.00	4.00	5.00
	Period 15 (54 - 58 weeks)	108	3.00	0.97	2.00	2.00	3.00	4.00	5.00
	Period 16 (58 - 62 weeks)	45	2.96	1.00	2.00	2.00	3.00	4.00	5.00
	Period 17 (62 - 66 weeks)	19	3.05	1.03	2.00	2.00	3.00	4.00	5.00
	Period 18 (66 - 70 weeks)	9	3.33	1.12	2.00	2.00	4.00	4.00	5.00
	Period 19 (70 - 74 weeks)	4	3.25	0.96	2.00	2.50	3.50	4.00	4.00

* per patient within a period (each patient was only counted once in each period)
0: No analgesic, 1: Non-opioid analgesics, 2: Weak opioids (e.g. meperidine, codeine, tramadol), 3: Strong opioids <= 75 mg OME per day, 4: Strong opioids > 75-150 mg OME per day
5: Strong opioids > 150-300 mg OME per day, 6: Strong opioids > 300-600 mg OME per day, 7: Strong opioids > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked
Period 1: 0 week to 2 weeks, period 2: 2 weeks to 6 weeks, period 3, 6 weeks to 10 weeks, period 4: 10 weeks to 14 weeks, ...

15.7.11 Worst analgesic score (AQA)* of pain medications given throughout the study as numeric variable by period - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Breast cancer	Period 20 (74 - 78 weeks)	2	3.50	0.71	3.00	3.00	3.50	4.00	4.00
	Period 21 (78 - 82 weeks)	1	4.00		4.00	4.00	4.00	4.00	4.00
	Period 22 (82 - 86 weeks)	1	4.00		4.00	4.00	4.00	4.00	4.00
	Period 23 (86 - 90 weeks)	1	4.00		4.00	4.00	4.00	4.00	4.00

* per patient within a period (each patient was only counted once in each period)
0: No analgesic, 1: Non-opioid analgesics, 2: Weak opioids (e.g. meperidine, codeine, tramadol), 3: Strong opioids <= 75 mg OME per day, 4: Strong opioids > 75-150 mg OME per day
5: Strong opioids > 150-300 mg OME per day, 6: Strong opioids > 300-600 mg OME per day, 7: Strong opioids > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked
Period 1: 0 week to 2 weeks, period 2: 2 weeks to 6 weeks, period 3, 6 weeks to 10 weeks, period 4: 10 weeks to 14 weeks, ...

15.7.11 Worst analgesic score (AQA)* of pain medications given throughout the study as numeric variable by period - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Prostate cancer	Period 1 (0 - 2 weeks)	61	2.93	0.93	2.00	2.00	3.00	4.00	5.00
	Period 2 (2 - 6 weeks)	79	2.85	0.91	2.00	2.00	3.00	4.00	5.00
	Period 3 (6 - 10 weeks)	88	2.78	0.88	2.00	2.00	3.00	3.50	5.00
	Period 4 (10 - 14 weeks)	88	2.78	0.86	2.00	2.00	3.00	3.00	5.00
	Period 5 (14 - 18 weeks)	85	2.78	0.88	2.00	2.00	3.00	3.00	5.00
	Period 6 (18 - 22 weeks)	82	2.96	0.92	2.00	2.00	3.00	4.00	5.00
	Period 7 (22 - 26 weeks)	79	3.08	0.92	2.00	2.00	3.00	4.00	5.00
	Period 8 (26 - 30 weeks)	74	3.04	0.96	2.00	2.00	3.00	4.00	5.00
	Period 9 (30 - 34 weeks)	72	3.01	0.96	1.00	2.00	3.00	4.00	5.00
	Period 10 (34 - 38 weeks)	70	3.03	0.95	1.00	2.00	3.00	4.00	5.00
	Period 11 (38 - 42 weeks)	64	3.13	0.97	1.00	2.00	3.00	4.00	5.00
	Period 12 (42 - 46 weeks)	65	3.26	1.18	1.00	2.00	3.00	4.00	8.00
	Period 13 (46 - 50 weeks)	65	3.25	1.19	1.00	2.00	3.00	4.00	8.00
	Period 14 (50 - 54 weeks)	57	3.16	1.21	1.00	2.00	3.00	4.00	8.00
	Period 15 (54 - 58 weeks)	32	3.00	0.92	2.00	2.00	3.00	4.00	4.00
	Period 16 (58 - 62 weeks)	7	2.57	0.79	2.00	2.00	2.00	3.00	4.00
	Period 17 (62 - 66 weeks)	4	2.25	0.50	2.00	2.00	2.00	2.50	3.00
	Period 18 (66 - 70 weeks)	2	2.00	0.00	2.00	2.00	2.00	2.00	2.00
	Period 19 (70 - 74 weeks)	2	2.00	0.00	2.00	2.00	2.00	2.00	2.00

* per patient within a period (each patient was only counted once in each period)
0: No analgesic, 1: Non-opioid analgesics, 2: Weak opioids (e.g. meperidine, codeine, tramadol), 3: Strong opioids <= 75 mg OME per day, 4: Strong opioids > 75-150 mg OME per day
5: Strong opioids > 150-300 mg OME per day, 6: Strong opioids > 300-600 mg OME per day, 7: Strong opioids > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked
Period 1: 0 week to 2 weeks, period 2: 2 weeks to 6 weeks, period 3, 6 weeks to 10 weeks, period 4: 10 weeks to 14 weeks, ...

15.7.11 Worst analgesic score (AQA)* of pain medications given throughout the study as numeric variable by period - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Prostate cancer	Period 20 (74 - 78 weeks)	2	2.00	0.00	2.00	2.00	2.00	2.00	2.00
	Period 21 (78 - 82 weeks)	2	2.00	0.00	2.00	2.00	2.00	2.00	2.00
	Period 22 (82 - 86 weeks)	2	2.00	0.00	2.00	2.00	2.00	2.00	2.00
	Period 23 (86 - 90 weeks)	2	2.00	0.00	2.00	2.00	2.00	2.00	2.00

* per patient within a period (each patient was only counted once in each period)
0: No analgesic, 1: Non-opioid analgesics, 2: Weak opioids (e.g. meperidine, codeine, tramadol), 3: Strong opioids <= 75 mg OME per day, 4: Strong opioids > 75-150 mg OME per day
5: Strong opioids > 150-300 mg OME per day, 6: Strong opioids > 300-600 mg OME per day, 7: Strong opioids > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked
Period 1: 0 week to 2 weeks, period 2: 2 weeks to 6 weeks, period 3, 6 weeks to 10 weeks, period 4: 10 weeks to 14 weeks, ...

15.7.11 Worst analgesic score (AQA)* of pain medications given throughout the study as numeric variable by period - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Lung cancer	Period 1 (0 - 2 weeks)	72	3.26	1.22	2.00	2.00	3.00	4.00	7.00
	Period 2 (2 - 6 weeks)	78	3.45	1.17	2.00	2.00	4.00	4.00	7.00
	Period 3 (6 - 10 weeks)	81	3.54	1.23	2.00	2.00	4.00	4.00	7.00
	Period 4 (10 - 14 weeks)	75	3.61	1.29	2.00	3.00	4.00	4.00	7.00
	Period 5 (14 - 18 weeks)	71	3.62	1.22	2.00	3.00	4.00	4.00	7.00
	Period 6 (18 - 22 weeks)	66	3.58	1.28	2.00	2.00	4.00	4.00	7.00
	Period 7 (22 - 26 weeks)	57	3.61	1.32	2.00	3.00	4.00	4.00	8.00
	Period 8 (26 - 30 weeks)	49	3.49	1.29	2.00	2.00	4.00	4.00	8.00
	Period 9 (30 - 34 weeks)	44	3.52	1.34	2.00	2.00	3.50	4.00	8.00
	Period 10 (34 - 38 weeks)	38	3.53	1.29	2.00	3.00	3.50	4.00	8.00
	Period 11 (38 - 42 weeks)	31	3.35	1.28	2.00	2.00	3.00	4.00	8.00
	Period 12 (42 - 46 weeks)	27	3.26	1.38	2.00	2.00	3.00	4.00	8.00
	Period 13 (46 - 50 weeks)	24	3.42	1.41	2.00	2.00	3.50	4.00	8.00
	Period 14 (50 - 54 weeks)	17	3.00	1.00	2.00	2.00	3.00	4.00	5.00
	Period 15 (54 - 58 weeks)	12	3.08	1.08	2.00	2.00	3.00	4.00	5.00
	Period 16 (58 - 62 weeks)	4	3.25	0.96	2.00	2.50	3.50	4.00	4.00
	Period 17 (62 - 66 weeks)	1	3.00		3.00	3.00	3.00	3.00	3.00

* per patient within a period (each patient was only counted once in each period)
0: No analgesic, 1: Non-opioid analgesics, 2: Weak opioids (e.g. meperidine, codeine, tramadol), 3: Strong opioids <= 75 mg OME per day, 4: Strong opioids > 75-150 mg OME per day
5: Strong opioids > 150-300 mg OME per day, 6: Strong opioids > 300-600 mg OME per day, 7: Strong opioids > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked
Period 1: 0 week to 2 weeks, period 2: 2 weeks to 6 weeks, period 3, 6 weeks to 10 weeks, period 4: 10 weeks to 14 weeks, ...

15.7.11 Worst analgesic score (AQA)* of pain medications given throughout the study as numeric variable by period - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Kidney cancer	Period 1 (0 - 2 weeks)	24	3.29	1.40	2.00	2.00	3.00	4.00	8.00
	Period 2 (2 - 6 weeks)	28	3.43	1.40	2.00	2.00	4.00	4.00	8.00
	Period 3 (6 - 10 weeks)	30	3.33	1.40	2.00	2.00	3.50	4.00	8.00
	Period 4 (10 - 14 weeks)	27	3.30	1.17	2.00	2.00	4.00	4.00	5.00
	Period 5 (14 - 18 weeks)	28	3.36	1.19	2.00	2.00	4.00	4.00	5.00
	Period 6 (18 - 22 weeks)	26	3.35	1.16	2.00	2.00	4.00	4.00	5.00
	Period 7 (22 - 26 weeks)	24	3.25	1.15	2.00	2.00	4.00	4.00	5.00
	Period 8 (26 - 30 weeks)	21	3.29	1.19	2.00	2.00	4.00	4.00	5.00
	Period 9 (30 - 34 weeks)	19	3.32	1.20	2.00	2.00	4.00	4.00	5.00
	Period 10 (34 - 38 weeks)	17	3.35	1.22	2.00	2.00	4.00	4.00	5.00
	Period 11 (38 - 42 weeks)	16	3.44	1.21	2.00	2.00	4.00	4.00	5.00
	Period 12 (42 - 46 weeks)	16	3.44	1.21	2.00	2.00	4.00	4.00	5.00
	Period 13 (46 - 50 weeks)	14	3.21	1.05	2.00	2.00	3.50	4.00	5.00
	Period 14 (50 - 54 weeks)	12	3.50	1.00	2.00	2.50	4.00	4.00	5.00
	Period 15 (54 - 58 weeks)	9	3.44	1.13	2.00	2.00	4.00	4.00	5.00
	Period 16 (58 - 62 weeks)	5	3.40	1.34	2.00	2.00	4.00	4.00	5.00
	Period 17 (62 - 66 weeks)	2	3.50	2.12	2.00	2.00	3.50	5.00	5.00

* per patient within a period (each patient was only counted once in each period)
0: No analgesic, 1: Non-opioid analgesics, 2: Weak opioids (e.g. meperidine, codeine, tramadol), 3: Strong opioids <= 75 mg OME per day, 4: Strong opioids > 75-150 mg OME per day
5: Strong opioids > 150-300 mg OME per day, 6: Strong opioids > 300-600 mg OME per day, 7: Strong opioids > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked
Period 1: 0 week to 2 weeks, period 2: 2 weeks to 6 weeks, period 3, 6 weeks to 10 weeks, period 4: 10 weeks to 14 weeks, ...

15.7.11 Worst analgesic score (AQA)* of pain medications given throughout the study as numeric variable by period - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Other cancer type	Period 1 (0 - 2 weeks)	61	3.30	1.17	2.00	2.00	3.00	4.00	6.00
	Period 2 (2 - 6 weeks)	73	3.40	1.24	2.00	2.00	4.00	4.00	7.00
	Period 3 (6 - 10 weeks)	75	3.52	1.32	2.00	2.00	4.00	4.00	7.00
	Period 4 (10 - 14 weeks)	70	3.61	1.34	2.00	2.00	4.00	4.00	7.00
	Period 5 (14 - 18 weeks)	63	3.70	1.40	2.00	2.00	4.00	4.00	7.00
	Period 6 (18 - 22 weeks)	60	3.80	1.42	2.00	2.50	4.00	4.00	7.00
	Period 7 (22 - 26 weeks)	54	3.76	1.45	2.00	2.00	4.00	4.00	7.00
	Period 8 (26 - 30 weeks)	48	3.69	1.31	2.00	2.50	4.00	4.00	7.00
	Period 9 (30 - 34 weeks)	43	3.56	1.40	2.00	2.00	4.00	4.00	7.00
	Period 10 (34 - 38 weeks)	38	3.55	1.48	2.00	2.00	4.00	4.00	7.00
	Period 11 (38 - 42 weeks)	39	3.67	1.34	2.00	2.00	4.00	4.00	7.00
	Period 12 (42 - 46 weeks)	36	3.67	1.17	2.00	3.00	4.00	4.00	7.00
	Period 13 (46 - 50 weeks)	32	3.75	1.16	2.00	3.00	4.00	4.00	7.00
	Period 14 (50 - 54 weeks)	30	3.87	1.25	2.00	3.00	4.00	4.00	7.00
	Period 15 (54 - 58 weeks)	21	4.05	1.24	2.00	4.00	4.00	4.00	7.00
	Period 16 (58 - 62 weeks)	10	3.80	0.79	2.00	4.00	4.00	4.00	5.00
	Period 17 (62 - 66 weeks)	2	3.50	2.12	2.00	2.00	3.50	5.00	5.00
	Period 18 (66 - 70 weeks)	1	5.00		5.00	5.00	5.00	5.00	5.00

* per patient within a period (each patient was only counted once in each period)
0: No analgesic, 1: Non-opioid analgesics, 2: Weak opioids (e.g. meperidine, codeine, tramadol), 3: Strong opioids <= 75 mg OME per day, 4: Strong opioids > 75-150 mg OME per day
5: Strong opioids > 150-300 mg OME per day, 6: Strong opioids > 300-600 mg OME per day, 7: Strong opioids > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked
Period 1: 0 week to 2 weeks, period 2: 2 weeks to 6 weeks, period 3, 6 weeks to 10 weeks, period 4: 10 weeks to 14 weeks, ...

15.7.11 Worst analgesic score (AQA)* of pain medications given throughout the study as numeric variable by period - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Total	Period 1 (0 - 2 weeks)	344	3.08	1.11	1.00	2.00	3.00	4.00	8.00
	Period 2 (2 - 6 weeks)	418	3.15	1.15	2.00	2.00	3.00	4.00	8.00
	Period 3 (6 - 10 weeks)	445	3.16	1.17	2.00	2.00	3.00	4.00	8.00
	Period 4 (10 - 14 weeks)	436	3.17	1.16	2.00	2.00	3.00	4.00	7.00
	Period 5 (14 - 18 weeks)	419	3.21	1.18	2.00	2.00	3.00	4.00	7.00
	Period 6 (18 - 22 weeks)	407	3.25	1.19	2.00	2.00	3.00	4.00	7.00
	Period 7 (22 - 26 weeks)	386	3.23	1.18	2.00	2.00	3.00	4.00	8.00
	Period 8 (26 - 30 weeks)	357	3.18	1.15	2.00	2.00	3.00	4.00	8.00
	Period 9 (30 - 34 weeks)	343	3.14	1.16	1.00	2.00	3.00	4.00	8.00
	Period 10 (34 - 38 weeks)	323	3.14	1.14	1.00	2.00	3.00	4.00	8.00
	Period 11 (38 - 42 weeks)	310	3.15	1.11	1.00	2.00	3.00	4.00	8.00
	Period 12 (42 - 46 weeks)	299	3.16	1.12	1.00	2.00	3.00	4.00	8.00
	Period 13 (46 - 50 weeks)	284	3.17	1.13	1.00	2.00	3.00	4.00	8.00
	Period 14 (50 - 54 weeks)	262	3.13	1.08	1.00	2.00	3.00	4.00	8.00
	Period 15 (54 - 58 weeks)	182	3.15	1.05	2.00	2.00	3.00	4.00	7.00
	Period 16 (58 - 62 weeks)	71	3.08	1.01	2.00	2.00	3.00	4.00	5.00
	Period 17 (62 - 66 weeks)	28	3.00	1.09	2.00	2.00	3.00	4.00	5.00
	Period 18 (66 - 70 weeks)	12	3.25	1.22	2.00	2.00	3.50	4.00	5.00
	Period 19 (70 - 74 weeks)	6	2.83	0.98	2.00	2.00	2.50	4.00	4.00

* per patient within a period (each patient was only counted once in each period)
0: No analgesic, 1: Non-opioid analgesics, 2: Weak opioids (e.g. meperidine, codeine, tramadol), 3: Strong opioids <= 75 mg OME per day, 4: Strong opioids > 75-150 mg OME per day
5: Strong opioids > 150-300 mg OME per day, 6: Strong opioids > 300-600 mg OME per day, 7: Strong opioids > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked
Period 1: 0 week to 2 weeks, period 2: 2 weeks to 6 weeks, period 3, 6 weeks to 10 weeks, period 4: 10 weeks to 14 weeks, ...

15.7.11 Worst analgesic score (AQA)* of pain medications given throughout the study as numeric variable by period - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Total	Period 20 (74 - 78 weeks)	4	2.75	0.96	2.00	2.00	2.50	3.50	4.00
	Period 21 (78 - 82 weeks)	3	2.67	1.15	2.00	2.00	2.00	4.00	4.00
	Period 22 (82 - 86 weeks)	3	2.67	1.15	2.00	2.00	2.00	4.00	4.00
	Period 23 (86 - 90 weeks)	3	2.67	1.15	2.00	2.00	2.00	4.00	4.00

* per patient within a period (each patient was only counted once in each period)
0: No analgesic, 1: Non-opioid analgesics, 2: Weak opioids (e.g. meperidine, codeine, tramadol), 3: Strong opioids <= 75 mg OME per day, 4: Strong opioids > 75-150 mg OME per day
5: Strong opioids > 150-300 mg OME per day, 6: Strong opioids > 300-600 mg OME per day, 7: Strong opioids > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked
Period 1: 0 week to 2 weeks, period 2: 2 weeks to 6 weeks, period 3, 6 weeks to 10 weeks, period 4: 10 weeks to 14 weeks, ...

15.7.12 Absolute changes from baseline in worst analgesic score (AQA)* of pain medications by period - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Breast cancer	Period 1 (0 - 2 weeks)	116	0.03	0.18	0.00	0.00	0.00	0.00	1.00
	Period 2 (2 - 6 weeks)	115	0.17	0.62	0.00	0.00	0.00	0.00	5.00
	Period 3 (6 - 10 weeks)	110	0.23	0.69	0.00	0.00	0.00	0.00	5.00
	Period 4 (10 - 14 weeks)	108	0.18	0.73	-2.00	0.00	0.00	0.00	5.00
	Period 5 (14 - 18 weeks)	101	0.25	0.92	-2.00	0.00	0.00	0.00	5.00
	Period 6 (18 - 22 weeks)	98	0.26	0.93	-2.00	0.00	0.00	0.00	5.00
	Period 7 (22 - 26 weeks)	92	0.24	0.89	-2.00	0.00	0.00	0.00	5.00
	Period 8 (26 - 30 weeks)	89	0.22	0.88	-2.00	0.00	0.00	0.00	5.00
	Period 9 (30 - 34 weeks)	86	0.17	0.91	-2.00	0.00	0.00	0.00	5.00
	Period 10 (34 - 38 weeks)	80	0.14	0.84	-2.00	0.00	0.00	0.00	5.00
	Period 11 (38 - 42 weeks)	80	0.13	0.83	-2.00	0.00	0.00	0.00	5.00
	Period 12 (42 - 46 weeks)	76	0.13	0.85	-2.00	0.00	0.00	0.00	5.00
	Period 13 (46 - 50 weeks)	75	0.13	0.86	-2.00	0.00	0.00	0.00	5.00
	Period 14 (50 - 54 weeks)	72	0.06	0.65	-2.00	0.00	0.00	0.00	2.00
	Period 15 (54 - 58 weeks)	52	0.06	0.75	-2.00	0.00	0.00	0.00	2.00
	Period 16 (58 - 62 weeks)	26	0.15	0.73	-2.00	0.00	0.00	0.00	2.00
	Period 17 (62 - 66 weeks)	8	-0.13	0.83	-2.00	0.00	0.00	0.00	1.00
	Period 18 (66 - 70 weeks)	4	0.25	0.50	0.00	0.00	0.00	0.50	1.00
	Period 19 (70 - 74 weeks)	2	0.00	0.00	0.00	0.00	0.00	0.00	0.00

* per patient within a period (each patient was only counted once in each period)
0: No analgesic, 1: Non-opioid analgesics, 2: Weak opioids (e.g. meperidine, codeine, tramadol), 3: Strong opioids <= 75 mg OME per day, 4: Strong opioids > 75-150 mg OME per day
5: Strong opioids > 150-300 mg OME per day, 6: Strong opioids > 300-600 mg OME per day, 7: Strong opioids > 600 mg OME per day
Baseline is defined as the value between day -15 and day 5. If more than one values available in this time window the value nearest to day 1 was used as baseline value. If different AQA scores were available at day 1 the worst score was used as baseline value. In case of missing start and stop date it is assumed that medication was given for all periods including baseline.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked
Period 1: 0 week to 2 weeks, period 2: 2 weeks to 6 weeks, period 3, 6 weeks to 10 weeks, period 4: 10 weeks to 14 weeks, ...

15.7.12 Absolute changes from baseline in worst analgesic score (AQA)* of pain medications by period - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Breast cancer	Period 20 (74 - 78 weeks)	1	0.00		0.00	0.00	0.00	0.00	0.00
	Period 21 (78 - 82 weeks)	0							
	Period 22 (82 - 86 weeks)	0							
	Period 23 (86 - 90 weeks)	0							

* per patient within a period (each patient was only counted once in each period)
0: No analgesic, 1: Non-opioid analgesics, 2: Weak opioids (e.g. meperidine, codeine, tramadol), 3: Strong opioids <= 75 mg OME per day, 4: Strong opioids > 75-150 mg OME per day
5: Strong opioids > 150-300 mg OME per day, 6: Strong opioids > 300-600 mg OME per day, 7: Strong opioids > 600 mg OME per day
Baseline is defined as the value between day -15 and day 5. If more than one values available in this time window the value nearest to day 1 was used as baseline value. If different AQA scores were available at day 1 the worst score was used as baseline value. In case of missing start and stop date it is assumed that medication was given for all periods including baseline.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked
Period 1: 0 week to 2 weeks, period 2: 2 weeks to 6 weeks, period 3, 6 weeks to 10 weeks, period 4: 10 weeks to 14 weeks, ...

15.7.12 Absolute changes from baseline in worst analgesic score (AQA)* of pain medications by period - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Prostate cancer	Period 1 (0 - 2 weeks)	54	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Period 2 (2 - 6 weeks)	52	0.06	0.31	0.00	0.00	0.00	0.00	2.00
	Period 3 (6 - 10 weeks)	52	0.02	0.14	0.00	0.00	0.00	0.00	1.00
	Period 4 (10 - 14 weeks)	48	0.02	0.44	-2.00	0.00	0.00	0.00	2.00
	Period 5 (14 - 18 weeks)	46	0.02	0.45	-2.00	0.00	0.00	0.00	2.00
	Period 6 (18 - 22 weeks)	43	0.12	0.59	-2.00	0.00	0.00	0.00	2.00
	Period 7 (22 - 26 weeks)	40	0.23	0.70	-2.00	0.00	0.00	0.00	2.00
	Period 8 (26 - 30 weeks)	36	0.28	0.74	-2.00	0.00	0.00	0.50	2.00
	Period 9 (30 - 34 weeks)	34	0.26	0.79	-2.00	0.00	0.00	1.00	2.00
	Period 10 (34 - 38 weeks)	35	0.29	0.79	-2.00	0.00	0.00	1.00	2.00
	Period 11 (38 - 42 weeks)	32	0.22	0.87	-2.00	0.00	0.00	1.00	2.00
	Period 12 (42 - 46 weeks)	31	0.42	0.96	-2.00	0.00	0.00	1.00	2.00
	Period 13 (46 - 50 weeks)	31	0.52	1.00	-2.00	0.00	0.00	1.00	2.00
	Period 14 (50 - 54 weeks)	28	0.36	1.06	-2.00	0.00	0.00	1.00	2.00
	Period 15 (54 - 58 weeks)	16	0.56	1.09	-2.00	0.00	1.00	1.00	2.00
	Period 16 (58 - 62 weeks)	3	0.67	1.53	-1.00	-1.00	1.00	2.00	2.00
	Period 17 (62 - 66 weeks)	1	-1.00		-1.00	-1.00	-1.00	-1.00	-1.00
	Period 18 (66 - 70 weeks)	0							
	Period 19 (70 - 74 weeks)	0							

* per patient within a period (each patient was only counted once in each period)
0: No analgesic, 1: Non-opioid analgesics, 2: Weak opioids (e.g. meperidine, codeine, tramadol), 3: Strong opioids <= 75 mg OME per day, 4: Strong opioids > 75-150 mg OME per day
5: Strong opioids > 150-300 mg OME per day, 6: Strong opioids > 300-600 mg OME per day, 7: Strong opioids > 600 mg OME per day
Baseline is defined as the value between day -15 and day 5. If more than one values available in this time window the value nearest to day 1 was used as baseline value. If different AQA scores were available at day 1 the worst score was used as baseline value. In case of missing start and stop date it is assumed that medication was given for all periods including baseline.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked
Period 1: 0 week to 2 weeks, period 2: 2 weeks to 6 weeks, period 3, 6 weeks to 10 weeks, period 4: 10 weeks to 14 weeks, ...

15.7.12 Absolute changes from baseline in worst analgesic score (AQA)* of pain medications by period - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Prostate cancer	Period 20 (74 - 78 weeks)	0							
	Period 21 (78 - 82 weeks)	0							
	Period 22 (82 - 86 weeks)	0							
	Period 23 (86 - 90 weeks)	0							

* per patient within a period (each patient was only counted once in each period)
0: No analgesic, 1: Non-opioid analgesics, 2: Weak opioids (e.g. meperidine, codeine, tramadol), 3: Strong opioids <= 75 mg OME per day, 4: Strong opioids > 75-150 mg OME per day
5: Strong opioids > 150-300 mg OME per day, 6: Strong opioids > 300-600 mg OME per day, 7: Strong opioids > 600 mg OME per day
Baseline is defined as the value between day -15 and day 5. If more than one values available in this time window the value nearest to day 1 was used as baseline value. If different AQA scores were available at day 1 the worst score was used as baseline value. In case of missing start and stop date it is assumed that medication was given for all periods including baseline.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked
Period 1: 0 week to 2 weeks, period 2: 2 weeks to 6 weeks, period 3, 6 weeks to 10 weeks, period 4: 10 weeks to 14 weeks, ...

15.7.12 Absolute changes from baseline in worst analgesic score (AQA)* of pain medications by period - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Lung cancer	Period 1 (0 - 2 weeks)	66	0.12	0.67	0.00	0.00	0.00	0.00	5.00
	Period 2 (2 - 6 weeks)	64	0.34	0.93	-1.00	0.00	0.00	0.00	5.00
	Period 3 (6 - 10 weeks)	62	0.50	1.07	-1.00	0.00	0.00	0.00	5.00
	Period 4 (10 - 14 weeks)	57	0.54	1.17	-1.00	0.00	0.00	0.00	5.00
	Period 5 (14 - 18 weeks)	51	0.45	0.99	0.00	0.00	0.00	0.00	5.00
	Period 6 (18 - 22 weeks)	46	0.41	0.93	0.00	0.00	0.00	0.00	5.00
	Period 7 (22 - 26 weeks)	38	0.45	1.18	-2.00	0.00	0.00	1.00	6.00
	Period 8 (26 - 30 weeks)	30	0.43	1.17	0.00	0.00	0.00	0.00	6.00
	Period 9 (30 - 34 weeks)	28	0.50	1.20	0.00	0.00	0.00	1.00	6.00
	Period 10 (34 - 38 weeks)	23	0.43	1.27	0.00	0.00	0.00	0.00	6.00
	Period 11 (38 - 42 weeks)	20	0.45	1.36	0.00	0.00	0.00	0.00	6.00
	Period 12 (42 - 46 weeks)	15	0.67	1.54	0.00	0.00	0.00	1.00	6.00
	Period 13 (46 - 50 weeks)	13	0.85	1.68	0.00	0.00	0.00	1.00	6.00
	Period 14 (50 - 54 weeks)	9	0.33	0.71	0.00	0.00	0.00	0.00	2.00
	Period 15 (54 - 58 weeks)	6	0.50	0.84	0.00	0.00	0.00	1.00	2.00
	Period 16 (58 - 62 weeks)	0							
	Period 17 (62 - 66 weeks)	0							

* per patient within a period (each patient was only counted once in each period)
0: No analgesic, 1: Non-opioid analgesics, 2: Weak opioids (e.g. meperidine, codeine, tramadol), 3: Strong opioids <= 75 mg OME per day, 4: Strong opioids > 75-150 mg OME per day
5: Strong opioids > 150-300 mg OME per day, 6: Strong opioids > 300-600 mg OME per day, 7: Strong opioids > 600 mg OME per day
Baseline is defined as the value between day -15 and day 5. If more than one values available in this time window the value nearest to day 1 was used as baseline value. If different AQA scores were available at day 1 the worst score was used as baseline value. In case of missing start and stop date it is assumed that medication was given for all periods including baseline.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked
Period 1: 0 week to 2 weeks, period 2: 2 weeks to 6 weeks, period 3, 6 weeks to 10 weeks, period 4: 10 weeks to 14 weeks, ...

15.7.12 Absolute changes from baseline in worst analgesic score (AQA)* of pain medications by period - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Kidney cancer	Period 1 (0 - 2 weeks)	21	0.14	0.48	0.00	0.00	0.00	0.00	2.00
	Period 2 (2 - 6 weeks)	21	0.19	0.51	0.00	0.00	0.00	0.00	2.00
	Period 3 (6 - 10 weeks)	21	0.19	0.51	0.00	0.00	0.00	0.00	2.00
	Period 4 (10 - 14 weeks)	20	0.25	0.55	0.00	0.00	0.00	0.00	2.00
	Period 5 (14 - 18 weeks)	20	0.30	0.66	0.00	0.00	0.00	0.00	2.00
	Period 6 (18 - 22 weeks)	19	0.32	0.67	0.00	0.00	0.00	0.00	2.00
	Period 7 (22 - 26 weeks)	16	0.31	0.70	0.00	0.00	0.00	0.00	2.00
	Period 8 (26 - 30 weeks)	14	0.14	0.53	0.00	0.00	0.00	0.00	2.00
	Period 9 (30 - 34 weeks)	13	0.15	0.55	0.00	0.00	0.00	0.00	2.00
	Period 10 (34 - 38 weeks)	11	0.18	0.60	0.00	0.00	0.00	0.00	2.00
	Period 11 (38 - 42 weeks)	9	0.22	0.67	0.00	0.00	0.00	0.00	2.00
	Period 12 (42 - 46 weeks)	9	0.22	0.67	0.00	0.00	0.00	0.00	2.00
	Period 13 (46 - 50 weeks)	8	0.13	0.35	0.00	0.00	0.00	0.00	1.00
	Period 14 (50 - 54 weeks)	6	0.17	0.41	0.00	0.00	0.00	0.00	1.00
	Period 15 (54 - 58 weeks)	4	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Period 16 (58 - 62 weeks)	2	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Period 17 (62 - 66 weeks)	1	0.00		0.00	0.00	0.00	0.00	0.00

* per patient within a period (each patient was only counted once in each period)
0: No analgesic, 1: Non-opioid analgesics, 2: Weak opioids (e.g. meperidine, codeine, tramadol), 3: Strong opioids <= 75 mg OME per day, 4: Strong opioids > 75-150 mg OME per day
5: Strong opioids > 150-300 mg OME per day, 6: Strong opioids > 300-600 mg OME per day, 7: Strong opioids > 600 mg OME per day
Baseline is defined as the value between day -15 and day 5. If more than one values available in this time window the value nearest to day 1 was used as baseline value. If different AQA scores were available at day 1 the worst score was used as baseline value. In case of missing start and stop date it is assumed that medication was given for all periods including baseline.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked
Period 1: 0 week to 2 weeks, period 2: 2 weeks to 6 weeks, period 3, 6 weeks to 10 weeks, period 4: 10 weeks to 14 weeks, ...

15.7.12 Absolute changes from baseline in worst analgesic score (AQA)* of pain medications by period - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Other cancer type	Period 1 (0 - 2 weeks)	58	0.05	0.39	0.00	0.00	0.00	0.00	3.00
	Period 2 (2 - 6 weeks)	58	0.16	0.62	0.00	0.00	0.00	0.00	3.00
	Period 3 (6 - 10 weeks)	56	0.23	0.83	-2.00	0.00	0.00	0.00	4.00
	Period 4 (10 - 14 weeks)	51	0.33	0.91	-1.00	0.00	0.00	0.00	4.00
	Period 5 (14 - 18 weeks)	48	0.52	1.05	-1.00	0.00	0.00	1.00	4.00
	Period 6 (18 - 22 weeks)	47	0.66	1.11	-1.00	0.00	0.00	2.00	4.00
	Period 7 (22 - 26 weeks)	41	0.56	1.10	-1.00	0.00	0.00	1.00	4.00
	Period 8 (26 - 30 weeks)	37	0.59	1.09	-1.00	0.00	0.00	1.00	4.00
	Period 9 (30 - 34 weeks)	32	0.41	0.95	-1.00	0.00	0.00	0.00	3.00
	Period 10 (34 - 38 weeks)	29	0.48	1.09	-1.00	0.00	0.00	0.00	3.00
	Period 11 (38 - 42 weeks)	29	0.48	0.99	-1.00	0.00	0.00	1.00	3.00
	Period 12 (42 - 46 weeks)	27	0.48	0.94	-1.00	0.00	0.00	1.00	3.00
	Period 13 (46 - 50 weeks)	25	0.52	0.96	-1.00	0.00	0.00	1.00	3.00
	Period 14 (50 - 54 weeks)	23	0.61	1.08	-1.00	0.00	0.00	1.00	3.00
	Period 15 (54 - 58 weeks)	15	0.60	1.18	-1.00	0.00	0.00	1.00	3.00
	Period 16 (58 - 62 weeks)	6	0.50	1.05	-1.00	0.00	0.50	1.00	2.00
	Period 17 (62 - 66 weeks)	2	0.00	1.41	-1.00	-1.00	0.00	1.00	1.00
	Period 18 (66 - 70 weeks)	1	1.00		1.00	1.00	1.00	1.00	1.00

* per patient within a period (each patient was only counted once in each period)
0: No analgesic, 1: Non-opioid analgesics, 2: Weak opioids (e.g. meperidine, codeine, tramadol), 3: Strong opioids <= 75 mg OME per day, 4: Strong opioids > 75-150 mg OME per day
5: Strong opioids > 150-300 mg OME per day, 6: Strong opioids > 300-600 mg OME per day, 7: Strong opioids > 600 mg OME per day
Baseline is defined as the value between day -15 and day 5. If more than one values available in this time window the value nearest to day 1 was used as baseline value. If different AQA scores were available at day 1 the worst score was used as baseline value. In case of missing start and stop date it is assumed that medication was given for all periods including baseline.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked
Period 1: 0 week to 2 weeks, period 2: 2 weeks to 6 weeks, period 3, 6 weeks to 10 weeks, period 4: 10 weeks to 14 weeks, ...

15.7.12 Absolute changes from baseline in worst analgesic score (AQA)* of pain medications by period - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Total	Period 1 (0 - 2 weeks)	315	0.06	0.39	0.00	0.00	0.00	0.00	5.00
	Period 2 (2 - 6 weeks)	310	0.18	0.65	-1.00	0.00	0.00	0.00	5.00
	Period 3 (6 - 10 weeks)	301	0.25	0.76	-2.00	0.00	0.00	0.00	5.00
	Period 4 (10 - 14 weeks)	284	0.26	0.84	-2.00	0.00	0.00	0.00	5.00
	Period 5 (14 - 18 weeks)	266	0.30	0.89	-2.00	0.00	0.00	0.00	5.00
	Period 6 (18 - 22 weeks)	253	0.34	0.91	-2.00	0.00	0.00	0.00	5.00
	Period 7 (22 - 26 weeks)	227	0.33	0.95	-2.00	0.00	0.00	0.00	6.00
	Period 8 (26 - 30 weeks)	206	0.33	0.93	-2.00	0.00	0.00	0.00	6.00
	Period 9 (30 - 34 weeks)	193	0.27	0.93	-2.00	0.00	0.00	0.00	6.00
	Period 10 (34 - 38 weeks)	178	0.26	0.93	-2.00	0.00	0.00	0.00	6.00
	Period 11 (38 - 42 weeks)	170	0.25	0.93	-2.00	0.00	0.00	0.00	6.00
	Period 12 (42 - 46 weeks)	158	0.30	0.97	-2.00	0.00	0.00	0.00	6.00
	Period 13 (46 - 50 weeks)	152	0.34	1.00	-2.00	0.00	0.00	0.50	6.00
	Period 14 (50 - 54 weeks)	138	0.23	0.84	-2.00	0.00	0.00	0.00	3.00
	Period 15 (54 - 58 weeks)	93	0.26	0.91	-2.00	0.00	0.00	0.00	3.00
	Period 16 (58 - 62 weeks)	37	0.24	0.83	-2.00	0.00	0.00	0.00	2.00
	Period 17 (62 - 66 weeks)	12	-0.17	0.83	-2.00	-0.50	0.00	0.00	1.00
	Period 18 (66 - 70 weeks)	5	0.40	0.55	0.00	0.00	0.00	1.00	1.00
	Period 19 (70 - 74 weeks)	2	0.00	0.00	0.00	0.00	0.00	0.00	0.00

* per patient within a period (each patient was only counted once in each period)
0: No analgesic, 1: Non-opioid analgesics, 2: Weak opioids (e.g. meperidine, codeine, tramadol), 3: Strong opioids <= 75 mg OME per day, 4: Strong opioids > 75-150 mg OME per day
5: Strong opioids > 150-300 mg OME per day, 6: Strong opioids > 300-600 mg OME per day, 7: Strong opioids > 600 mg OME per day
Baseline is defined as the value between day -15 and day 5. If more than one values available in this time window the value nearest to day 1 was used as baseline value. If different AQA scores were available at day 1 the worst score was used as baseline value. In case of missing start and stop date it is assumed that medication was given for all periods including baseline.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked
Period 1: 0 week to 2 weeks, period 2: 2 weeks to 6 weeks, period 3, 6 weeks to 10 weeks, period 4: 10 weeks to 14 weeks, ...

15.7.12 Absolute changes from baseline in worst analgesic score (AQA)* of pain medications by period - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Total	Period 20 (74 - 78 weeks)	1	0.00		0.00	0.00	0.00	0.00	0.00
	Period 21 (78 - 82 weeks)	0							
	Period 22 (82 - 86 weeks)	0							
	Period 23 (86 - 90 weeks)	0							

* per patient within a period (each patient was only counted once in each period)
0: No analgesic, 1: Non-opioid analgesics, 2: Weak opioids (e.g. meperidine, codeine, tramadol), 3: Strong opioids <= 75 mg OME per day, 4: Strong opioids > 75-150 mg OME per day
5: Strong opioids > 150-300 mg OME per day, 6: Strong opioids > 300-600 mg OME per day, 7: Strong opioids > 600 mg OME per day
Baseline is defined as the value between day -15 and day 5. If more than one values available in this time window the value nearest to day 1 was used as baseline value. If different AQA scores were available at day 1 the worst score was used as baseline value. In case of missing start and stop date it is assumed that medication was given for all periods including baseline.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked
Period 1: 0 week to 2 weeks, period 2: 2 weeks to 6 weeks, period 3, 6 weeks to 10 weeks, period 4: 10 weeks to 14 weeks, ...

15.7.13 Best analgesic score (AQA)* of pain medications given throughout the study as numeric variable by period - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Breast cancer	Period 1 (0 - 2 weeks)	126	2.32	0.71	1.00	2.00	2.00	2.00	5.00
	Period 2 (2 - 6 weeks)	160	2.33	0.75	1.00	2.00	2.00	2.00	5.00
	Period 3 (6 - 10 weeks)	171	2.33	0.77	1.00	2.00	2.00	2.00	5.00
	Period 4 (10 - 14 weeks)	176	2.31	0.76	1.00	2.00	2.00	2.00	5.00
	Period 5 (14 - 18 weeks)	172	2.31	0.77	1.00	2.00	2.00	2.00	5.00
	Period 6 (18 - 22 weeks)	173	2.36	0.86	1.00	2.00	2.00	2.00	7.00
	Period 7 (22 - 26 weeks)	172	2.31	0.77	1.00	2.00	2.00	2.00	5.00
	Period 8 (26 - 30 weeks)	165	2.33	0.77	1.00	2.00	2.00	2.00	5.00
	Period 9 (30 - 34 weeks)	165	2.35	0.81	1.00	2.00	2.00	2.00	5.00
	Period 10 (34 - 38 weeks)	160	2.37	0.83	1.00	2.00	2.00	2.00	5.00
	Period 11 (38 - 42 weeks)	160	2.36	0.84	1.00	2.00	2.00	2.00	5.00
	Period 12 (42 - 46 weeks)	155	2.35	0.83	1.00	2.00	2.00	2.00	5.00
	Period 13 (46 - 50 weeks)	149	2.34	0.81	1.00	2.00	2.00	2.00	5.00
	Period 14 (50 - 54 weeks)	146	2.36	0.82	1.00	2.00	2.00	2.00	5.00
	Period 15 (54 - 58 weeks)	108	2.34	0.82	1.00	2.00	2.00	2.00	5.00
	Period 16 (58 - 62 weeks)	45	2.36	0.86	1.00	2.00	2.00	2.00	5.00
	Period 17 (62 - 66 weeks)	19	2.32	0.82	1.00	2.00	2.00	2.00	4.00
	Period 18 (66 - 70 weeks)	9	2.22	0.83	1.00	2.00	2.00	2.00	4.00
	Period 19 (70 - 74 weeks)	4	2.50	1.29	1.00	1.50	2.50	3.50	4.00

* per patient within a period (each patient was only counted once in each period)
0: No analgesic, 1: Non-opioid analgesics, 2: Weak opioids (e.g. meperidine, codeine, tramadol), 3: Strong opioids <= 75 mg OME per day, 4: Strong opioids > 75-150 mg OME per day
5: Strong opioids > 150-300 mg OME per day, 6: Strong opioids > 300-600 mg OME per day, 7: Strong opioids > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked
Period 1: 0 week to 2 weeks, period 2: 2 weeks to 6 weeks, period 3, 6 weeks to 10 weeks, period 4: 10 weeks to 14 weeks, ...

15.7.13 Best analgesic score (AQA)* of pain medications given throughout the study as numeric variable by period - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Breast cancer	Period 20 (74 - 78 weeks)	2	2.00	1.41	1.00	1.00	2.00	3.00	3.00
	Period 21 (78 - 82 weeks)	1	1.00		1.00	1.00	1.00	1.00	1.00
	Period 22 (82 - 86 weeks)	1	1.00		1.00	1.00	1.00	1.00	1.00
	Period 23 (86 - 90 weeks)	1	1.00		1.00	1.00	1.00	1.00	1.00

* per patient within a period (each patient was only counted once in each period)
0: No analgesic, 1: Non-opioid analgesics, 2: Weak opioids (e.g. meperidine, codeine, tramadol), 3: Strong opioids <= 75 mg OME per day, 4: Strong opioids > 75-150 mg OME per day
5: Strong opioids > 150-300 mg OME per day, 6: Strong opioids > 300-600 mg OME per day, 7: Strong opioids > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked
Period 1: 0 week to 2 weeks, period 2: 2 weeks to 6 weeks, period 3, 6 weeks to 10 weeks, period 4: 10 weeks to 14 weeks, ...

15.7.13 Best analgesic score (AQA)* of pain medications given throughout the study as numeric variable by period - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Prostate cancer	Period 1 (0 - 2 weeks)	61	2.43	0.87	1.00	2.00	2.00	3.00	5.00
	Period 2 (2 - 6 weeks)	79	2.37	0.83	1.00	2.00	2.00	3.00	5.00
	Period 3 (6 - 10 weeks)	88	2.27	0.74	1.00	2.00	2.00	2.00	5.00
	Period 4 (10 - 14 weeks)	88	2.23	0.69	1.00	2.00	2.00	2.00	5.00
	Period 5 (14 - 18 weeks)	85	2.22	0.70	1.00	2.00	2.00	2.00	5.00
	Period 6 (18 - 22 weeks)	82	2.28	0.76	1.00	2.00	2.00	2.00	5.00
	Period 7 (22 - 26 weeks)	79	2.29	0.83	1.00	2.00	2.00	2.00	5.00
	Period 8 (26 - 30 weeks)	74	2.27	0.82	1.00	2.00	2.00	2.00	5.00
	Period 9 (30 - 34 weeks)	72	2.32	0.87	1.00	2.00	2.00	2.00	5.00
	Period 10 (34 - 38 weeks)	70	2.29	0.82	1.00	2.00	2.00	2.00	5.00
	Period 11 (38 - 42 weeks)	64	2.27	0.78	1.00	2.00	2.00	2.00	5.00
	Period 12 (42 - 46 weeks)	65	2.26	0.85	1.00	2.00	2.00	2.00	5.00
	Period 13 (46 - 50 weeks)	65	2.31	0.88	1.00	2.00	2.00	2.00	5.00
	Period 14 (50 - 54 weeks)	57	2.33	0.89	1.00	2.00	2.00	2.00	5.00
	Period 15 (54 - 58 weeks)	32	2.28	0.81	1.00	2.00	2.00	2.00	4.00
	Period 16 (58 - 62 weeks)	7	2.00	0.00	2.00	2.00	2.00	2.00	2.00
	Period 17 (62 - 66 weeks)	4	2.00	0.00	2.00	2.00	2.00	2.00	2.00
	Period 18 (66 - 70 weeks)	2	2.00	0.00	2.00	2.00	2.00	2.00	2.00
	Period 19 (70 - 74 weeks)	2	2.00	0.00	2.00	2.00	2.00	2.00	2.00

* per patient within a period (each patient was only counted once in each period)
0: No analgesic, 1: Non-opioid analgesics, 2: Weak opioids (e.g. meperidine, codeine, tramadol), 3: Strong opioids <= 75 mg OME per day, 4: Strong opioids > 75-150 mg OME per day
5: Strong opioids > 150-300 mg OME per day, 6: Strong opioids > 300-600 mg OME per day, 7: Strong opioids > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked
Period 1: 0 week to 2 weeks, period 2: 2 weeks to 6 weeks, period 3, 6 weeks to 10 weeks, period 4: 10 weeks to 14 weeks, ...

15.7.13 Best analgesic score (AQA)* of pain medications given throughout the study as numeric variable by period - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Prostate cancer	Period 20 (74 - 78 weeks)	2	2.00	0.00	2.00	2.00	2.00	2.00	2.00
	Period 21 (78 - 82 weeks)	2	2.00	0.00	2.00	2.00	2.00	2.00	2.00
	Period 22 (82 - 86 weeks)	2	2.00	0.00	2.00	2.00	2.00	2.00	2.00
	Period 23 (86 - 90 weeks)	2	2.00	0.00	2.00	2.00	2.00	2.00	2.00

* per patient within a period (each patient was only counted once in each period)
0: No analgesic, 1: Non-opioid analgesics, 2: Weak opioids (e.g. meperidine, codeine, tramadol), 3: Strong opioids <= 75 mg OME per day, 4: Strong opioids > 75-150 mg OME per day
5: Strong opioids > 150-300 mg OME per day, 6: Strong opioids > 300-600 mg OME per day, 7: Strong opioids > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked
Period 1: 0 week to 2 weeks, period 2: 2 weeks to 6 weeks, period 3, 6 weeks to 10 weeks, period 4: 10 weeks to 14 weeks, ...

15.7.13 Best analgesic score (AQA)* of pain medications given throughout the study as numeric variable by period - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Lung cancer	Period 1 (0 - 2 weeks)	72	2.35	0.92	1.00	2.00	2.00	2.00	6.00
	Period 2 (2 - 6 weeks)	78	2.33	0.92	1.00	2.00	2.00	2.00	6.00
	Period 3 (6 - 10 weeks)	81	2.37	0.94	1.00	2.00	2.00	2.00	6.00
	Period 4 (10 - 14 weeks)	75	2.33	0.92	1.00	2.00	2.00	2.00	6.00
	Period 5 (14 - 18 weeks)	71	2.34	0.96	1.00	2.00	2.00	2.00	6.00
	Period 6 (18 - 22 weeks)	66	2.29	0.91	1.00	2.00	2.00	2.00	6.00
	Period 7 (22 - 26 weeks)	57	2.32	0.97	1.00	2.00	2.00	2.00	6.00
	Period 8 (26 - 30 weeks)	49	2.31	0.85	1.00	2.00	2.00	2.00	5.00
	Period 9 (30 - 34 weeks)	44	2.16	0.78	1.00	2.00	2.00	2.00	5.00
	Period 10 (34 - 38 weeks)	38	2.18	0.77	1.00	2.00	2.00	2.00	5.00
	Period 11 (38 - 42 weeks)	31	2.19	0.75	1.00	2.00	2.00	2.00	5.00
	Period 12 (42 - 46 weeks)	27	2.26	0.76	1.00	2.00	2.00	2.00	5.00
	Period 13 (46 - 50 weeks)	24	2.29	0.81	1.00	2.00	2.00	2.00	5.00
	Period 14 (50 - 54 weeks)	17	2.29	0.85	1.00	2.00	2.00	2.00	5.00
	Period 15 (54 - 58 weeks)	12	2.25	0.87	2.00	2.00	2.00	2.00	5.00
	Period 16 (58 - 62 weeks)	4	2.00	0.00	2.00	2.00	2.00	2.00	2.00
	Period 17 (62 - 66 weeks)	1	2.00		2.00	2.00	2.00	2.00	2.00

* per patient within a period (each patient was only counted once in each period)
0: No analgesic, 1: Non-opioid analgesics, 2: Weak opioids (e.g. meperidine, codeine, tramadol), 3: Strong opioids <= 75 mg OME per day, 4: Strong opioids > 75-150 mg OME per day
5: Strong opioids > 150-300 mg OME per day, 6: Strong opioids > 300-600 mg OME per day, 7: Strong opioids > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked
Period 1: 0 week to 2 weeks, period 2: 2 weeks to 6 weeks, period 3, 6 weeks to 10 weeks, period 4: 10 weeks to 14 weeks, ...

15.7.13 Best analgesic score (AQA)* of pain medications given throughout the study as numeric variable by period - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Kidney cancer	Period 1 (0 - 2 weeks)	24	2.42	1.38	1.00	2.00	2.00	2.00	8.00
	Period 2 (2 - 6 weeks)	28	2.36	1.34	1.00	2.00	2.00	2.00	8.00
	Period 3 (6 - 10 weeks)	30	2.17	1.15	1.00	2.00	2.00	2.00	8.00
	Period 4 (10 - 14 weeks)	27	2.04	0.65	1.00	2.00	2.00	2.00	5.00
	Period 5 (14 - 18 weeks)	28	2.18	0.82	1.00	2.00	2.00	2.00	5.00
	Period 6 (18 - 22 weeks)	26	2.08	0.63	1.00	2.00	2.00	2.00	4.00
	Period 7 (22 - 26 weeks)	24	2.21	0.72	1.00	2.00	2.00	2.00	4.00
	Period 8 (26 - 30 weeks)	21	2.24	0.77	1.00	2.00	2.00	2.00	4.00
	Period 9 (30 - 34 weeks)	19	2.16	0.69	1.00	2.00	2.00	2.00	4.00
	Period 10 (34 - 38 weeks)	17	2.24	0.75	1.00	2.00	2.00	2.00	4.00
	Period 11 (38 - 42 weeks)	16	2.25	0.77	1.00	2.00	2.00	2.00	4.00
	Period 12 (42 - 46 weeks)	16	2.25	0.77	1.00	2.00	2.00	2.00	4.00
	Period 13 (46 - 50 weeks)	14	2.29	0.83	1.00	2.00	2.00	2.00	4.00
	Period 14 (50 - 54 weeks)	12	2.17	0.94	1.00	2.00	2.00	2.00	4.00
	Period 15 (54 - 58 weeks)	9	2.44	0.88	2.00	2.00	2.00	2.00	4.00
	Period 16 (58 - 62 weeks)	5	2.00	0.00	2.00	2.00	2.00	2.00	2.00
	Period 17 (62 - 66 weeks)	2	2.00	0.00	2.00	2.00	2.00	2.00	2.00

* per patient within a period (each patient was only counted once in each period)
0: No analgesic, 1: Non-opioid analgesics, 2: Weak opioids (e.g. meperidine, codeine, tramadol), 3: Strong opioids <= 75 mg OME per day, 4: Strong opioids > 75-150 mg OME per day
5: Strong opioids > 150-300 mg OME per day, 6: Strong opioids > 300-600 mg OME per day, 7: Strong opioids > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked
Period 1: 0 week to 2 weeks, period 2: 2 weeks to 6 weeks, period 3, 6 weeks to 10 weeks, period 4: 10 weeks to 14 weeks, ...

15.7.13 Best analgesic score (AQA)* of pain medications given throughout the study as numeric variable by period - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Other cancer type	Period 1 (0 - 2 weeks)	61	2.43	0.88	1.00	2.00	2.00	2.00	5.00
	Period 2 (2 - 6 weeks)	73	2.41	0.88	1.00	2.00	2.00	2.00	5.00
	Period 3 (6 - 10 weeks)	75	2.37	0.87	1.00	2.00	2.00	2.00	5.00
	Period 4 (10 - 14 weeks)	70	2.31	0.81	1.00	2.00	2.00	2.00	5.00
	Period 5 (14 - 18 weeks)	63	2.30	0.82	1.00	2.00	2.00	2.00	5.00
	Period 6 (18 - 22 weeks)	60	2.32	0.83	1.00	2.00	2.00	2.00	5.00
	Period 7 (22 - 26 weeks)	54	2.26	0.81	1.00	2.00	2.00	2.00	5.00
	Period 8 (26 - 30 weeks)	48	2.19	0.70	1.00	2.00	2.00	2.00	4.00
	Period 9 (30 - 34 weeks)	43	2.19	0.70	1.00	2.00	2.00	2.00	4.00
	Period 10 (34 - 38 weeks)	38	2.21	0.74	1.00	2.00	2.00	2.00	4.00
	Period 11 (38 - 42 weeks)	39	2.21	0.73	1.00	2.00	2.00	2.00	4.00
	Period 12 (42 - 46 weeks)	36	2.31	0.79	1.00	2.00	2.00	2.00	4.00
	Period 13 (46 - 50 weeks)	32	2.28	0.77	1.00	2.00	2.00	2.00	4.00
	Period 14 (50 - 54 weeks)	30	2.30	0.79	1.00	2.00	2.00	2.00	4.00
	Period 15 (54 - 58 weeks)	21	2.62	0.86	2.00	2.00	2.00	3.00	4.00
	Period 16 (58 - 62 weeks)	10	2.80	1.03	2.00	2.00	2.00	4.00	4.00
	Period 17 (62 - 66 weeks)	2	3.00	1.41	2.00	2.00	3.00	4.00	4.00
	Period 18 (66 - 70 weeks)	1	4.00		4.00	4.00	4.00	4.00	4.00

* per patient within a period (each patient was only counted once in each period)
0: No analgesic, 1: Non-opioid analgesics, 2: Weak opioids (e.g. meperidine, codeine, tramadol), 3: Strong opioids <= 75 mg OME per day, 4: Strong opioids > 75-150 mg OME per day
5: Strong opioids > 150-300 mg OME per day, 6: Strong opioids > 300-600 mg OME per day, 7: Strong opioids > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked
Period 1: 0 week to 2 weeks, period 2: 2 weeks to 6 weeks, period 3, 6 weeks to 10 weeks, period 4: 10 weeks to 14 weeks, ...

15.7.13 Best analgesic score (AQA)* of pain medications given throughout the study as numeric variable by period - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Total	Period 1 (0 - 2 weeks)	344	2.37	0.87	1.00	2.00	2.00	2.00	8.00
	Period 2 (2 - 6 weeks)	418	2.35	0.87	1.00	2.00	2.00	2.00	8.00
	Period 3 (6 - 10 weeks)	445	2.32	0.84	1.00	2.00	2.00	2.00	8.00
	Period 4 (10 - 14 weeks)	436	2.28	0.78	1.00	2.00	2.00	2.00	6.00
	Period 5 (14 - 18 weeks)	419	2.29	0.80	1.00	2.00	2.00	2.00	6.00
	Period 6 (18 - 22 weeks)	407	2.31	0.83	1.00	2.00	2.00	2.00	7.00
	Period 7 (22 - 26 weeks)	386	2.30	0.81	1.00	2.00	2.00	2.00	6.00
	Period 8 (26 - 30 weeks)	357	2.29	0.78	1.00	2.00	2.00	2.00	5.00
	Period 9 (30 - 34 weeks)	343	2.29	0.80	1.00	2.00	2.00	2.00	5.00
	Period 10 (34 - 38 weeks)	323	2.30	0.80	1.00	2.00	2.00	2.00	5.00
	Period 11 (38 - 42 weeks)	310	2.30	0.80	1.00	2.00	2.00	2.00	5.00
	Period 12 (42 - 46 weeks)	299	2.31	0.82	1.00	2.00	2.00	2.00	5.00
	Period 13 (46 - 50 weeks)	284	2.32	0.82	1.00	2.00	2.00	2.00	5.00
	Period 14 (50 - 54 weeks)	262	2.33	0.84	1.00	2.00	2.00	2.00	5.00
	Period 15 (54 - 58 weeks)	182	2.36	0.83	1.00	2.00	2.00	2.00	5.00
	Period 16 (58 - 62 weeks)	71	2.34	0.81	1.00	2.00	2.00	2.00	5.00
	Period 17 (62 - 66 weeks)	28	2.29	0.76	1.00	2.00	2.00	2.00	4.00
	Period 18 (66 - 70 weeks)	12	2.33	0.89	1.00	2.00	2.00	2.50	4.00
	Period 19 (70 - 74 weeks)	6	2.33	1.03	1.00	2.00	2.00	3.00	4.00

* per patient within a period (each patient was only counted once in each period)
0: No analgesic, 1: Non-opioid analgesics, 2: Weak opioids (e.g. meperidine, codeine, tramadol), 3: Strong opioids <= 75 mg OME per day, 4: Strong opioids > 75-150 mg OME per day
5: Strong opioids > 150-300 mg OME per day, 6: Strong opioids > 300-600 mg OME per day, 7: Strong opioids > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked
Period 1: 0 week to 2 weeks, period 2: 2 weeks to 6 weeks, period 3, 6 weeks to 10 weeks, period 4: 10 weeks to 14 weeks, ...

15.7.13 Best analgesic score (AQA)* of pain medications given throughout the study as numeric variable by period - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Total	Period 20 (74 - 78 weeks)	4	2.00	0.82	1.00	1.50	2.00	2.50	3.00
	Period 21 (78 - 82 weeks)	3	1.67	0.58	1.00	1.00	2.00	2.00	2.00
	Period 22 (82 - 86 weeks)	3	1.67	0.58	1.00	1.00	2.00	2.00	2.00
	Period 23 (86 - 90 weeks)	3	1.67	0.58	1.00	1.00	2.00	2.00	2.00

* per patient within a period (each patient was only counted once in each period)
0: No analgesic, 1: Non-opioid analgesics, 2: Weak opioids (e.g. meperidine, codeine, tramadol), 3: Strong opioids <= 75 mg OME per day, 4: Strong opioids > 75-150 mg OME per day
5: Strong opioids > 150-300 mg OME per day, 6: Strong opioids > 300-600 mg OME per day, 7: Strong opioids > 600 mg OME per day
In case of missing start and stop date it is assumed that medication was given for all periods.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked
Period 1: 0 week to 2 weeks, period 2: 2 weeks to 6 weeks, period 3, 6 weeks to 10 weeks, period 4: 10 weeks to 14 weeks, ...

15.7.14 Absolute changes from baseline in best analgesic score (AQA)* of pain medications given throughout the study by period - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Breast cancer	Period 1 (0 - 2 weeks)	116	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Period 2 (2 - 6 weeks)	115	-0.03	0.26	-2.00	0.00	0.00	0.00	0.00
	Period 3 (6 - 10 weeks)	110	-0.06	0.37	-2.00	0.00	0.00	0.00	1.00
	Period 4 (10 - 14 weeks)	108	-0.15	0.56	-4.00	0.00	0.00	0.00	0.00
	Period 5 (14 - 18 weeks)	101	-0.19	0.63	-4.00	0.00	0.00	0.00	0.00
	Period 6 (18 - 22 weeks)	98	-0.13	0.74	-4.00	0.00	0.00	0.00	4.00
	Period 7 (22 - 26 weeks)	92	-0.16	0.67	-4.00	0.00	0.00	0.00	2.00
	Period 8 (26 - 30 weeks)	89	-0.13	0.71	-4.00	0.00	0.00	0.00	2.00
	Period 9 (30 - 34 weeks)	86	-0.14	0.72	-4.00	0.00	0.00	0.00	2.00
	Period 10 (34 - 38 weeks)	80	-0.14	0.57	-2.00	0.00	0.00	0.00	2.00
	Period 11 (38 - 42 weeks)	80	-0.13	0.58	-2.00	0.00	0.00	0.00	2.00
	Period 12 (42 - 46 weeks)	76	-0.18	0.58	-2.00	0.00	0.00	0.00	1.00
	Period 13 (46 - 50 weeks)	75	-0.19	0.59	-2.00	0.00	0.00	0.00	1.00
	Period 14 (50 - 54 weeks)	72	-0.19	0.60	-2.00	0.00	0.00	0.00	1.00
	Period 15 (54 - 58 weeks)	52	-0.12	0.51	-2.00	0.00	0.00	0.00	1.00
	Period 16 (58 - 62 weeks)	26	0.00	0.28	-1.00	0.00	0.00	0.00	1.00
	Period 17 (62 - 66 weeks)	8	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Period 18 (66 - 70 weeks)	4	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Period 19 (70 - 74 weeks)	2	0.00	0.00	0.00	0.00	0.00	0.00	0.00

* per patient within a period (each patient was only counted once in each period)
0: No analgesic, 1: Non-opioid analgesics, 2: Weak opioids (e.g. meperidine, codeine, tramadol), 3: Strong opioids <= 75 mg OME per day, 4: Strong opioids > 75-150 mg OME per day
5: Strong opioids > 150-300 mg OME per day, 6: Strong opioids > 300-600 mg OME per day, 7: Strong opioids > 600 mg OME per day
Baseline is defined as the value between day -15 and day 5. If more than one values available in this time window the value nearest to day 1 was used as baseline value. If different AQA scores were available at day 1 the worst score was used as baseline value. In case of missing start and stop date it is assumed that medication was given for all periods including baseline.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked
Period 1: 0 week to 2 weeks, period 2: 2 weeks to 6 weeks, period 3, 6 weeks to 10 weeks, period 4: 10 weeks to 14 weeks, ...

15.7.14 Absolute changes from baseline in best analgesic score (AQA)* of pain medications given throughout the study by period - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Breast cancer	Period 20 (74 - 78 weeks)	1	0.00		0.00	0.00	0.00	0.00	0.00
	Period 21 (78 - 82 weeks)	0							
	Period 22 (82 - 86 weeks)	0							
	Period 23 (86 - 90 weeks)	0							

* per patient within a period (each patient was only counted once in each period)
0: No analgesic, 1: Non-opioid analgesics, 2: Weak opioids (e.g. meperidine, codeine, tramadol), 3: Strong opioids <= 75 mg OME per day, 4: Strong opioids > 75-150 mg OME per day
5: Strong opioids > 150-300 mg OME per day, 6: Strong opioids > 300-600 mg OME per day, 7: Strong opioids > 600 mg OME per day
Baseline is defined as the value between day -15 and day 5. If more than one values available in this time window the value nearest to day 1 was used as baseline value. If different AQA scores were available at day 1 the worst score was used as baseline value. In case of missing start and stop date it is assumed that medication was given for all periods including baseline.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked
Period 1: 0 week to 2 weeks, period 2: 2 weeks to 6 weeks, period 3, 6 weeks to 10 weeks, period 4: 10 weeks to 14 weeks, ...

15.7.14 Absolute changes from baseline in best analgesic score (AQA)* of pain medications given throughout the study by period - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Prostate cancer	Period 1 (0 - 2 weeks)	54	-0.02	0.14	-1.00	0.00	0.00	0.00	0.00
	Period 2 (2 - 6 weeks)	52	-0.04	0.19	-1.00	0.00	0.00	0.00	0.00
	Period 3 (6 - 10 weeks)	52	-0.13	0.44	-2.00	0.00	0.00	0.00	0.00
	Period 4 (10 - 14 weeks)	48	-0.21	0.54	-2.00	0.00	0.00	0.00	0.00
	Period 5 (14 - 18 weeks)	46	-0.15	0.51	-2.00	0.00	0.00	0.00	0.00
	Period 6 (18 - 22 weeks)	43	-0.19	0.55	-2.00	0.00	0.00	0.00	0.00
	Period 7 (22 - 26 weeks)	40	-0.15	0.92	-2.00	0.00	0.00	0.00	4.00
	Period 8 (26 - 30 weeks)	36	-0.11	1.04	-2.00	0.00	0.00	0.00	4.00
	Period 9 (30 - 34 weeks)	34	-0.15	0.74	-2.00	0.00	0.00	0.00	2.00
	Period 10 (34 - 38 weeks)	35	-0.11	0.68	-2.00	0.00	0.00	0.00	2.00
	Period 11 (38 - 42 weeks)	32	-0.19	0.78	-2.00	0.00	0.00	0.00	2.00
	Period 12 (42 - 46 weeks)	31	-0.23	0.84	-2.00	0.00	0.00	0.00	2.00
	Period 13 (46 - 50 weeks)	31	-0.23	0.84	-2.00	0.00	0.00	0.00	2.00
	Period 14 (50 - 54 weeks)	28	-0.18	0.98	-2.00	0.00	0.00	0.00	2.00
	Period 15 (54 - 58 weeks)	16	-0.06	1.06	-2.00	0.00	0.00	0.00	2.00
	Period 16 (58 - 62 weeks)	3	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Period 17 (62 - 66 weeks)	1	0.00		0.00	0.00	0.00	0.00	0.00
	Period 18 (66 - 70 weeks)	0							
	Period 19 (70 - 74 weeks)	0							

* per patient within a period (each patient was only counted once in each period)
0: No analgesic, 1: Non-opioid analgesics, 2: Weak opioids (e.g. meperidine, codeine, tramadol), 3: Strong opioids <= 75 mg OME per day, 4: Strong opioids > 75-150 mg OME per day
5: Strong opioids > 150-300 mg OME per day, 6: Strong opioids > 300-600 mg OME per day, 7: Strong opioids > 600 mg OME per day
Baseline is defined as the value between day -15 and day 5. If more than one values available in this time window the value nearest to day 1 was used as baseline value. If different AQA scores were available at day 1 the worst score was used as baseline value. In case of missing start and stop date it is assumed that medication was given for all periods including baseline.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked
Period 1: 0 week to 2 weeks, period 2: 2 weeks to 6 weeks, period 3, 6 weeks to 10 weeks, period 4: 10 weeks to 14 weeks, ...

15.7.14 Absolute changes from baseline in best analgesic score (AQA)* of pain medications given throughout the study by period - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Prostate cancer	Period 20 (74 - 78 weeks)	0							
	Period 21 (78 - 82 weeks)	0							
	Period 22 (82 - 86 weeks)	0							
	Period 23 (86 - 90 weeks)	0							

* per patient within a period (each patient was only counted once in each period)
0: No analgesic, 1: Non-opioid analgesics, 2: Weak opioids (e.g. meperidine, codeine, tramadol), 3: Strong opioids <= 75 mg OME per day, 4: Strong opioids > 75-150 mg OME per day
5: Strong opioids > 150-300 mg OME per day, 6: Strong opioids > 300-600 mg OME per day, 7: Strong opioids > 600 mg OME per day
Baseline is defined as the value between day -15 and day 5. If more than one values available in this time window the value nearest to day 1 was used as baseline value. If different AQA scores were available at day 1 the worst score was used as baseline value. In case of missing start and stop date it is assumed that medication was given for all periods including baseline.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked
Period 1: 0 week to 2 weeks, period 2: 2 weeks to 6 weeks, period 3, 6 weeks to 10 weeks, period 4: 10 weeks to 14 weeks, ...

15.7.14 Absolute changes from baseline in best analgesic score (AQA)* of pain medications given throughout the study by period - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Lung cancer	Period 1 (0 - 2 weeks)	66	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Period 2 (2 - 6 weeks)	64	-0.05	0.28	-2.00	0.00	0.00	0.00	0.00
	Period 3 (6 - 10 weeks)	62	-0.05	0.28	-2.00	0.00	0.00	0.00	0.00
	Period 4 (10 - 14 weeks)	57	-0.02	0.13	-1.00	0.00	0.00	0.00	0.00
	Period 5 (14 - 18 weeks)	51	-0.02	0.14	-1.00	0.00	0.00	0.00	0.00
	Period 6 (18 - 22 weeks)	46	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Period 7 (22 - 26 weeks)	38	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Period 8 (26 - 30 weeks)	30	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Period 9 (30 - 34 weeks)	28	-0.11	0.57	-3.00	0.00	0.00	0.00	0.00
	Period 10 (34 - 38 weeks)	23	-0.13	0.63	-3.00	0.00	0.00	0.00	0.00
	Period 11 (38 - 42 weeks)	20	-0.15	0.67	-3.00	0.00	0.00	0.00	0.00
	Period 12 (42 - 46 weeks)	15	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Period 13 (46 - 50 weeks)	13	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Period 14 (50 - 54 weeks)	9	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Period 15 (54 - 58 weeks)	6	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Period 16 (58 - 62 weeks)	0							
	Period 17 (62 - 66 weeks)	0							

* per patient within a period (each patient was only counted once in each period)
0: No analgesic, 1: Non-opioid analgesics, 2: Weak opioids (e.g. meperidine, codeine, tramadol), 3: Strong opioids <= 75 mg OME per day, 4: Strong opioids > 75-150 mg OME per day
5: Strong opioids > 150-300 mg OME per day, 6: Strong opioids > 300-600 mg OME per day, 7: Strong opioids > 600 mg OME per day
Baseline is defined as the value between day -15 and day 5. If more than one values available in this time window the value nearest to day 1 was used as baseline value. If different AQA scores were available at day 1 the worst score was used as baseline value. In case of missing start and stop date it is assumed that medication was given for all periods including baseline.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked
Period 1: 0 week to 2 weeks, period 2: 2 weeks to 6 weeks, period 3, 6 weeks to 10 weeks, period 4: 10 weeks to 14 weeks, ...

15.7.14 Absolute changes from baseline in best analgesic score (AQA)* of pain medications given throughout the study by period - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Kidney cancer	Period 1 (0 - 2 weeks)	21	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Period 2 (2 - 6 weeks)	21	-0.05	0.22	-1.00	0.00	0.00	0.00	0.00
	Period 3 (6 - 10 weeks)	21	-0.14	0.48	-2.00	0.00	0.00	0.00	0.00
	Period 4 (10 - 14 weeks)	20	-0.15	0.49	-2.00	0.00	0.00	0.00	0.00
	Period 5 (14 - 18 weeks)	20	-0.05	0.94	-2.00	0.00	0.00	0.00	3.00
	Period 6 (18 - 22 weeks)	19	-0.05	0.97	-2.00	0.00	0.00	0.00	3.00
	Period 7 (22 - 26 weeks)	16	0.19	1.05	-2.00	0.00	0.00	0.00	3.00
	Period 8 (26 - 30 weeks)	14	0.21	1.12	-2.00	0.00	0.00	0.00	3.00
	Period 9 (30 - 34 weeks)	13	0.23	1.17	-2.00	0.00	0.00	0.00	3.00
	Period 10 (34 - 38 weeks)	11	0.27	1.27	-2.00	0.00	0.00	0.00	3.00
	Period 11 (38 - 42 weeks)	9	0.33	1.41	-2.00	0.00	0.00	0.00	3.00
	Period 12 (42 - 46 weeks)	9	0.33	1.41	-2.00	0.00	0.00	0.00	3.00
	Period 13 (46 - 50 weeks)	8	0.13	1.36	-2.00	0.00	0.00	0.00	3.00
	Period 14 (50 - 54 weeks)	6	0.17	1.60	-2.00	0.00	0.00	0.00	3.00
	Period 15 (54 - 58 weeks)	4	0.75	1.50	0.00	0.00	0.00	1.50	3.00
	Period 16 (58 - 62 weeks)	2	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Period 17 (62 - 66 weeks)	1	0.00		0.00	0.00	0.00	0.00	0.00

* per patient within a period (each patient was only counted once in each period)
0: No analgesic, 1: Non-opioid analgesics, 2: Weak opioids (e.g. meperidine, codeine, tramadol), 3: Strong opioids <= 75 mg OME per day, 4: Strong opioids > 75-150 mg OME per day
5: Strong opioids > 150-300 mg OME per day, 6: Strong opioids > 300-600 mg OME per day, 7: Strong opioids > 600 mg OME per day
Baseline is defined as the value between day -15 and day 5. If more than one values available in this time window the value nearest to day 1 was used as baseline value. If different AQA scores were available at day 1 the worst score was used as baseline value. In case of missing start and stop date it is assumed that medication was given for all periods including baseline.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked
Period 1: 0 week to 2 weeks, period 2: 2 weeks to 6 weeks, period 3, 6 weeks to 10 weeks, period 4: 10 weeks to 14 weeks, ...

15.7.14 Absolute changes from baseline in best analgesic score (AQA)* of pain medications given throughout the study by period - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Other cancer type	Period 1 (0 - 2 weeks)	58	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Period 2 (2 - 6 weeks)	58	-0.05	0.29	-2.00	0.00	0.00	0.00	0.00
	Period 3 (6 - 10 weeks)	56	-0.11	0.49	-3.00	0.00	0.00	0.00	0.00
	Period 4 (10 - 14 weeks)	51	-0.12	0.52	-3.00	0.00	0.00	0.00	0.00
	Period 5 (14 - 18 weeks)	48	-0.13	0.53	-3.00	0.00	0.00	0.00	0.00
	Period 6 (18 - 22 weeks)	47	-0.06	0.32	-2.00	0.00	0.00	0.00	0.00
	Period 7 (22 - 26 weeks)	41	-0.07	0.35	-2.00	0.00	0.00	0.00	0.00
	Period 8 (26 - 30 weeks)	37	-0.03	0.16	-1.00	0.00	0.00	0.00	0.00
	Period 9 (30 - 34 weeks)	32	-0.03	0.18	-1.00	0.00	0.00	0.00	0.00
	Period 10 (34 - 38 weeks)	29	-0.03	0.19	-1.00	0.00	0.00	0.00	0.00
	Period 11 (38 - 42 weeks)	29	-0.10	0.41	-2.00	0.00	0.00	0.00	0.00
	Period 12 (42 - 46 weeks)	27	-0.04	0.19	-1.00	0.00	0.00	0.00	0.00
	Period 13 (46 - 50 weeks)	25	-0.12	0.44	-2.00	0.00	0.00	0.00	0.00
	Period 14 (50 - 54 weeks)	23	-0.13	0.46	-2.00	0.00	0.00	0.00	0.00
	Period 15 (54 - 58 weeks)	15	0.00	1.00	-2.00	0.00	0.00	0.00	3.00
	Period 16 (58 - 62 weeks)	6	0.17	0.98	-1.00	0.00	0.00	0.00	2.00
	Period 17 (62 - 66 weeks)	2	-0.50	0.71	-1.00	-1.00	-0.50	0.00	0.00
	Period 18 (66 - 70 weeks)	1	0.00		0.00	0.00	0.00	0.00	0.00

* per patient within a period (each patient was only counted once in each period)
0: No analgesic, 1: Non-opioid analgesics, 2: Weak opioids (e.g. meperidine, codeine, tramadol), 3: Strong opioids <= 75 mg OME per day, 4: Strong opioids > 75-150 mg OME per day
5: Strong opioids > 150-300 mg OME per day, 6: Strong opioids > 300-600 mg OME per day, 7: Strong opioids > 600 mg OME per day
Baseline is defined as the value between day -15 and day 5. If more than one values available in this time window the value nearest to day 1 was used as baseline value. If different AQA scores were available at day 1 the worst score was used as baseline value. In case of missing start and stop date it is assumed that medication was given for all periods including baseline.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked
Period 1: 0 week to 2 weeks, period 2: 2 weeks to 6 weeks, period 3, 6 weeks to 10 weeks, period 4: 10 weeks to 14 weeks, ...

15.7.14 Absolute changes from baseline in best analgesic score (AQA)* of pain medications given throughout the study by period - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Total	Period 1 (0 - 2 weeks)	315	-0.00	0.06	-1.00	0.00	0.00	0.00	0.00
	Period 2 (2 - 6 weeks)	310	-0.04	0.26	-2.00	0.00	0.00	0.00	0.00
	Period 3 (6 - 10 weeks)	301	-0.09	0.40	-3.00	0.00	0.00	0.00	1.00
	Period 4 (10 - 14 weeks)	284	-0.13	0.49	-4.00	0.00	0.00	0.00	0.00
	Period 5 (14 - 18 weeks)	266	-0.13	0.56	-4.00	0.00	0.00	0.00	3.00
	Period 6 (18 - 22 weeks)	253	-0.10	0.59	-4.00	0.00	0.00	0.00	4.00
	Period 7 (22 - 26 weeks)	227	-0.09	0.66	-4.00	0.00	0.00	0.00	4.00
	Period 8 (26 - 30 weeks)	206	-0.07	0.70	-4.00	0.00	0.00	0.00	4.00
	Period 9 (30 - 34 weeks)	193	-0.09	0.69	-4.00	0.00	0.00	0.00	3.00
	Period 10 (34 - 38 weeks)	178	-0.09	0.62	-3.00	0.00	0.00	0.00	3.00
	Period 11 (38 - 42 weeks)	170	-0.11	0.67	-3.00	0.00	0.00	0.00	3.00
	Period 12 (42 - 46 weeks)	158	-0.12	0.65	-2.00	0.00	0.00	0.00	3.00
	Period 13 (46 - 50 weeks)	152	-0.15	0.66	-2.00	0.00	0.00	0.00	3.00
	Period 14 (50 - 54 weeks)	138	-0.15	0.71	-2.00	0.00	0.00	0.00	3.00
	Period 15 (54 - 58 weeks)	93	-0.04	0.76	-2.00	0.00	0.00	0.00	3.00
	Period 16 (58 - 62 weeks)	37	0.03	0.44	-1.00	0.00	0.00	0.00	2.00
	Period 17 (62 - 66 weeks)	12	-0.08	0.29	-1.00	0.00	0.00	0.00	0.00
	Period 18 (66 - 70 weeks)	5	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Period 19 (70 - 74 weeks)	2	0.00	0.00	0.00	0.00	0.00	0.00	0.00

* per patient within a period (each patient was only counted once in each period)
0: No analgesic, 1: Non-opioid analgesics, 2: Weak opioids (e.g. meperidine, codeine, tramadol), 3: Strong opioids <= 75 mg OME per day, 4: Strong opioids > 75-150 mg OME per day
5: Strong opioids > 150-300 mg OME per day, 6: Strong opioids > 300-600 mg OME per day, 7: Strong opioids > 600 mg OME per day
Baseline is defined as the value between day -15 and day 5. If more than one values available in this time window the value nearest to day 1 was used as baseline value. If different AQA scores were available at day 1 the worst score was used as baseline value. In case of missing start and stop date it is assumed that medication was given for all periods including baseline.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked
Period 1: 0 week to 2 weeks, period 2: 2 weeks to 6 weeks, period 3, 6 weeks to 10 weeks, period 4: 10 weeks to 14 weeks, ...

15.7.14 Absolute changes from baseline in best analgesic score (AQA)* of pain medications given throughout the study by period - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Total	Period 20 (74 - 78 weeks)	1	0.00		0.00	0.00	0.00	0.00	0.00
	Period 21 (78 - 82 weeks)	0							
	Period 22 (82 - 86 weeks)	0							
	Period 23 (86 - 90 weeks)	0							

* per patient within a period (each patient was only counted once in each period)
0: No analgesic, 1: Non-opioid analgesics, 2: Weak opioids (e.g. meperidine, codeine, tramadol), 3: Strong opioids <= 75 mg OME per day, 4: Strong opioids > 75-150 mg OME per day
5: Strong opioids > 150-300 mg OME per day, 6: Strong opioids > 300-600 mg OME per day, 7: Strong opioids > 600 mg OME per day
Baseline is defined as the value between day -15 and day 5. If more than one values available in this time window the value nearest to day 1 was used as baseline value. If different AQA scores were available at day 1 the worst score was used as baseline value. In case of missing start and stop date it is assumed that medication was given for all periods including baseline.
Therapy is counted as 'given throughout the study' if start of therapy was on are after study day 1 or if stop date was on or after day 1 or if 'ongoing' was ticked
Period 1: 0 week to 2 weeks, period 2: 2 weeks to 6 weeks, period 3, 6 weeks to 10 weeks, period 4: 10 weeks to 14 weeks, ...

15.8.1 Laboratory evaluation: Calcium in serum [mmol/l] by cancer type and visit - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Breast cancer	Baseline 1st application	336	2.36	0.23	1.9	2.2	2.35	2.4	5.0
	Baseline 2nd application	88	2.22	0.19	1.4	2.1	2.28	2.3	2.7
	Visit 1	331	2.25	0.16	1.5	2.2	2.26	2.4	3.0
	Visit 2	330	2.29	0.24	1.4	2.2	2.29	2.4	4.6
	Visit 3	329	2.31	0.19	1.7	2.2	2.31	2.4	4.2
	Visit 4	315	2.30	0.15	1.7	2.2	2.31	2.4	2.7
	Visit 5	320	2.32	0.18	1.8	2.2	2.32	2.4	3.9
	Visit 6	296	2.32	0.16	1.2	2.2	2.33	2.4	2.7
	Visit 7	290	2.33	0.15	1.7	2.2	2.33	2.4	3.1
	Visit 8	284	2.33	0.14	1.9	2.2	2.33	2.4	2.8
	Visit 9	272	2.35	0.21	1.9	2.3	2.34	2.4	5.0
	Visit 10	277	2.32	0.23	0.6	2.2	2.31	2.4	4.8
	Visit 11	253	2.34	0.23	0.7	2.3	2.35	2.4	4.6
	Visit 12	220	2.36	0.16	1.5	2.3	2.36	2.4	3.0
	Visit 13	150	2.36	0.14	2.1	2.3	2.35	2.4	2.9
	Visit 14	48	2.37	0.13	2.1	2.3	2.35	2.4	2.8
	Visit 15	10	2.37	0.15	2.1	2.3	2.40	2.5	2.6
	Visit 16	4	2.33	0.13	2.2	2.2	2.35	2.4	2.5
	Visit 17	2	2.54	0.12	2.5	2.5	2.54	2.6	2.6
	Visit 19	2	2.28	0.10	2.2	2.2	2.28	2.4	2.4

For patient 26104-025 incorrect calcium values were documented for visit 1, 2, 3 and 4. Therefore the high maximum value for prostate cancer is not correct for visit 1 to visit 4.
Only planned visits according to protocol were included into the analysis.
Patients could have had up to two XGEVA applications before inclusion into the study. These applications are the 1st and 2nd baseline applications.

15.8.1 Laboratory evaluation: Calcium in serum [mmol/l] by cancer type and visit - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
	Visit 21	1	2.62		2.6	2.6	2.62	2.6	2.6
	Study end	148	2.33	0.28	1.4	2.2	2.34	2.4	4.3

For patient 26104-025 incorrect calcium values were documented for visit 1, 2, 3 and 4. Therefore the high maximum value for prostate cancer is not correct for visit 1 to visit 4.
Only planned visits according to protocol were included into the analysis.
Patients could have had up to two XGEVA applications before inclusion into the study. These applications are the 1st and 2nd baseline applications.

15.8.1 Laboratory evaluation: Calcium in serum [mmol/l] by cancer type and visit - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Prostate cancer	Baseline 1st application	156	2.29	0.15	1.8	2.2	2.30	2.4	2.9
	Baseline 2nd application	27	2.11	0.23	1.4	1.9	2.18	2.3	2.4
	Visit 1	186	2.73	7.18	1.4	2.1	2.20	2.3	100.0
	Visit 2	190	2.72	7.17	1.2	2.1	2.23	2.3	101.0
	Visit 3	194	2.73	7.09	1.4	2.1	2.27	2.4	101.0
	Visit 4	171	2.83	7.63	1.5	2.2	2.29	2.4	102.0
	Visit 5	178	2.24	0.18	1.3	2.2	2.26	2.4	2.6
	Visit 6	173	2.28	0.16	1.4	2.2	2.30	2.4	2.7
	Visit 7	170	2.26	0.17	1.5	2.2	2.29	2.4	2.6
	Visit 8	153	2.28	0.17	1.7	2.2	2.30	2.4	2.7
	Visit 9	148	2.30	0.15	1.6	2.2	2.31	2.4	2.7
	Visit 10	138	2.29	0.15	1.7	2.2	2.30	2.4	2.7
	Visit 11	136	2.27	0.16	1.6	2.2	2.29	2.4	2.6
	Visit 12	115	2.28	0.18	1.8	2.2	2.30	2.4	3.4
	Visit 13	66	2.29	0.15	1.9	2.2	2.31	2.4	2.6
	Visit 14	16	2.24	0.23	1.8	2.1	2.26	2.4	2.6
	Visit 15	1	2.07		2.1	2.1	2.07	2.1	2.1
	Visit 16	2	2.21	0.13	2.1	2.1	2.21	2.3	2.3
	Visit 17	1	2.16		2.2	2.2	2.16	2.2	2.2
	Visit 19	0							
	Study end	93	2.23	0.24	0.8	2.2	2.30	2.4	2.7

For patient 26104-025 incorrect calcium values were documented for visit 1, 2, 3 and 4. Therefore the high maximum value for prostate cancer is not correct for visit 1 to visit 4.
Only planned visits according to protocol were included into the analysis.
Patients could have had up to two XGEVA applications before inclusion into the study. These applications are the 1st and 2nd baseline applications.

15.8.1 Laboratory evaluation: Calcium in serum [mmol/l] by cancer type and visit - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Lung cancer	Baseline 1st application	115	2.29	0.18	1.1	2.2	2.31	2.4	2.9
	Baseline 2nd application	26	2.23	0.17	1.8	2.2	2.23	2.3	2.6
	Visit 1	97	2.18	0.19	1.3	2.1	2.18	2.3	2.8
	Visit 2	82	2.22	0.18	1.6	2.1	2.24	2.3	2.8
	Visit 3	72	2.25	0.15	1.8	2.1	2.27	2.4	2.7
	Visit 4	66	2.25	0.23	1.1	2.2	2.26	2.4	2.7
	Visit 5	61	2.25	0.20	1.6	2.2	2.27	2.4	2.7
	Visit 6	46	2.28	0.16	1.9	2.2	2.30	2.4	2.7
	Visit 7	42	2.26	0.16	1.8	2.2	2.26	2.3	2.5
	Visit 8	43	2.21	0.16	1.7	2.2	2.21	2.3	2.6
	Visit 9	40	2.24	0.16	1.7	2.2	2.25	2.4	2.5
	Visit 10	36	2.24	0.26	1.4	2.1	2.26	2.4	2.8
	Visit 11	30	2.22	0.18	1.6	2.2	2.23	2.3	2.5
	Visit 12	18	2.24	0.25	1.6	2.1	2.23	2.3	2.8
	Visit 13	14	2.31	0.19	2.1	2.2	2.27	2.4	2.7
	Visit 14	3	2.32	0.11	2.2	2.2	2.33	2.4	2.4
	Visit 15	1	2.27		2.3	2.3	2.27	2.3	2.3
	Study end	14	2.13	0.48	1.0	2.1	2.26	2.4	2.7

For patient 26104-025 incorrect calcium values were documented for visit 1, 2, 3 and 4. Therefore the high maximum value for prostate cancer is not correct for visit 1 to visit 4.
Only planned visits according to protocol were included into the analysis.
Patients could have had up to two XGEVA applications before inclusion into the study. These applications are the 1st and 2nd baseline applications.

15.8.1 Laboratory evaluation: Calcium in serum [mmol/l] by cancer type and visit - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Kidney cancer	Baseline 1st application	31	2.36	0.22	2.1	2.2	2.33	2.4	3.3
	Baseline 2nd application	6	2.21	0.11	2.1	2.2	2.18	2.3	2.4
	Visit 1	35	2.21	0.23	1.2	2.1	2.25	2.3	2.6
	Visit 2	32	2.19	0.23	1.3	2.1	2.23	2.3	2.5
	Visit 3	29	2.19	0.26	1.6	2.1	2.20	2.4	2.6
	Visit 4	31	2.29	0.18	1.8	2.2	2.27	2.4	2.7
	Visit 5	29	2.21	0.22	1.6	2.1	2.24	2.3	2.6
	Visit 6	23	2.20	0.22	1.4	2.1	2.20	2.3	2.5
	Visit 7	22	2.23	0.27	1.2	2.2	2.29	2.4	2.5
	Visit 8	15	2.28	0.17	1.9	2.1	2.29	2.5	2.5
	Visit 9	16	2.31	0.11	2.1	2.2	2.32	2.4	2.5
	Visit 10	16	2.30	0.22	1.7	2.2	2.29	2.4	2.6
	Visit 11	13	2.27	0.28	1.6	2.2	2.27	2.5	2.6
	Visit 12	15	2.26	0.32	1.2	2.2	2.35	2.5	2.5
	Visit 13	9	2.34	0.20	2.1	2.3	2.30	2.4	2.8
	Visit 14	4	2.37	0.08	2.3	2.3	2.33	2.4	2.5
	Study end	17	2.22	0.22	1.7	2.1	2.26	2.4	2.5

For patient 26104-025 incorrect calcium values were documented for visit 1, 2, 3 and 4. Therefore the high maximum value for prostate cancer is not correct for visit 1 to visit 4.
Only planned visits according to protocol were included into the analysis.
Patients could have had up to two XGEVA applications before inclusion into the study. These applications are the 1st and 2nd baseline applications.

15.8.1 Laboratory evaluation: Calcium in serum [mmol/l] by cancer type and visit - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Other cancer type	Baseline 1st application	87	2.27	0.21	1.3	2.2	2.27	2.4	2.7
	Baseline 2nd application	16	2.11	0.25	1.3	2.0	2.14	2.3	2.4
	Visit 1	67	2.18	0.21	1.1	2.1	2.19	2.3	2.6
	Visit 2	69	2.18	0.18	1.6	2.1	2.18	2.3	2.5
	Visit 3	66	2.17	0.22	1.5	2.1	2.21	2.3	2.5
	Visit 4	53	2.21	0.21	1.6	2.1	2.23	2.3	2.6
	Visit 5	52	2.21	0.17	1.5	2.2	2.24	2.3	2.5
	Visit 6	41	2.22	0.26	1.6	2.1	2.20	2.3	3.4
	Visit 7	32	2.19	0.24	1.3	2.0	2.25	2.3	2.6
	Visit 8	33	2.23	0.19	1.5	2.1	2.25	2.3	2.5
	Visit 9	30	2.24	0.18	1.9	2.1	2.24	2.3	2.7
	Visit 10	22	2.22	0.15	1.9	2.1	2.23	2.4	2.5
	Visit 11	23	2.22	0.18	1.8	2.1	2.24	2.4	2.5
	Visit 12	21	2.18	0.18	1.7	2.1	2.20	2.3	2.5
	Visit 13	12	2.22	0.24	1.6	2.1	2.28	2.4	2.4
	Visit 14	1	2.11		2.1	2.1	2.11	2.1	2.1
	Study end	25	2.07	0.35	0.6	2.0	2.16	2.3	2.4

For patient 26104-025 incorrect calcium values were documented for visit 1, 2, 3 and 4. Therefore the high maximum value for prostate cancer is not correct for visit 1 to visit 4.
Only planned visits according to protocol were included into the analysis.
Patients could have had up to two XGEVA applications before inclusion into the study. These applications are the 1st and 2nd baseline applications.

15.8.1 Laboratory evaluation: Calcium in serum [mmol/l] by cancer type and visit - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Total	Baseline 1st application	725	2.32	0.20	1.1	2.2	2.31	2.4	5.0
	Baseline 2nd application	163	2.19	0.21	1.3	2.1	2.23	2.3	2.7
	Visit 1	716	2.36	3.66	1.1	2.1	2.23	2.3	100.0
	Visit 2	703	2.38	3.73	1.2	2.2	2.25	2.4	101.0
	Visit 3	690	2.40	3.76	1.4	2.2	2.28	2.4	101.0
	Visit 4	636	2.43	3.96	1.1	2.2	2.30	2.4	102.0
	Visit 5	640	2.28	0.19	1.3	2.2	2.29	2.4	3.9
	Visit 6	579	2.29	0.17	1.2	2.2	2.30	2.4	3.4
	Visit 7	556	2.29	0.18	1.2	2.2	2.30	2.4	3.1
	Visit 8	528	2.30	0.16	1.5	2.2	2.31	2.4	2.8
	Visit 9	506	2.32	0.19	1.6	2.2	2.32	2.4	5.0
	Visit 10	489	2.30	0.21	0.6	2.2	2.30	2.4	4.8
	Visit 11	455	2.30	0.21	0.7	2.2	2.31	2.4	4.6
	Visit 12	389	2.32	0.19	1.2	2.2	2.33	2.4	3.4
	Visit 13	251	2.33	0.15	1.6	2.2	2.33	2.4	2.9
	Visit 14	72	2.33	0.16	1.8	2.2	2.33	2.4	2.8
	Visit 15	12	2.34	0.16	2.1	2.2	2.38	2.4	2.6
	Visit 16	6	2.29	0.13	2.1	2.2	2.31	2.4	2.5
	Visit 17	3	2.41	0.23	2.2	2.2	2.45	2.6	2.6
	Visit 19	2	2.28	0.10	2.2	2.2	2.28	2.4	2.4
	Visit 21	1	2.62		2.6	2.6	2.62	2.6	2.6
	Study end	297	2.26	0.30	0.6	2.2	2.30	2.4	4.3

For patient 26104-025 incorrect calcium values were documented for visit 1, 2, 3 and 4. Therefore the high maximum value for prostate cancer is not correct for visit 1 to visit 4.
Only planned visits according to protocol were included into the analysis.
Patients could have had up to two XGEVA applications before inclusion into the study. These applications are the 1st and 2nd baseline applications.

15.8.2 Laboratory evaluation: Creatinine in serum [µmol/l] by cancer type and visit - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Breast cancer	Baseline 1st application	358	75.6	34.4	34	60	69.0	82	531
	Baseline 2nd application	92	69.2	21.3	35	54	66.4	80	159
	Visit 1	346	70.3	22.1	29	56	66.4	80	180
	Visit 2	337	71.3	23.5	35	58	66.4	80	206
	Visit 3	345	73.3	35.1	26	58	67.3	80	540
	Visit 4	321	73.8	43.6	35	56	66.4	80	570
	Visit 5	323	73.3	41.8	35	58	68.0	80	714
	Visit 6	304	74.5	39.6	35	59	69.0	81	617
	Visit 7	293	74.2	28.0	36	61	69.0	82	377
	Visit 8	291	74.5	40.4	32	58	68.1	80	622
	Visit 9	278	76.6	39.6	30	61	70.8	82	605
	Visit 10	279	75.8	39.4	1	60	70.8	83	580
	Visit 11	256	76.0	40.8	32	60	69.9	83	615
	Visit 12	222	76.2	20.5	35	63	70.8	83	151
	Visit 13	153	76.1	21.0	41	62	70.8	86	148
	Visit 14	49	73.2	17.6	44	59	70.8	82	120
	Visit 15	9	73.1	18.7	44	59	70.8	88	97
	Visit 16	5	121.8	81.1	71	80	95.6	97	265
	Visit 17	2	110.6	18.8	97	97	110.6	124	124
	Visit 19	2	89.8	10.7	82	82	89.8	97	97
	Visit 21	1	123.9		124	124	123.9	124	124
	Study end	153	80.0	51.1	26	62	70.8	82	565

Only planned visits according to protocol were included into the analysis.
Patients could have had up to two XGEVA applications before inclusion into the study. These applications are the 1st and 2nd baseline applications.

15.8.2 Laboratory evaluation: Creatinine in serum [µmol/l] by cancer type and visit - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Prostate cancer	Baseline 1st application	173	99.8	48.0	50	73	88.0	114	487
	Baseline 2nd application	30	94.6	29.9	58	73	84.5	119	171
	Visit 1	198	90.5	33.3	44	70	81.4	101	267
	Visit 2	199	93.2	40.5	38	70	82.3	104	378
	Visit 3	207	94.6	37.9	42	71	85.8	106	332
	Visit 4	181	94.2	40.8	47	73	84.9	104	430
	Visit 5	189	95.1	39.9	43	73	86.7	105	394
	Visit 6	185	92.8	30.8	35	72	87.6	107	203
	Visit 7	183	93.4	34.8	47	71	87.6	104	327
	Visit 8	161	94.8	38.2	35	73	88.5	102	371
	Visit 9	158	93.2	32.3	43	73	87.2	104	248
	Visit 10	142	93.2	33.2	39	74	85.0	102	237
	Visit 11	140	92.4	33.5	35	69	85.8	104	234
	Visit 12	121	95.3	35.2	44	70	88.5	108	243
	Visit 13	67	99.2	40.3	51	73	86.7	119	286
	Visit 14	17	83.7	20.9	44	71	85.8	88	124
	Visit 15	1	126.5		127	127	126.5	127	127
	Visit 16	2	106.2	12.5	97	97	106.2	115	115
	Visit 17	1	115.0		115	115	115.0	115	115
	Visit 19	1	79.6		80	80	79.6	80	80
	Study end	94	95.6	47.7	44	70	84.1	106	397

Only planned visits according to protocol were included into the analysis.
Patients could have had up to two XGEVA applications before inclusion into the study. These applications are the 1st and 2nd baseline applications.

15.8.2 Laboratory evaluation: Creatinine in serum [µmol/l] by cancer type and visit - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Lung cancer	Baseline 1st application	124	82.4	30.1	35	64	77.0	97	248
	Baseline 2nd application	30	69.7	18.3	31	60	70.8	82	116
	Visit 1	108	77.7	24.5	34	62	73.7	89	155
	Visit 2	88	81.6	24.2	38	67	79.6	91	150
	Visit 3	78	82.4	21.5	37	71	79.6	95	178
	Visit 4	74	82.1	23.3	35	69	79.6	97	146
	Visit 5	67	84.3	23.2	37	71	82.0	96	176
	Visit 6	55	86.7	29.0	29	71	84.0	103	175
	Visit 7	45	85.0	22.6	33	74	88.0	97	138
	Visit 8	43	85.4	29.7	33	62	82.3	106	156
	Visit 9	41	88.8	23.5	39	72	89.0	106	137
	Visit 10	37	87.7	26.3	33	66	85.8	106	148
	Visit 11	31	86.5	22.3	48	71	85.0	106	129
	Visit 12	21	86.8	26.8	50	64	88.5	105	137
	Visit 13	15	84.1	23.6	47	71	82.3	93	135
	Visit 14	4	81.4	28.7	57	58	76.8	105	115
	Visit 15	1	56.0		56	56	56.0	56	56
	Study end	15	107.2	79.7	56	62	74.3	100	363

Only planned visits according to protocol were included into the analysis.
Patients could have had up to two XGEVA applications before inclusion into the study. These applications are the 1st and 2nd baseline applications.

15.8.2 Laboratory evaluation: Creatinine in serum [µmol/l] by cancer type and visit - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Kidney cancer	Baseline 1st application	35	120.8	64.4	57	88	107.1	132	425
	Baseline 2nd application	6	97.0	20.2	78	79	91.3	115	127
	Visit 1	34	123.5	82.2	55	86	105.8	132	531
	Visit 2	34	121.7	91.7	54	84	100.0	134	602
	Visit 3	32	128.1	106.2	53	80	104.9	136	664
	Visit 4	30	139.5	118.0	57	89	108.4	150	717
	Visit 5	30	136.4	107.9	58	89	106.6	151	655
	Visit 6	22	148.4	121.6	70	90	110.2	162	655
	Visit 7	22	140.9	125.4	68	82	109.1	133	673
	Visit 8	15	114.9	39.9	75	86	98.0	142	195
	Visit 9	16	107.5	42.2	65	80	95.1	126	221
	Visit 10	16	110.3	42.1	65	83	100.4	119	212
	Visit 11	13	111.5	50.5	64	76	99.1	115	231
	Visit 12	15	106.5	33.3	58	74	102.7	127	168
	Visit 13	9	113.7	48.7	12	96	124.8	133	186
	Visit 14	4	135.8	54.3	91	98	119.9	174	212
	Study end	16	108.0	35.6	49	91	101.3	131	189

Only planned visits according to protocol were included into the analysis.
Patients could have had up to two XGEVA applications before inclusion into the study. These applications are the 1st and 2nd baseline applications.

15.8.2 Laboratory evaluation: Creatinine in serum [µmol/l] by cancer type and visit - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Other cancer type	Baseline 1st application	91	80.7	29.4	40	62	73.5	94	207
	Baseline 2nd application	16	89.8	31.3	53	66	77.0	108	165
	Visit 1	68	81.4	29.0	31	62	76.1	99	171
	Visit 2	72	79.9	32.1	36	56	73.3	91	159
	Visit 3	69	84.3	44.7	31	58	75.0	96	345
	Visit 4	56	78.8	32.1	26	58	71.2	93	168
	Visit 5	54	75.8	27.0	30	58	70.8	85	155
	Visit 6	43	80.4	28.9	35	59	72.6	98	151
	Visit 7	34	84.2	31.8	44	62	74.0	98	159
	Visit 8	35	78.2	29.9	32	60	70.0	85	160
	Visit 9	34	77.9	26.6	41	63	70.9	90	152
	Visit 10	23	89.1	39.3	36	62	72.6	109	188
	Visit 11	26	84.5	29.8	30	65	79.2	96	154
	Visit 12	22	78.2	33.4	35	58	68.5	85	155
	Visit 13	12	81.1	32.7	35	56	74.4	107	141
	Visit 14	1	51.0		51	51	51.0	51	51
	Study end	26	75.7	33.4	27	55	64.6	106	156

Only planned visits according to protocol were included into the analysis.
Patients could have had up to two XGEVA applications before inclusion into the study. These applications are the 1st and 2nd baseline applications.

15.8.2 Laboratory evaluation: Creatinine in serum [µmol/l] by cancer type and visit - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Total	Baseline 1st application	781	84.6	40.3	34	63	75.2	96	531
	Baseline 2nd application	174	76.5	25.8	31	60	70.8	87	171
	Visit 1	754	80.1	33.6	29	62	72.6	90	531
	Visit 2	730	81.7	37.6	35	62	73.5	89	602
	Visit 3	731	83.7	43.2	26	62	76.0	93	664
	Visit 4	662	83.7	48.5	26	62	74.3	94	717
	Visit 5	663	83.7	46.3	30	62	74.3	92	714
	Visit 6	609	84.3	44.0	29	62	77.0	96	655
	Visit 7	577	84.2	40.6	33	63	76.1	96	673
	Visit 8	545	82.7	39.7	32	62	74.3	93	622
	Visit 9	527	83.5	36.7	30	64	77.0	95	605
	Visit 10	497	83.4	38.0	1	63	77.0	93	580
	Visit 11	466	83.1	38.3	30	63	74.3	94	615
	Visit 12	401	83.8	28.8	35	65	77.0	97	243
	Visit 13	256	84.2	31.1	12	63	76.1	97	286
	Visit 14	75	79.0	25.7	44	62	72.6	91	212
	Visit 15	11	76.4	24.2	44	56	70.8	96	127
	Visit 16	7	117.3	66.8	71	80	97.3	115	265
	Visit 17	3	112.1	13.5	97	97	115.0	124	124
	Visit 19	3	86.4	9.6	80	80	82.2	97	97
	Visit 21	1	123.9		124	124	123.9	124	124
	Study end	304	87.2	50.6	26	64	75.6	96	565

Only planned visits according to protocol were included into the analysis.
Patients could have had up to two XGEVA applications before inclusion into the study. These applications are the 1st and 2nd baseline applications.

15.8.3 Laboratory evaluation: Creatinine clearance [ml/min] by cancer type and visit - FAS

Cancer type	Visit	N evaluable	Mean	Std. dev.	Min	Q1	Median	Q3	Max
Breast cancer	Baseline 1st application	115	78.5	20.1	23	64	79.8	90	145
	Baseline 2nd application	31	82.6	22.1	39	66	83.0	94	151
Prostate cancer	Baseline 1st application	26	83.5	33.4	41	58	71.2	106	165
	Baseline 2nd application	3	63.7	31.5	44	44	47.0	100	100
Lung cancer	Baseline 1st application	18	92.1	51.2	45	60	73.4	110	263
	Baseline 2nd application	0							
Kidney cancer	Baseline 1st application	9	56.7	19.0	22	52	59.8	60	91
	Baseline 2nd application	2	80.1	25.6	62	62	80.1	98	98
Other cancer type	Baseline 1st application	24	85.7	29.1	37	59	89.0	102	150
	Baseline 2nd application	3	70.5	34.6	31	31	84.6	96	96
Total	Baseline 1st application	192	80.3	28.0	22	60	77.5	93	263
	Baseline 2nd application	39	80.1	23.5	31	60	83.0	96	151

Only planned visits according to protocol were included into the analysis.
Patients could have had up to two XGEVA applications before inclusion into the study. These applications are the 1st and 2nd baseline applications.

15.9.1 Overall summary of reported Adverse Drug Reactions - FAS

	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	Event n	Pat. n	Pat. %	Event n	Pat. n	Pat. %	Event n	Pat. n	Pat. %	Event n	Pat. n	Pat. %	Event n	Pat. n	Pat. %	Event n	Pat. n	Pat. %
All documented Adverse Drug Reactions	43	33	(6.5%)	16	15	(5.1%)	22	14	(8.8%)	5	3	(6.0%)	9	7	(6.0%)	95	72	(6.4%)
that are fatal	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)
leading to withdrawal of product	6	4	(0.8%)	4	4	(1.4%)	2	2	(1.3%)	0	0	(0.0%)	0	0	(0.0%)	12	10	(0.9%)
related to XGEVA	43	33	(6.5%)	16	15	(5.1%)	22	14	(8.8%)	5	3	(6.0%)	9	7	(6.0%)	95	72	(6.4%)

Suspected osteonecrosis of the jaw events are excluded from this table. They are listed separately.

15.9.2 Summary of serious reported Adverse Drug Reactions - FAS

MedDRA System Organ Class Preferred Term	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	Ev. n	Pat. n	Pat. %	Ev. n	Pat. n	Pat. %	Ev. n	Pat. n	Pat. %	Ev. n	Pat. n	Pat. %	Ev. n	Pat. n	Pat. %	Ev. n	Pat. n	Pat. %
Total	2	2	(0.4%)	0	0	(0.0%)	2	2	(1.3%)	0	0	(0.0%)	0	0	(0.0%)	4	4	(0.4%)
Metabolism and nutrition disorders																		
Total	1	1	(0.2%)	0	0	(0.0%)	1	1	(0.6%)	0	0	(0.0%)	0	0	(0.0%)	2	2	(0.2%)
Hypocalcaemia	1	1	(0.2%)	0	0	(0.0%)	1	1	(0.6%)	0	0	(0.0%)	0	0	(0.0%)	2	2	(0.2%)
Blood and lymphatic system disorders																		
Total	1	1	(0.2%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Thrombocytopenia	1	1	(0.2%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Infections and infestations																		
Total	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.6%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Respiratory tract infection	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.6%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)

15.9.3 Summary of reported Adverse Drug Reactions related to XGEVA - FAS

MedDRA System Organ Class Preferred Term	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	Ev. n	Pat. n	Pat. %	Ev. n	Pat. n	Pat. %	Ev. n	Pat. n	Pat. %	Ev. n	Pat. n	Pat. %	Ev. n	Pat. n	Pat. %	Ev. n	Pat. n	Pat. %
Total	43	33	(6.5%)	16	15	(5.1%)	22	14	(8.8%)	5	3	(6.0%)	9	7	(6.0%)	95	72	(6.4%)
Metabolism and nutrition disorders																		
Total	27	19	(3.7%)	12	11	(3.7%)	10	9	(5.7%)	5	3	(6.0%)	9	7	(6.0%)	63	49	(4.3%)
Hypocalcaemia	27	19	(3.7%)	11	10	(3.4%)	10	9	(5.7%)	5	3	(6.0%)	9	7	(6.0%)	62	48	(4.3%)
Decreased appetite	0	0	(0.0%)	1	1	(0.3%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Musculoskeletal and connective tissue disorders																		
Total	3	3	(0.6%)	2	2	(0.7%)	3	3	(1.9%)	0	0	(0.0%)	0	0	(0.0%)	8	8	(0.7%)
Arthralgia	0	0	(0.0%)	2	2	(0.7%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	2	2	(0.2%)
Back pain	0	0	(0.0%)	0	0	(0.0%)	2	2	(1.3%)	0	0	(0.0%)	0	0	(0.0%)	2	2	(0.2%)
Bone pain	1	1	(0.2%)	0	0	(0.0%)	1	1	(0.6%)	0	0	(0.0%)	0	0	(0.0%)	2	2	(0.2%)
Musculoskeletal pain	1	1	(0.2%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Myalgia	1	1	(0.2%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Skin and subcutaneous tissue disorders																		
Total	3	3	(0.6%)	0	0	(0.0%)	2	2	(1.3%)	0	0	(0.0%)	0	0	(0.0%)	5	5	(0.4%)
Rash	2	2	(0.4%)	0	0	(0.0%)	1	1	(0.6%)	0	0	(0.0%)	0	0	(0.0%)	3	3	(0.3%)
Hyperhidrosis	1	1	(0.2%)	0	0	(0.0%)	1	1	(0.6%)	0	0	(0.0%)	0	0	(0.0%)	2	2	(0.2%)
General disorders and administration site conditions																		
Total	3	3	(0.6%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	3	3	(0.3%)
Fatigue	2	2	(0.4%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	2	2	(0.2%)

Suspected osteonecrosis of the jaw events are excluded from this table. They are tabulated separately.

15.9.3 Summary of reported Adverse Drug Reactions related to XGEVA - FAS

MedDRA System Organ Class Preferred Term	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	Ev. n	Pat. n	Pat. %	Ev. n	Pat. n	Pat. %	Ev. n	Pat. n	Pat. %	Ev. n	Pat. n	Pat. %	Ev. n	Pat. n	Pat. %	Ev. n	Pat. n	Pat. %
General physical health deterioration	1	1	(0.2%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Infections and infestations																		
Total	0	0	(0.0%)	1	1	(0.3%)	2	2	(1.3%)	0	0	(0.0%)	0	0	(0.0%)	3	3	(0.3%)
Bronchopneumonia	0	0	(0.0%)	1	1	(0.3%)	1	1	(0.6%)	0	0	(0.0%)	0	0	(0.0%)	2	2	(0.2%)
Respiratory tract infection	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.6%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Gastrointestinal disorders																		
Total	1	1	(0.2%)	0	0	(0.0%)	2	1	(0.6%)	0	0	(0.0%)	0	0	(0.0%)	3	2	(0.2%)
Diarrhoea	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.6%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Nausea	1	1	(0.2%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Vomiting	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.6%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Investigations																		
Total	2	2	(0.4%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	2	2	(0.2%)
Blood calcium increased	1	1	(0.2%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Blood potassium decreased	1	1	(0.2%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Nervous system disorders																		
Total	0	0	(0.0%)	1	1	(0.3%)	1	1	(0.6%)	0	0	(0.0%)	0	0	(0.0%)	2	2	(0.2%)
Dizziness	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.6%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Paraesthesia	0	0	(0.0%)	1	1	(0.3%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Vascular disorders																		
Total	2	2	(0.4%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	2	2	(0.2%)
Circulatory collapse	1	1	(0.2%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Vasculitis	1	1	(0.2%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)

Suspected osteonecrosis of the jaw events are excluded from this table. They are tabulated separately.

15.9.3 Summary of reported Adverse Drug Reactions related to XGEVA - FAS

MedDRA System Organ Class Preferred Term	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	Ev. n	Pat. n	Pat. %	Ev. n	Pat. n	Pat. %	Ev. n	Pat. n	Pat. %	Ev. n	Pat. n	Pat. %	Ev. n	Pat. n	Pat. %	Ev. n	Pat. n	Pat. %
Blood and lymphatic system disorders																		
Total	1	1	(0.2%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Thrombocytopenia	1	1	(0.2%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Immune system disorders																		
Total	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.6%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Reaction to drug excipients	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.6%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Psychiatric disorders																		
Total	1	1	(0.2%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Depression	1	1	(0.2%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Renal and urinary disorders																		
Total	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.6%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Dysuria	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.6%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)

Suspected osteonecrosis of the jaw events are excluded from this table. They are tabulated separately.

15.9.4 Summary of fatal reported Adverse Drug Reactions related to XGEVA - FAS

No fatal reported adverse drug reactions were reported.

Suspected osteonecrosis of the jaw events are excluded from this table. They are tabulated separately.

15.9.5 Summary of serious reported Adverse Drug Reactions related to XGEVA - FAS

MedDRA System Organ Class Preferred Term	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	Ev. n	Pat. n	Pat. %	Ev. n	Pat. n	Pat. %	Ev. n	Pat. n	Pat. %	Ev. n	Pat. n	Pat. %	Ev. n	Pat. n	Pat. %	Ev. n	Pat. n	Pat. %
Total	2	2	(0.4%)	0	0	(0.0%)	2	2	(1.3%)	0	0	(0.0%)	0	0	(0.0%)	4	4	(0.4%)
Metabolism and nutrition disorders																		
Total	1	1	(0.2%)	0	0	(0.0%)	1	1	(0.6%)	0	0	(0.0%)	0	0	(0.0%)	2	2	(0.2%)
Hypocalcaemia	1	1	(0.2%)	0	0	(0.0%)	1	1	(0.6%)	0	0	(0.0%)	0	0	(0.0%)	2	2	(0.2%)
Blood and lymphatic system disorders																		
Total	1	1	(0.2%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Thrombocytopenia	1	1	(0.2%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Infections and infestations																		
Total	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.6%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Respiratory tract infection	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.6%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)

Suspected osteonecrosis of the jaw events are excluded from this table. They are tabulated separately.

15.9.6 Summary of reported Adverse Drug Reactions related to XGEVA leading to withdrawal of product - FAS

MedDRA System Organ Class Preferred Term	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	Ev. n	Pat. n	Pat. %	Ev. n	Pat. n	Pat. %	Ev. n	Pat. n	Pat. %	Ev. n	Pat. n	Pat. %	Ev. n	Pat. n	Pat. %	Ev. n	Pat. n	Pat. %
Total	6	4	(0.8%)	4	4	(1.4%)	2	2	(1.3%)	0	0	(0.0%)	0	0	(0.0%)	12	10	(0.9%)
Metabolism and nutrition disorders																		
Total	0	0	(0.0%)	3	3	(1.0%)	1	1	(0.6%)	0	0	(0.0%)	0	0	(0.0%)	4	4	(0.4%)
Hypocalcaemia	0	0	(0.0%)	2	2	(0.7%)	1	1	(0.6%)	0	0	(0.0%)	0	0	(0.0%)	3	3	(0.3%)
Decreased appetite	0	0	(0.0%)	1	1	(0.3%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Musculoskeletal and connective tissue disorders																		
Total	0	0	(0.0%)	1	1	(0.3%)	1	1	(0.6%)	0	0	(0.0%)	0	0	(0.0%)	2	2	(0.2%)
Arthralgia	0	0	(0.0%)	1	1	(0.3%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Bone pain	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.6%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Skin and subcutaneous tissue disorders																		
Total	2	2	(0.4%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	2	2	(0.2%)
Rash	2	2	(0.4%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	2	2	(0.2%)
Vascular disorders																		
Total	2	2	(0.4%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	2	2	(0.2%)
Circulatory collapse	1	1	(0.2%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Vasculitis	1	1	(0.2%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Gastrointestinal disorders																		
Total	1	1	(0.2%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Nausea	1	1	(0.2%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)

Suspected osteonecrosis of the jaw events are excluded from this table. They are tabulated separately.

15.9.6 Summary of reported Adverse Drug Reactions related to XGEVA leading to withdrawal of product - FAS

	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
MedDRA System Organ Class Preferred Term	Ev. n	Pat. n	Pat. %	Ev. n	Pat. n	Pat. %	Ev. n	Pat. n	Pat. %	Ev. n	Pat. n	Pat. %	Ev. n	Pat. n	Pat. %	Ev. n	Pat. n	Pat. %
General disorders and administration site conditions																		
Total	1	1	(0.2%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
General physical health deterioration	1	1	(0.2%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)

Suspected osteonecrosis of the jaw events are excluded from this table. They are tabulated separately.

15.9.7 Reported Adverse Drug Reactions: suspected osteonecrosis of the jaw events by number of injections received - FAS

MedDRA System Organ Class Preferred Term	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	Ev. n	Pat. n	Pat. %	Ev. n	Pat. n	Pat. %	Ev. n	Pat. n	Pat. %	Ev. n	Pat. n	Pat. %	Ev. n	Pat. n	Pat. %	Ev. n	Pat. n	Pat. %
Total	7	7	(1.4%)	2	2	(0.7%)	0	0	(0.0%)	5	5	(10.0%)	1	1	(0.9%)	15	15	(1.3%)
Musculoskeletal and connective tissue disorders																		
Total	7	7	(1.4%)	2	2	(0.7%)	0	0	(0.0%)	5	5	(10.0%)	1	1	(0.9%)	15	15	(1.3%)
Osteonecrosis of jaw	7	7	(1.4%)	2	2	(0.7%)	0	0	(0.0%)	5	5	(10.0%)	1	1	(0.9%)	15	15	(1.3%)

15.9.7 Reported Adverse Drug Reactions: suspected osteonecrosis of the jaw events by number of injections received - FAS

	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
Number of injections **MedDRA System Organ Class** **Preferred Term**	**Ev. n**	**Pat. n**	**Pat. %**	**Ev. n**	**Pat. n**	**Pat. %**	**Ev. n**	**Pat. n**	**Pat. %**	**Ev. n**	**Pat. n**	**Pat. %**	**Ev. n**	**Pat. n**	**Pat. %**	**Ev. n**	**Pat. n**	**Pat. %**
3 Injections	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(2.0%)	0	0	(0.0%)	1	1	(0.1%)
Musculoskeletal and connective tissue disorders																		
Total	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(2.0%)	0	0	(0.0%)	1	1	(0.1%)
Osteonecrosis of jaw	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(2.0%)	0	0	(0.0%)	1	1	(0.1%)

15.9.7 Reported Adverse Drug Reactions: suspected osteonecrosis of the jaw events by number of injections received - FAS

	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
Number of injections **MedDRA System Organ Class** **Preferred Term**	**Ev. n**	**Pat. n**	**Pat. %**	**Ev. n**	**Pat. n**	**Pat. %**	**Ev. n**	**Pat. n**	**Pat. %**	**Ev. n**	**Pat. n**	**Pat. %**	**Ev. n**	**Pat. n**	**Pat. %**	**Ev. n**	**Pat. n**	**Pat. %**
4 Injections	0	0	(0.0%)	1	1	(0.3%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Musculoskeletal and connective tissue disorders																		
Total	0	0	(0.0%)	1	1	(0.3%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Osteonecrosis of jaw	0	0	(0.0%)	1	1	(0.3%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)

15.9.7 Reported Adverse Drug Reactions: suspected osteonecrosis of the jaw events by number of injections received - FAS

Number of injections MedDRA System Organ Class Preferred Term	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
	Ev. n	Pat. n	Pat. %	Ev. n	Pat. n	Pat. %	Ev. n	Pat. n	Pat. %	Ev. n	Pat. n	Pat. %	Ev. n	Pat. n	Pat. %	Ev. n	Pat. n	Pat. %
5 Injections	2	2	(0.4%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	2	2	(0.2%)
Musculoskeletal and connective tissue disorders																		
Total	2	2	(0.4%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	2	2	(0.2%)
Osteonecrosis of jaw	2	2	(0.4%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	2	2	(0.2%)

15.9.7 Reported Adverse Drug Reactions: suspected osteonecrosis of the jaw events by number of injections received - FAS

	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
Number of injections **MedDRA System Organ Class** **Preferred Term**	**Ev. n**	**Pat. n**	**Pat. %**	**Ev. n**	**Pat. n**	**Pat. %**	**Ev. n**	**Pat. n**	**Pat. %**	**Ev. n**	**Pat. n**	**Pat. %**	**Ev. n**	**Pat. n**	**Pat. %**	**Ev. n**	**Pat. n**	**Pat. %**
6 Injections	2	2	(0.4%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(2.0%)	0	0	(0.0%)	3	3	(0.3%)
Musculoskeletal and connective tissue disorders																		
Total	2	2	(0.4%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(2.0%)	0	0	(0.0%)	3	3	(0.3%)
Osteonecrosis of jaw	2	2	(0.4%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(2.0%)	0	0	(0.0%)	3	3	(0.3%)

15.9.7 Reported Adverse Drug Reactions: suspected osteonecrosis of the jaw events by number of injections received - FAS

	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
Number of injections **MedDRA System Organ Class** **Preferred Term**	**Ev. n**	**Pat. n**	**Pat. %**	**Ev. n**	**Pat. n**	**Pat. %**	**Ev. n**	**Pat. n**	**Pat. %**	**Ev. n**	**Pat. n**	**Pat. %**	**Ev. n**	**Pat. n**	**Pat. %**	**Ev. n**	**Pat. n**	**Pat. %**
7 Injections	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(2.0%)	0	0	(0.0%)	1	1	(0.1%)
Musculoskeletal and connective tissue disorders																		
Total	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(2.0%)	0	0	(0.0%)	1	1	(0.1%)
Osteonecrosis of jaw	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(2.0%)	0	0	(0.0%)	1	1	(0.1%)

15.9.7 Reported Adverse Drug Reactions: suspected osteonecrosis of the jaw events by number of injections received - FAS

	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
Number of injections **MedDRA System Organ Class** **Preferred Term**	**Ev. n**	**Pat. n**	**Pat. %**	**Ev. n**	**Pat. n**	**Pat. %**	**Ev. n**	**Pat. n**	**Pat. %**	**Ev. n**	**Pat. n**	**Pat. %**	**Ev. n**	**Pat. n**	**Pat. %**	**Ev. n**	**Pat. n**	**Pat. %**
8 Injections	0	0	(0.0%)	1	1	(0.3%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Musculoskeletal and connective tissue disorders																		
Total	0	0	(0.0%)	1	1	(0.3%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)
Osteonecrosis of jaw	0	0	(0.0%)	1	1	(0.3%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.1%)

15.9.7 Reported Adverse Drug Reactions: suspected osteonecrosis of the jaw events by number of injections received - FAS

	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
Number of injections **MedDRA System Organ Class** **Preferred Term**	**Ev. n**	**Pat. n**	**Pat. %**	**Ev. n**	**Pat. n**	**Pat. %**	**Ev. n**	**Pat. n**	**Pat. %**	**Ev. n**	**Pat. n**	**Pat. %**	**Ev. n**	**Pat. n**	**Pat. %**	**Ev. n**	**Pat. n**	**Pat. %**
9 Injections	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.9%)	1	1	(0.1%)
Musculoskeletal and connective tissue disorders																		
Total	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.9%)	1	1	(0.1%)
Osteonecrosis of jaw	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(0.9%)	1	1	(0.1%)

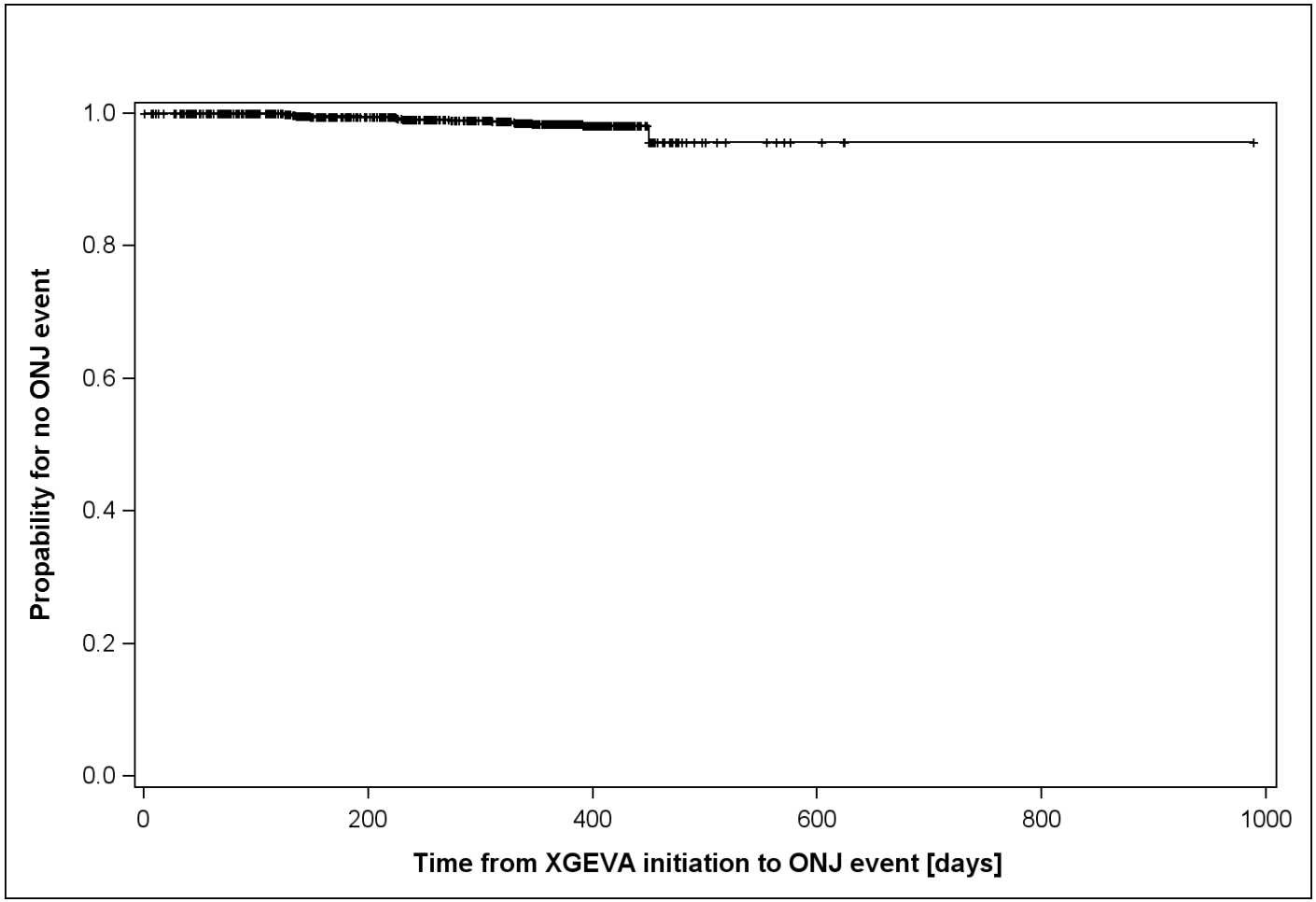
15.9.7 Reported Adverse Drug Reactions: suspected osteonecrosis of the jaw events by number of injections received - FAS

	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
Number of injections **MedDRA System Organ Class** **Preferred Term**	**Ev. n**	**Pat. n**	**Pat. %**	**Ev. n**	**Pat. n**	**Pat. %**	**Ev. n**	**Pat. n**	**Pat. %**	**Ev. n**	**Pat. n**	**Pat. %**	**Ev. n**	**Pat. n**	**Pat. %**	**Ev. n**	**Pat. n**	**Pat. %**
10 Injections	2	2	(0.4%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(2.0%)	0	0	(0.0%)	3	3	(0.3%)
Musculoskeletal and connective tissue disorders																		
Total	2	2	(0.4%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(2.0%)	0	0	(0.0%)	3	3	(0.3%)
Osteonecrosis of jaw	2	2	(0.4%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(2.0%)	0	0	(0.0%)	3	3	(0.3%)

15.9.7 Reported Adverse Drug Reactions: suspected osteonecrosis of the jaw events by number of injections received - FAS

	Breast cancer (N=509)			Prostate cancer (N=294)			Lung cancer (N=159)			Kidney cancer (N=50)			Other cancer type (N=116)			Total (N=1128)		
Number of injections **MedDRA System Organ Class** **Preferred Term**	**Ev. n**	**Pat. n**	**Pat. %**	**Ev. n**	**Pat. n**	**Pat. %**	**Ev. n**	**Pat. n**	**Pat. %**	**Ev. n**	**Pat. n**	**Pat. %**	**Ev. n**	**Pat. n**	**Pat. %**	**Ev. n**	**Pat. n**	**Pat. %**
13 Injections	1	1	(0.2%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(2.0%)	0	0	(0.0%)	2	2	(0.2%)
Musculoskeletal and connective tissue disorders																		
Total	1	1	(0.2%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(2.0%)	0	0	(0.0%)	2	2	(0.2%)
Osteonecrosis of jaw	1	1	(0.2%)	0	0	(0.0%)	0	0	(0.0%)	1	1	(2.0%)	0	0	(0.0%)	2	2	(0.2%)

15.9.8.1 Time from XGEVA initiation to suspected osteonecrosis of the jaw event (ONJ event) - overall analysis Kaplan-Meier curve - FAS



Time from XGEVA initiation to ONJ event was calculated starting from the first study treatment application ('day 1').

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15.9.8.2 Time from XGEVA initiation to ONJ event - overall analysis Kaplan-Meier estimates - FAS

	Kaplan-Meier Quartiles [days]			
			95% CI	
	Quartile	Point Estimate	Lower Limit	Upper Limit
Overall (N=1128)	1st Quartile	not estimable	not estimable	not estimable
	Median	not estimable	not estimable	not estimable
	3rd Quartile	not estimable	not estimable	not estimable

Time from XGEVA initiation to ONJ event was calculated starting from the first study treatment application ('day 1').

Annex 2. Study Protocol and Amendments

Beobachtungsplan

X-TREME

Anwendungsbeobachtung zur Therapie-Persistenz von Denosumab (XGEVA®) im routinemäßigen Einsatz bei Erwachsenen mit Knochenmetastasen aufgrund solider Tumoren

Auftraggeber (Sponsor)	AMGEN GmbH Riesstraße 24 80992 München
Medizinische Betreuung	[redacted] AMGEN GmbH München Tel.: [redacted]
Koordination	[redacted] AMGEN GmbH München Tel.: [redacted]
Unerwünschte Arzneimittelwirkungen	[redacted] AMGEN GmbH München Tel.: [redacted] Fax: [redacted]
Statistik	Metronomia Clinical Research GmbH Paul-Gerhardt-Allee 42 81245 München
Technische Beratung	Metronomia Clinical Research GmbH Paul-Gerhardt-Allee 42 81245 München
Version	**6.0**
Stand	**10.10.2016**

Einverständnis des teilnehmenden Arztes

Ich habe den beigefügten Beobachtungsplan mit dem Titel Anwendungsbeobachtung zum routinemäßigen Einsatz von Denosumab (XGEVA®) bei Erwachsenen mit Knochenmetastasen aufgrund solider Tumoren vom 10. Oktober 2016 gelesen und erkläre mich einverstanden, alle darin dargelegten Bestimmungen einzuhalten.

Ich versichere, dass dieses Dokument bzw. die enthaltenen vertraulichen Informationen ausschließlich zur Durchführung oder Auswertung dieser Beobachtung verwendet werden. Ausnahmeregelungen bedürfen der vorherigen schriftlichen Zustimmung der AMGEN GmbH München.

Unterschrift (Hauptverantwortlicher teilnehmender Arzt)	Datum
Name des Arztes in Druckbuchstaben	

ZUSAMMENFASSUNG DES BEOBACHTUNGSPLANES

Titel	Anwendungsbeobachtung zur Therapie-Persistenz von Denosumab (XGEVA®) im routinemäßigen Einsatz bei Erwachsenen mit Knochenmetastasen aufgrund solider Tumoren
Kurztitel	X-TREME
Art der Beobachtung	Anwendungsbeobachtung (AWB) im Sinne von §4 Abs. 23 Satz 3 AMG, Anzeige gemäß §67 (6) AMG
Design	Nicht-interventionell, multizentrisch, retrospektiv und prospektiv
Kontrollgruppe	Keine
Indikation	Prävention von skelettbezogenen Komplikationen (pathologische Fraktur, Bestrahlung des Knochens, Rückenmarkkompression oder operative Eingriffe am Knochen) bei Erwachsenen mit Knochenmetastasen aufgrund solider Tumoren
Ziele	**Primäres Ziel:** Bewertung der Persistenz bei Denosumab (XGEVA®) nach 24 Wochen im klinischen Routineeinsatz **Sekundäre Ziele:** • Bewertung der Persistenz bei Denosumab (XGEVA®) nach 48 Wochen im klinischen Routineeinsatz • Bewertung der Zeit bis zur Nicht-Persistenz bei Denosumab (XGEVA®) am Ende des Beobachtungzeitraumes • Beschreibung der primären und sekundären Persistenz-Endpunkte nach Tumorart • Beschreibung der Demographie, des Krankheitsbildes, der begleitenden Tumor-Therapie, der unerwünschten Arzneimittelwirkungen von Denosumab (XGEVA®) und der Krankengeschichte von Patienten, die in der klinischen Routine mit Denosumab (XGEVA®) behandelt werden • Beschreibung der Dosis und Frequenz der Kalzium- und Vitamin D-Supplementierung bei Patienten, die in der klinischen Routine mit Denosumab (XGEVA®) behandelt werden **Explorative Ziele:** • Beschreibung der Veränderung der individuellen Schmerz-Scores zwischen der ersten Denosumab (XGEVA®)-Applikation und Woche 24 unter Behandlung mit Denosumab (XGEVA®) im klinischen Routineeinsatz

- Beschreibung der Veränderung der individuellen Schmerzmedikation zwischen der ersten Denosumab (XGEVA®)-Applikation und Woche 24 unter Behandlung mit Denosumab (XGEVA®) im klinischen Routineeinsatz
- Beschreibung von patientenbezogenen Endpunkten zwischen der ersten Denosumab (XGEVA®)-Applikation und unter Behandlung mit Denosumab (XGEVA®) bis zum Ende des Beobachtungszeitraumes in Form von Patientenbeurteilungen bezüglich Problemen bei Mobilität, Selbstversorgung, alltäglichen Tätigkeiten, Schmerzen/körperlichen Beschwerden und Angst/Depression anhand eines präferenzbasierten Gesundheitsfragebogens zur Lebensqualitätsmessung (EQ-5D)
- Beschreibung aller unerwünschter Arzneimittelwirkungen unter Denosumab (XGEVA®)

Messparameter

Primäres Zielkriterium:

- Persistenz (ja/nein) einer Denosumab (XGEVA®)-Therapie nach 24 Wochen – nach 24 Wochen gilt ein Patient dann als „persistent“ unter einer Denosumab (XGEVA®)-Therapie, wenn er mindestens 6 Denosumab (XGEVA®)-Injektionen im Abstand von jeweils nicht mehr als 4 Wochen plus 7 Tagen erhalten hat

Sekundäre Zielkriterien:

- Persistenz (ja/nein) einer Denosumab (XGEVA®)-Therapie nach 48 Wochen – nach 48 Wochen gilt ein Patient dann als „persistent“ unter einer Denosumab (XGEVA®)-Therapie, wenn er mindestens 12 Denosumab (XGEVA®)-Injektionen im Abstand von jeweils nicht mehr als 4 Wochen plus 7 Tagen erhalten hat
- Die Zeit bis zur Nicht-Persistenz wird ermittelt als die Zeit in Tagen zwischen der ersten Injektion und dem Tag der letzten Injektion im Zeitraum, in dem der Patient noch als persistent klassifiziert wurde, plus 4 Wochen (max. 28 Tage)
- Primäre und sekundäre Persistenz-Endpunkte nach Tumorart – die Auswertung der Endpunkte wird für jede Tumorart separat durchgeführt.
- Patientencharakteristika vor Patienteneinschluss zur Beschreibung des Patientenkollektives, das mit Denosumab (XGEVA®) in der klinischen Routine behandelt wird, und der Bezug zur Persistenz/Nicht-Persistenz
- Begleitende Tumor-Therapie, die unerwünschten Arzneimittelwirkungen von Denosumab (XGEVA®) und die Krankengeschichte von Patienten, die in der klinischen Routine mit Denosumab (XGEVA®) behandelt werden, und der Bezug zur Persistenz/Nicht-Persistenz

	• Dosis und Frequenz der Einnahme von Kalzium- und Vitamin D-haltigen Präparaten vor und während der gesamten Behandlungszeit mit Denosumab (XGEVA®) **Explorative Zielkriterien:** • Veränderungen des Schmerz-Scores auf einer 10-Punkte Visuellen Analog Skala (VAS) im Therapieverlauf, beginnend mit der ersten Denosumab (XGEVA®)-Applikation und bei jeder weiteren Applikation bis zu 24 Wochen lang (oder bis zum Ende des Beobachtungszeitraums, je nachdem was früher eintritt) • Veränderungen der Schmerzmedikation mittels eines 8-Punkte Fragebogens (AQA) im Therapieverlauf, beginnend mit der ersten Denosumab (XGEVA®)-Applikation und bei jeder weiteren Applikation bis zu 24 Wochen lang (oder bis zum Ende des Beobachtungszeitraums, je nachdem was früher eintritt) • Messung der Lebensqualität mittels eines präferenzbasierten Gesundheitsfragebogens (EQ-5D) beginnend mit der ersten Denosumab (XGEVA®)-Applikation und jeweils zur 4., 7. und 10. Denosumab (XGEVA®)-Applikation bis zu 52 Wochen lang (oder bis zum Ende des Beobachtungszeitraums, je nachdem was früher eintritt) • Unerwünschte Arzneimittelwirkungen, beginnend mit der ersten Denosumab (XGEVA®)-Applikation und nach jeder weiteren Applikation von Denosumab (XGEVA®) bis zu 52 Wochen lang (oder bis zum Ende des Beobachtungszeitraums, je nachdem was früher eintritt)
Auswahlkriterien	• Patientenalter mindestens 18 Jahre • Patientinnen/Patienten mit einem dokumentierten Mamma-, Prostata-, Bronchialkarzinom oder einem anderen soliden Tumor mit dokumentierter Knochenmetastasierung • Patientinnen/Patienten, die mit Denosumab (XGEVA®) behandelt werden (maximal 2 Denosumab (XGEVA®)-Injektionen vor Einschluss) • Allgemeinzustand nach ECOG 0-2 • Vorliegen des Einverständnisses zur Weitergabe der persönlichen Daten Patienten werden aus folgenden Gründen ausgeschlossen: • Patientinnen/Patienten mit einem dokumentierten multiplem Myelom • Patientinnen/Patienten, die länger als 3 Monate mit einer Denosumab (XGEVA®)-Therapie in einer klinischen Studie oder in klinischer Routine behandelt werden • Patientinnen/Patienten, die länger als 6 Monate mit einer antiresorptiven Therapie (incl. maximal 2 Denosumab

	(XGEVA®)-Applikationen innerhalb von < 3 Monaten) in einer klinischen Studie oder in klinischer Routine behandelt werden • Vorherige Behandlung mit einer Radionuklid-Therapie (z. B. Strontium-98, Samarium-153, Radium-223) • Gleichzeitige Teilnahme an klinischen Studien, deren Studienziel die Prävention/Behandlung von Knochenmetastasen und SREs ist • Schwere, nicht behandelte Hypokalzämie (z. B. CTCAE ≥ Grad 3); eine bestehende Hypokalzämie muss vor Beginn der Denosumab (XGEVA®)-Therapie korrigiert werden • Überempfindlichkeiten gegen den Wirkstoff oder einen der sonstigen Bestandteile der Denosumab (XGEVA®)-Injektionslösung (Patienten mit der seltenen hereditären Fructose-Intoleranz)
Dosierung und Anwendung	Denosumab (XGEVA®) wird entsprechend der aktuellen Fachinformation angewendet. Darbietung: Durchstechflasche mit 120 mg Denosumab in 1,7 ml Lösung (70mg/ml). Entsprechend der Fachinformation beträgt die Anfangsdosis 120 mg. Diese wird einmal alle 4 Wochen als einzelne subkutane Injektion in den Oberschenkel, die Bauchregion oder den Oberarm gegeben. Zusätzlich müssen alle Patienten täglich mindestens 500 mg Kalzium und 400 IE Vitamin D erhalten, außer bei bestehender Hyperkalzämie.
Stichprobenumfang	1 400 Patienten aus ca. 80 Zentren in Deutschland (Zentren geografisch über das gesamte Bundesgebiet verteilt) Bis zum vorgesehenen Zeitpunkt des Einschlusses des letzten Patienten im Dezember 2015 wurden 1258 Patienten, in insgesamt 88 rekrutierenden Zentren, in die Anwendungsbeobachtung aufgenommen.
Ablauf	Es sind keine zusätzlichen diagnostischen oder therapeutischen Maßnahmen erforderlich als zum Zeitpunkt der Behandlung im Rahmen der Routineversorgung des Patienten vorgesehen sind. Die Beobachtung kann in 3 Abschnitte eingeteilt werden: I. Beobachtungsbeginn II. Beobachtungsphase (52 Wochen) III. Beobachtungsende (z.B. nach 52 Wochen nach Denosumab (XGEVA®)-Therapiebeginn, im Todesfall oder bei „Lost-to-Follow-up“)
Statistik	Diese Beobachtung wird als multizentrische, retrospektive und prospektive, Anwendungsbeobachtung (AWB) gemäß § 4(23) Satz 3 des AMG durchgeführt.

Patienten, die die Einschlusskriterien erfüllen, sind für die Beobachtung und Dokumentation im Rahmen dieser Studie geeignet. Die Daten werden bei jedem Patienten ab der ersten Anwendung von Denosumab (XGEVA®) über einen Zeitraum von maximal 52 Wochen erhoben. Das grundlegende Ziel dieser prospektiven Beobachtungsstudie ist es, die Persistenz der Behandlung mit Denosumab (XGEVA®) gemäß der Fachinformation in der ärztlichen Praxis in Deutschland zu zeigen. Aus diesem Grund sind alle statistischen Analysen in dieser Studie als deskriptiv anzusehen und basieren auf dem Full Analysis Set (FAS). Es werden keine formalen Hypothesen statistisch getestet. Schätzung der Persistenz raten schließen solche Patienten aus, die vor dem Erreichen von 24 bzw. 48 Wochen Beobachtungszeit gestorben sind, ihr Einverständnis zurückgenommen haben oder „Lost-to-follow-up“ sind.

Das primäre Zielkriterium der Beobachtung ist die Schätzung (95% KI) der Anzahl Patienten, die nach 24 Wochen persistent in Bezug auf die Behandlung mit Denosumab (XGEVA®) sind, wobei ein Patient dann als persistent in Bezug auf die Behandlung mit Denosumab (XGEVA®) nach 24 Wochen gilt, wenn er mindestens 6 XGEVA®-Injektionen in einem Abstand von nicht mehr als 4 Wochen plus 7 Tage erhalten hat.

Ein sekundäres Zielkriterium der Beobachtung ist die Schätzung (95% KI) der Anzahl Patienten, die nach 48 Wochen persistent in Bezug auf die Behandlung mit Denosumab (XGEVA®) sind, wobei ein Patient dann als persistent in Bezug auf die Behandlung mit Denosumab (XGEVA®) nach 48 Wochen gilt, wenn er mindestens 12 Denosumab (XGEVA®)-Injektionen in einem Abstand von nicht mehr als 4 Wochen plus 7 Tage erhalten hat.

Deskriptive statistische Auswertungen werden für alle Parameter erstellt, sowohl für das Gesamtkollektiv als auch stratifiziert nach Subgruppen bzw. Kovariaten.

Als Subgruppen bzw. Kovariate sind definiert:

- Tumorart (Mammakarzinom, Prostatakarzinom, Bronchialkarzinom, andere solide Tumoren)
- Vorherige antiresorptive Therapie (ja/nein)
- Art der systemischen antineoplastischen Therapie

Die metrischen Parameter werden mit folgenden deskriptiven Kennzahlen dargestellt: Anzahl der Beobachtungen, arithmetischer Mittelwert, Median, Standardabweichung, unteres und oberes 25% Quartil, Minimum und Maximum. Nominale und ordinale Größen werden mit ihren absoluten und relativen (prozentualen) Häufigkeiten angegeben. Konfidenzintervalle und Kaplan Meier-Analysen für zeitabhängige Endpunkte werden berechnet, soweit dieses sinnvoll erscheint.

Projektstart	Januar 2012
Projektende	Dezember 2017
Einschluss des ersten Patienten	Mai 2012
Einschluss des letzten Patienten	Dezember 2015
Abschluss des ersten Patienten	Mai 2013
Abschluss des letzten Patienten	Dezember 2016

INHALTSVERZEICHNIS

Seite

GLOSSAR

Abkürzung	Definition
AMG	Arzneimittelgesetz
AMG	Arzneimittelgesetz
AQA	Analgesic Quantification Algorithm
CRF	Case Report Form (Dokumentationsbogen)
CTCAE	Common Terminology Criteria for Adverse Events
d.h.	das heißt
ECOG	Classification Eastern Cooperative Oncology Group
EQ-5D	EuroQol –5 Dimensions
eCRF	Elektronischer Prüfbogen
KG	Körpergewicht
KI	Konfidenzintervall
NIS	Nicht-interventionelle Studie
ONJ	Osteonecrosis of the jaw (Kieferosteonekrose)
OPG	Osteoprotegerin
p.o.	per oral
RANK	Receptor Activator of NF-κB
RANK-L	Receptor Activator of NF-κB-Ligand
s.c.	Subkutan
SRE	Skeletal related events (=Skelettale Komplikationen)
SUAW	Schwerwiegende unerwünschte Arzneimittelwirkung
UAW	Unerwünschte Arzneimittelwirkung

1. HINTERGRUND

1.1 Krankheitsbild

Knochenmetastasen, die Streuung von Krebszellen eines Primärtumors in die Knochen, sind eine häufige und ernsthafte Komplikation bei Patienten mit fortgeschrittenen Krebserkrankungen. Je nach Tumorentität treten bei bis zu 75% aller Patienten, die an der Krankheit versterben, radiologisch oder autoptisch nachweisbare skelettale Läsionen auf (Solomayer et al. 2000).

Legt man beispielsweise bei Brustkrebs eine Mortalitätszahl von 18 000 Frauen pro Jahr in Deutschland zugrunde, ist bei einer durchschnittlichen Überlebenszeit von 3 Jahren nach Diagnose der Metastasierung von einer Prävalenz von circa 36 000 bis 40 000 Fällen auszugehen (Solomayer et al. 2000). Ähnliche Zahlen dürften auch für das Prostatakarzinom gelten. Daraus ergibt sich eine geschätzte Zahl von 100 000 bis 120 000 von Knochenmetastasen betroffenen Menschen allein in Deutschland.

Knochenmetastasen zerstören den Knochen, indem Tumorzellen über parakrine Sekretion von osteotropen Substanzen den Receptor Activator of NF-κB (RANK) / Receptor Activator of NF-κB- Ligand (RANK-L) / Osteoprotegerin (OPG) Signalweg aktivieren, der zu einer gesteigerten Osteoklastenaktivierung führt (siehe Abbildung 1). Bei der subsequenten Zerstörung der Knochenmatrix werden zuvor eingelagerte Wachstumsfaktoren freigesetzt, die zu einer Steigerung der proliferativen Aktivität der Tumorzellen beitragen können (Circulus vitiosus, maligner Dialog). Antiosteolytische Substanzen hemmen die Neubildung und/oder Aktivierung von Osteoklasten und reduzieren so das Ausmaß der skelettalen Zerstörung (Chamber et al. 2002, Mundy 2002, Roodmann 2004).

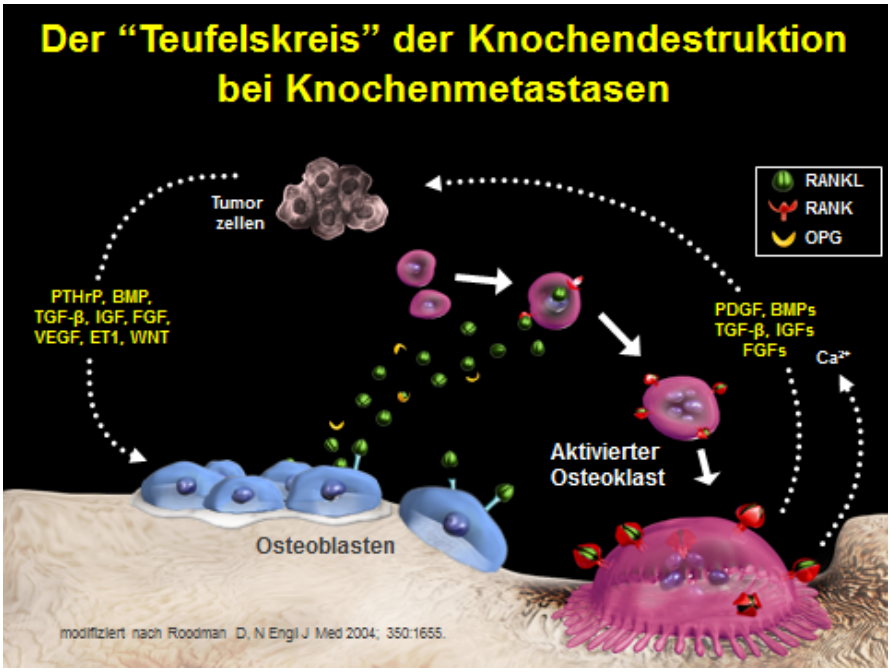

Abbildung 1. Teufelskreis der Knochendestruktion bei Knochenmetastasen

1.2 Therapieziele und therapeutische Möglichkeiten

Patienten mit metastatischen Knochenerkrankungen leiden oftmals unter Osteoklasten-vermittelter Knochendestruktion, die zu klinisch bedeutsamen Komplikationen wie pathologischen Frakturen, spinalen Kompressionssyndromen oder hyperkalzämischen Episoden führen (Coleman 2004, Vogel et al. 2004). Diese Komplikationen, die insgesamt unter dem Begriff der skelettalen Ereignisse (SREs = „skeletal-related events“) bekannt sind (Coleman 2001, Cook and Major 2001, Kosteva and Langer 2008, Yeh and Berenson 2006), verursachen Schmerzen und eine verminderte Lebensqualität (Weinfurth et al. 2005).

Das primäre Ziel von Therapiemaßnahmen bei Knochenmetastasen ist die Reduktion von SREs. In klinischen Studien, die die Effektivität von Therapiemaßnahmen untersuchen, wird zusätzlich der Einsatz von Strahlentherapie und operativen Techniken als SRE gewertet, da beide als Surrogatmarker für Knochenschmerz und drohende bzw. stattgefundene Frakturen gelten. Die Vermeidung aller dieser skelettalen Komplikationen führt nicht nur zu einer Erhöhung der Lebensqualität, sondern trägt auch zur Verlängerung der Überlebenszeit durch Vermeidung von Immobilität und Hospitalisierung bei (Weinfurth et al. 2005, Diel 2010, Diel et al. 2000).

Bisphosphonate sind Substanzen mit hoher Affinität zur Knochenmatrix, die sowohl zur Diagnostik von Knochenmetastasen (Skelettszintigraphie), als auch zu deren Behandlung eingesetzt werden. Bisphosphonate werden nach Anlagerung an die ossäre Oberfläche von aktiven Osteoklasten inkorporiert, was zu apoptotischen Effekten in den Zellen führt. Sie senken die Inzidenz von Hyperkalzämien, reduzieren skelettale Komplikationen und verringern den Knochenschmerz und werden daher von den Fachgesellschaften als supportiven Therapie bei Knochenmetastasen empfohlen (Rodan und Fleisch 1996, Rogers et al. 1999). In der Onkologie sind derzeit in Deutschland 4 Bisphosphonate zugelassen: Clodronat, Pamidronat, Ibandronat und Zoledronsäure (Solomayer et al. 2000, Chambers et al. 2002, Mundy 2002, Roodmann 2004, Diel 2010, Diel et al. 2000, Rodan und Fleisch 1996, Rogers et al. 1999, van Poznak et al. 2011).

Denosumab (XGEVA®) ist ein humaner monoklonaler Antikörper, der spezifisch die Signalübertragung zu RANK am Osteoklasten und zu den monozytären Vorläuferzellen unterbricht. Dadurch werden die Fusion von Osteoklasten und die Aktivität der ausgereiften mehrkernigen Riesenzellen gehemmt (Abbildung 2). Denosumab (XGEVA®) wirkt therapeutisch wie Osteoprotegerin (OPG), der physiologische Gegenspieler von RANKL (Lacey et al. 1998, Hofbauer und Heufelder 2001).

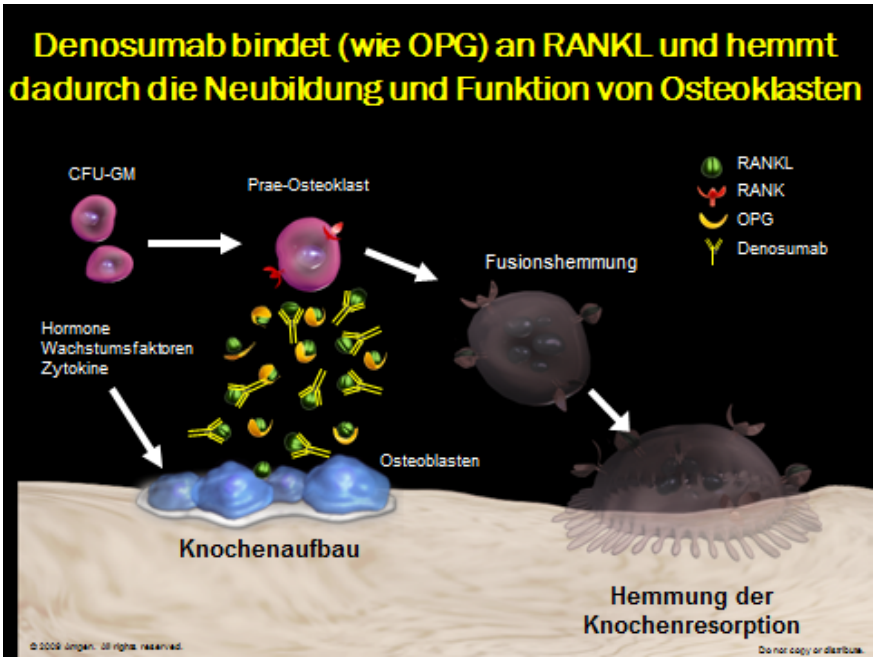

Abbildung 2. Spezifische Bindung von Denosumab (XGEVA®) an den RANK-Ligand

1.3 Prävention und Behandlung von SREs mit Denosumab (XGEVA®)

Denosumab (XGEVA®) wurde im Juli 2011 von der Europäischen Kommission zur Prävention von skelettbezogenen Komplikationen (SREs) bei Erwachsenen mit Knochenmetastasen aufgrund solider Tumoren zugelassen.

Die Wirksamkeit von Denosumab (XGEVA®) im Vergleich zu Zoledronsäure hinsichtlich der Verzögerung von SREs wurde in 3 zulassungsrelevanten Phase III-Studien untersucht. Dabei zeigte Denosumab (XGEVA®) gegenüber Zoledronsäure klinisch eine deutliche Verbesserung.

Denosumab (XGEVA®) wurde im Rahmen dieser Studien alle 4 Wochen als subkutane Injektion in einer Dosis von 120 mg verabreicht; Zoledronsäure dagegen wurde alle 4 Wochen als 15-minütige, intravenöse Infusion gegeben, wobei die Dosis gemäß Fachinformation für Zoledronsäure an die Nierenfunktion angepasst war. Bei Patienten mit Mamma- oder Prostatakarzinom und Knochenmetastasen erwies sich Denosumab (XGEVA®) bei der Senkung des SRE-Risikos gegenüber Zoledronsäure als signifikant überlegen (Stopeck et al. 2010; Fizazi et al. 2011). Bei Patienten mit Knochenmetastasen aufgrund anderer solider Tumoren oder Multiplem Myelom war Denosumab (XGEVA®) gegenüber Zoledronsäure bei der Reduktion des SRE-Risikos nicht unterlegen (Henry et al. 2011).

In einer integrierten Auswertung aller drei Studien zeigte sich Denosumab (XGEVA®) gegenüber Zoledronsäure bei der Zeitverzögerung bis zum ersten während der Studien aufgetretenen SRE um 17 % bzw. 8,2 Monate signifikant überlegen. Die mittlere Zeitdauer (Median) bis zum Auftreten des ersten skelettbezogenen Ereignisses innerhalb der Studie betrug 27,6 Monate unter Denosumab (XGEVA®) und 19,4 Monate unter Zoledronsäure ($p < 0,0001$).

In dieser Auswertung erwies sich Denosumab (XGEVA®) gegenüber Zoledronsäure auch im Hinblick auf die Verzögerung des ersten und folgenden während der Studie aufgetretenen SREs um 18 % überlegen ($p < 0,0001$).

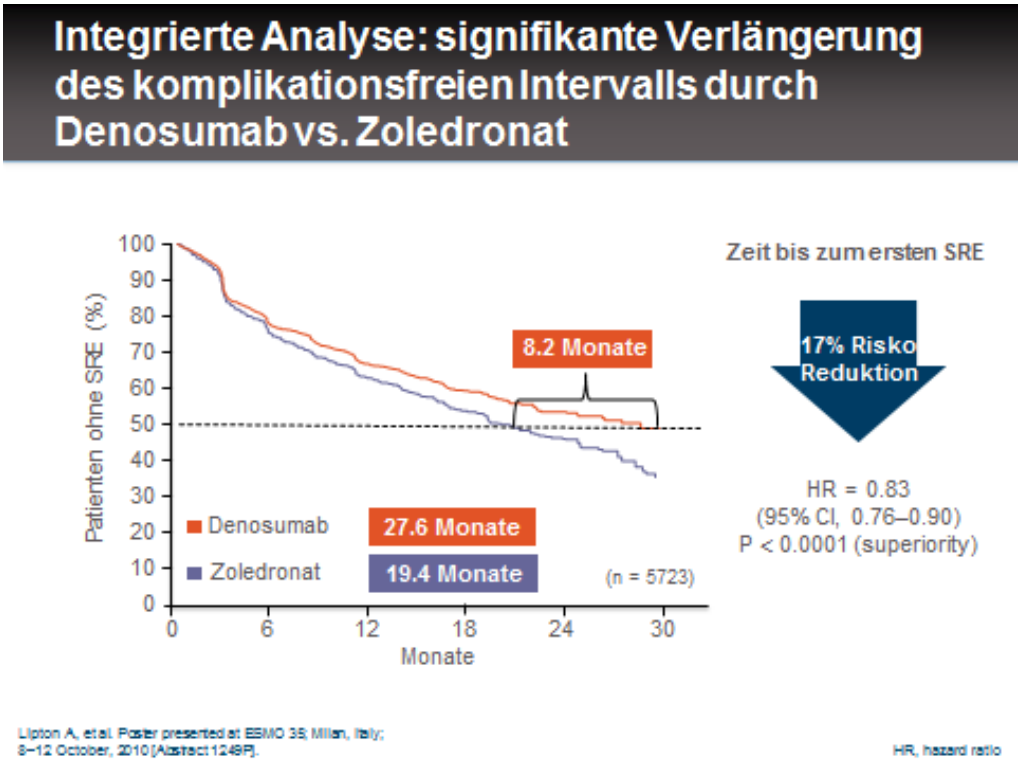

Abbildung 3. Komplikationsfreies Intervall in der integrierten Analyse

Bei Patienten, die bei Behandlungsbeginn keine oder leichte Schmerzen aufwiesen, verzögerte Denosumab (XGEVA®) gegenüber Zoledronsäure die Zeit bis zur Verschlimmerung des Schmerzes (198 gegenüber 143 Tage; p=0,0002). Die Zeitdauer bis zur Schmerzlinderung war für Denosumab (XGEVA®) und Zoledronsäure in den einzelnen Studien sowie der integrierten Auswertung vergleichbar.

Die Gesamtanzahl unerwünschter Ereignisse sowie schwerwiegender unerwünschter Ereignisse war im Allgemeinen vergleichbar bei Denosumab (XGEVA®) und Zoledronsäure. Kieferosteonekrose (ONJ) wurde bei ca. 1-2 % der Patienten verzeichnet, ein statistisch signifikanter Unterschied zwischen den beiden Behandlungsgruppen (Denosumab (XGEVA®) bzw. Zoledronsäure) bestand nicht. Hypokalzämie trat häufiger in der Denosumab (XGEVA®)-Behandlungsgruppe auf. Die Gesamtüberlebensrate und progressionsfreie Überlebensrate waren in allen Behandlungsgruppen der drei Studien vergleichbar (Lipton et al. 2010).

1.4 Rationale

Denosumab (XGEVA®) wurde im Juli 2011 in der Indikation „Prävention von skelettbezogenen Komplikationen bei Patienten mit soliden Tumoren und Knochenmetastasen“ zugelassen. Die Wirksamkeit von Denosumab (XGEVA®) hinsichtlich der Verzögerung von SREs wurde dabei in 3 Phase III-Studien nachgewiesen. In einer integrierten Auswertung aller drei Studien zeigte sich Denosumab (XGEVA®) gegenüber Zoledronsäure bei der Zeitverzögerung bis zum ersten während der Studien aufgetretenen SRE um 17 % bzw. 8,2 Monate signifikant überlegen. Mangelnde Patienten-„Compliance“ oder im Falle von Denosumab (XGEVA®) Therapie-„Persistenz“ über die Verschreibungsdauer könnten jedoch das in den klinischen Studien gezeigte therapeutische Potential beeinflussen.

Compliance und Persistenz

Der Begriff „Medikations-Compliance“ (Synonym: Adhärenz) beschreibt den Vorgang, den Empfehlungen des Verordners bezüglich der zeitlichen Abfolge, der Dosierung und der Frequenz der Einnahme eines Arzneimittels als Patient Folge zu leisten. Medikations-Compliance definiert sich also

als das „Maß, in dem ein Patient sich an das vorgeschriebene Intervall und die Dosierung innerhalb eines Therapieschemas hält“ (International Society for Pharmacoeconomics & Outcomes Research. Special Interest Group “Medication and Compliance” on http://www.ispor.org). Im Fall von Denosumab (XGEVA®) kann diese Compliance als gegeben angenommen werden, da es subkutan verabreicht wird.

Die „Persistenz“ hingegen beschreibt den Vorgang, den Empfehlungen bezüglich der kontinuierlichen Behandlung über einen gegebenen Zeitraum Folge zu leisten. Medikations-Persistenz ist somit definiert als die „Dauer von Beginn bis Absetzen einer Therapie“ (International Society for Pharmacoeconomics & Outcomes Research. Special Interest Group “Medication and Compliance” on http://www.ispor.org).

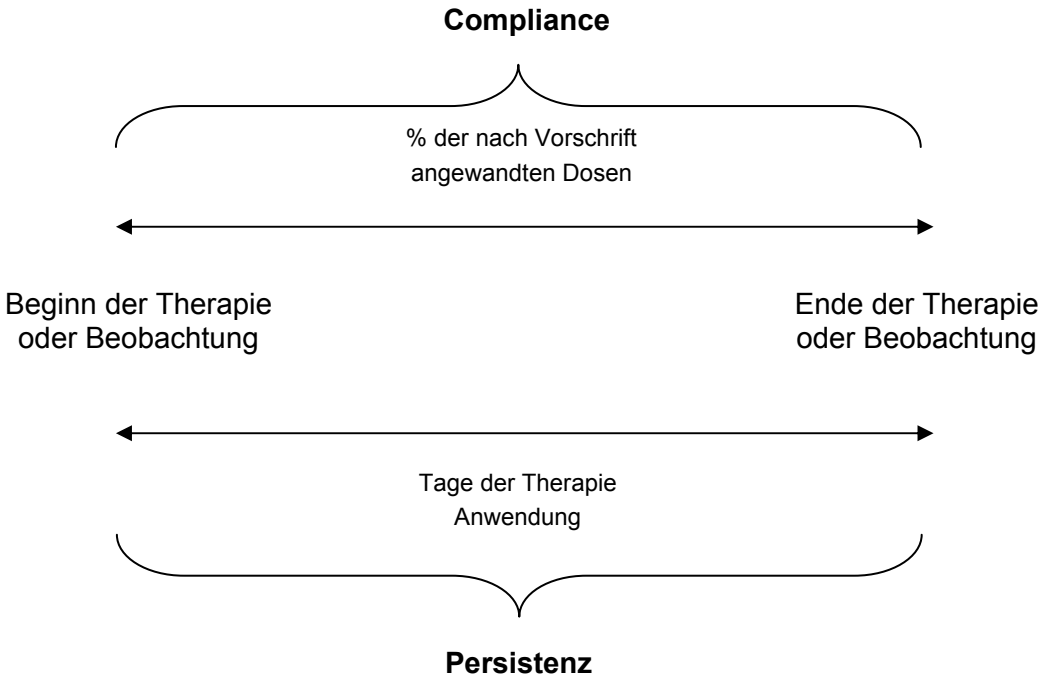

Abbildung 4. Definition von Compliance und Persistenz

Das genaue Ausmaß, in dem mangelnde Compliance und Persistenz die klinische Wirksamkeit eines Medikaments beeinflussen, ist eine komplexe Fragestellung. Aus Sicht der Kostenträger wirkt sich der Einfluss der Medikations-Compliance und –Persistenz auf die Arzneimittelkosten und den Ressourcenverbrauch im Gesundheitswesen oftmals entgegengesetzt aus: Mangelnde Compliance und Persistenz reduzieren in der Regel die Arzneimittelkosten, steigern aber den nachfolgenden Ressourcenverbrauch. Obgleich dieser Zusammenhang nicht notwendigerweise in allen Konstellationen im Gesundheitswesen zutreffen muss, zeigen Daten zum Ressourcenverbrauch aufgrund von SREs, dass SREs zu einer höheren Zahl stationärer Aufenthalte und nachfolgender Prozeduren führen (Lüftner et al. 2011).

Trotz der generell hohen Compliance bei Patienten in onkologischen Indikationen deuten publizierte Daten darauf hin, dass die Persistenz bei intravenös verabreichten Bisphosphonaten signifikant besser ist als bei oralen Präparaten (Mangiapane et al. 2006). Die Einhaltung des zugelassenen Dosierungsschemas korreliert dabei mit dem Auftreten von SREs, was die Bedeutung einer hoher Persistenz (und Compliance) für die Sicherstellung des Behandlungserfolgs unterstreicht. Die Rate skelettbezogener Komplikationen lag z. B. bei der in der Fachinformation empfohlenen Zoledronsäure-Dosierung bei 0,16 Ereignissen pro Monat gegenüber 0,31 Ereignissen bei nicht dieser Empfehlung entsprechenden Zoledronsäure-Regimen und 0,43 Ereignissen ohne Behandlung mit Zoledronsäure (Hatoum et al. 2008).

Systematische erhobene Daten zu Anwendbarkeit, klinischer Wirksamkeit und Sicherheit in der täglichen Routine gemäß aktueller Denosumab (XGEVA®)-Fachinformation liegen derzeit für Deutschland noch nicht vor. Ebenso ist gegenwärtig die Datenlage zum Einsatz in der klinischen Routine bezüglich der Compliance und Persistenz von Denosumab (XGEVA®) im deutschen Gesundheitswesen äußerst begrenzt.

Aus diesem Grund werden in der die vorliegenden nicht-interventionellen Beobachtungsstudie Daten zum tatsächlichen Gebrauch von Denosumab (XGEVA®) bei Patienten erhoben, die gemäß der gegenwärtigen therapeutischen Praxis und den Empfehlungen aus der Fachinformation behandelt werden.

Da Denosumab (XGEVA®) direkt vom behandelten Arzt appliziert wird, spielt die Compliance des Patienten eine sehr untergeordnete Rolle. So ist es das primäre Ziel der Anwendungsbeobachtung, die Persistenz bei Denosumab (XGEVA®) zu beurteilen. Nachfolgend wird ausschließlich der Begriff Persistenz verwendet und zwar als applizierte Dosis im Verhältnis zur Verschreibung und als Zeitraum zwischen dem Ansetzen der Behandlung und dem Ende der Beobachtungsperiode. Die Verwendung des Begriffs Persistenz erfolgt, um klar von der Patienten-Compliance zu unterscheiden.

Dabei können unterschiedliche Behandlungsszenarien wie Patienten unter Chemotherapie (3-wöchentlich/4-wöchentlich) oder Patienten unter antihormoneller Therapie betrachtet werden. Die Untersuchung des Zusammenhangs zwischen Persistenz-Daten und demographischen Daten, Unerwünschte Arzneimittelwirkungen, Krankheitsbild, begleitender Tumor-Therapie oder demographischen Informationen kann zum weitergehenden Verständnis der Persistenz bei Denosumab (XGEVA®) beitragen. Zudem können wichtige Persistenz-Daten für Denosumab (XGEVA®) vor dem Hintergrund patientenbezogener Variablen wie sozio-demographischer und krankheitsbezogener Charakteristika Hinweise liefern, wie die Wirksamkeit bei der Behandlung von SREs in diesen Patientengruppen weiter gesteigert werden kann.

1.5 Hypothesen

In dieser Anwendungsbeobachtung wird keine formale Hypothese getestet. Jedoch wird davon ausgegangen, dass Denosumab (XGEVA®) in der klinischen Routinepraxis gemäß der Fachinformation angewendet wird, d. h. alle vier Wochen als subkutane Injektion in einer Dosis von 120 mg.

2 FRAGESTELLUNG

2.1 Ziele

Ziel dieser Anwendungsbeobachtung ist die Beurteilung der Persistenz bei Denosumab (XGEVA®). Zudem werden Daten zur Demographie, dem Krankheitsbild, der begleitenden Tumor-Therapie und der Krankengeschichte von Patienten mit soliden Tumoren und Knochenmetastasen erhoben. Um Persistenz-Daten in Bezug zu patientenbezogenen Informationen setzen zu können, werden im Rahmen dieser Anwendungsbeobachtung Patientenbeurteilungen erhoben.

Primäres Ziel:

Das primäre Ziel dieser Anwendungsbeobachtung ist die Bewertung der Persistenz nach 24 Wochen bei Patienten mit soliden Tumoren und Knochenmetastasen, die in der klinischen Routine mit Denosumab (XGEVA®) behandelt werden.

Zusätzlich sollen Informationen zu folgenden weiteren Fragestellungen gesammelt werden:

Sekundäre Ziele:

- Bewertung der Persistenz bei Denosumab (XGEVA®) nach 48 Wochen im klinischen Routineeinsatz
- Bewertung der Zeit bis zur Nicht-Persistenz bei Denosumab (XGEVA®) am Ende des Beobachtungzeitraumes
- Beschreibung der primären und sekundären Persistenz-Endpunkte nach Tumorart
- Beschreibung der Demographie, des Krankheitsbildes, der begleitenden Tumor-Therapie, der unerwünschten Arzneimittelwirkungen von Denosumab (XGEVA®) und der Krankengeschichte von Patienten, die in der klinischen Routine mit Denosumab (XGEVA®) behandelt werden
- Beschreibung der Dosis und Frequenz der Kalzium- und Vitamin D-Supplementierung bei Patienten, die in der klinischen Routine mit Denosumab (XGEVA®) behandelt werden

Explorative Ziele:

- Beschreibung der Veränderung der individuellen Schmerz-Scores zwischen der ersten Denosumab (XGEVA®)-Applikation und Woche 24 unter Behandlung mit Denosumab (XGEVA®) im klinischen Routineeinsatz
- Beschreibung der Veränderung der individuellen Schmerzmedikation zwischen der ersten Denosumab (XGEVA®)-Applikation und Woche 24 unter Behandlung mit Denosumab (XGEVA®) im klinischen Routineeinsatz anhand des AQA-Fragebogens (Chung et al, 2009)
- Beschreibung von patientenbezogenen Endpunkten zwischen der ersten Denosumab (XGEVA®)-Applikation und unter Behandlung mit Denosumab (XGEVA®) bis zum Ende des Beoachtungszeitraumes in Form von Patientenbeurteilungen bezüglich Problemen bei Mobilität, Selbstversorgung, alltäglichen Tätigkeiten, Schmerzen/körperlichen Beschwerden und Angst/Depression anhand eines präferenzbasierten Gesundheitsfragebogens zur Lebensqualitätsmessung (EQ-5D) (Brooks R., 1996)
- Beschreibung aller unerwünschter Arzneimittelwirkungen unter Denosumab (XGEVA®)

3 DURCHFÜHRUNG

3.1 Design

In der vorliegenden Anwendungsbeobachtung werden Daten von Patienten ab 18 Jahren mit Knochenmetastasen aufgrund solider Tumore erhoben. Es können Patienten dokumentiert werden, die Denosumab (XGEVA®) gemäß der Fachinformation erhalten. Bei jedem Patienten werden die Daten ab der ersten Dosis Denosumab (XGEVA®) über einen Zeitraum von 52 Wochen erhoben, unabhängig von der Dauer ihrer Behandlung mit Denosumab (XGEVA®). Die Dokumentation schließt Patienten ein, die bereits vor dem Einschluss in diese Anwendungsbeobachtung maximal 2 Denosumab (XGEVA®)-Injektionen erhalten haben, so dass es sich bei dieser Anwendungsbeobachtung sowohl um eine retrospektive als auch prospektive Datenerhebung handelt.

Die Erhebung der Daten erfolgt nicht-interventionell (beobachtend) anhand einer Durchsicht von Krankenakten und mit Hilfe eines elektronisch verfügbaren Prüfbogens (eCRF).

Das vorliegende wissenschaftliche Projekt ist eine Anwendungsbeobachtung im Sinne von §4 Abs. 23 Satz 3 AMG, angezeigt gemäß §67 (6) AMG, in deren Rahmen „Erkenntnisse aus der Behandlung von Personen mit Arzneimitteln gemäß den in der Zulassung festgelegten Angaben für seine Anwendung anhand epidemiologischer Methoden analysiert werden; dabei folgt die Behandlung einschließlich der Diagnose und Überwachung nicht einem vorab festgelegten Prüfplan, sondern ausschließlich der ärztlichen Praxis.“ Die Entscheidung, einen Patienten in eine Anwendungsbeobachtung einzubeziehen, ist von der Entscheidung über die Verordnung des Arzneimittels getrennt. Auch sind keine zusätzlichen

diagnostischen oder therapeutischen Maßnahmen erforderlich als gegenwärtig im Rahmen der Routineversorgung des Patienten vorgesehen sind.

Die Beobachtung kann in 3 Abschnitte eingeteilt werden:

I. Beobachtungsbeginn

II. Beobachtungsphase (Dokumentation zu jeder Denosumab (XGEVA®)-Applikation)

III. Beobachtungsende (z.B. 52 Wochen nach Denosumab (XGEVA®)-Therapiebeginn, unabhängig von der Anzahl der Denosumab (XGEVA®)-Applikationen; bei vorzeitiger Beendigung der Denosumab (XGEVA®)-Therapie: im Todesfall, bei „Lost-to-Follow-up“ oder bei Rückzug der Einverständnis des Patienten. Zur Überprüfung andauernder unerwünschter Arzneimittelwirkungen sollten sämtliche unerwünschte Arzneimittelwirkungen im Zusammenhang mit Denosumab (XGEVA®) weiterhin bis zu 30 Tage, nachdem der Patient die Beobachtung beendet hat, erfasst werden (siehe Abschnitt 6.2).

3.2 Anzahl an Zentren

Voraussichtlich nehmen 80 Zentren an der Anwendungsbeobachtung teil. Die Zentren werden so ausgewählt, dass eine repräsentative geografische Verteilung über das gesamte Bundesgebiet gewährt ist.

3.3 Anzahl an Patienten

In der Beobachtung werden Daten von 1 400 Patienten erfasst. Um eine bundesweite Repräsentativität zu gewährleisten ist die Teilnehmerzahl pro Zentrum auf 15-20 Patienten begrenzt.

3.4 Geplante Projektdauer

Die Patienten sollen innerhalb von 36 Monaten eingeschlossen werden (2012 bis 2015). Der letzte Patient wird das Projekt voraussichtlich Ende 2016 nach einer 52-wöchigen Beobachtungsphase verlassen.

Für den individuellen Patienten dauert die Beobachtung 52 Wochen nach der ersten Anwendung von Denosumab (XGEVA®), oder z.B. bis der Patienten verstirbt, als „Lost-to-Follow-up“ gemeldet wird oder sein Einverständnis widerruft. Die Beobachtungsdauer ist pro Patient auf maximal 52 Wochen begrenzt und unabhängig von einer Weiterführung der Therapie mit Denosumab (XGEVA®).

4 AUSWAHLKRITERIEN

Von den teilnehmenden Ärzten wird erwartet, dass sie ein Screening-Logbuch über alle potenziellen Patienten für die Anwendungsbeobachtung führen, das begrenzte Angaben zu jedem Patienten (einschließlich Alter, Geschlecht) sowie Datum und Ergebnis des Screeningverfahrens (z.B. Einschluss in die Beobachtung, Begründung der mangelnden Eignung oder Ablehnung der Teilnahme) enthält.

Von den teilnehmenden Patienten muss ein schriftliches Einverständnis über die Weitergabe der persönlichen Daten eingeholt werden.

4.1 Patientenkriterien für den Einschluss in die Dokumentation

- Patientenalter mindestens 18 Jahre
- Patientinnen/Patienten mit einem dokumentierten Mamma-, Prostata-, Bronchialkarzinom oder einem anderen soliden Tumor und mit einer dokumentierten Knochenmetastasierung
- Patientinnen/Patienten, die bereits mit Denosumab (XGEVA®) behandelt werden (maximal 2 Denosumab (XGEVA®)-Injektionen vor Einschluss)

- Allgemeinzustand nach ECOG 0-2 (siehe Anhang 11.2)
- Vorliegen des Einverständnisses zur Weitergabe der persönlichen Daten

4.2 Patientenausschlusskriterien für die Dokumentation

- Patientinnen/Patienten mit einem dokumentierten multiplem Myelom
- Patientinnen/Patienten, die länger als 3 Monate mit einer Denosumab (XGEVA®)-Therapie in einer klinischen Studie oder in klinischer Routine behandelt werden
- Patientinnen/Patienten, die länger als 6 Monate mit einer antiresorptiven Therapie (inkl. maximal 2 Denosumab (XGEVA®)-Applikationen innerhalb von < 3 Monaten) in einer klinischen Studie oder in klinischer Routine behandelt werden
- Vorherige Behandlung mit einer Radionuklid-Therapie (z. B. Strontium-98, Samarium-153, Radium-223)
- Gleichzeitige Teilnahme an klinischen Studien, deren Studienziel die Prävention/Behandlung von Knochenmetastasen und SREs ist
- Schwere, nicht behandelte Hypokalzämie (z. B. CTCAE ≥ Grad 3); eine bestehende Hypokalzämie muss vor Beginn der Denosumab (XGEVA®)-Therapie korrigiert werden
- Überempfindlichkeiten gegen den Wirkstoff oder einen der sonstigen Bestandteile der Denosumab (XGEVA®)-Injektionslösung (Patienten mit der seltenen hereditären Fructose-Intoleranz)

5 ABLAUF DER ANWENDUNGSBEOBACHTUNG

Es werden keine Vorgaben zur Behandlung oder den diagnostischen klinischen Maßnahmen gemacht. Für den Einsatz von Denosumab (XGEVA®) ist ausschließlich die Fachinformation maßgeblich.

5.1 Auswahl der Zentren

Die potentiell an der Anwendungsbeobachtung teilnehmenden Zentren werden aufgrund der Schätzung des Patientenaufkommens, Studienerfahrung und der geografischen Lage ausgewählt. Soweit möglich, soll in der Beobachtung ein für Deutschland repräsentatives Kollektiv analysiert werden.

5.2 Identifikation und Auswahl der Patienten

In der Beobachtung werden Daten von 1 400 Patienten erfasst. Um eine bundesweite Repräsentativität zu gewährleisten wird eine Patientenzahl pro Zentrum von 15-20 angestrebt.

Bis zum vorgesehenen Zeitpunkt des Einschlusses des letzten Patienten im Dezember 2015 wurden 1258 Patienten in die Anwendungsbeobachtung aufgenommen.

Das teilnehmende Zentrum selektiert alle potentiellen teilnehmenden Patienten unter Berücksichtigung der Auswahlkriterien und führt ein Screening-Logbuch, in dem auch die Gründe für eine Nichtteilnahme dokumentiert werden (s. Abschnitt 3.3).

Für den Einschluss in die Beobachtung muss das schriftliche Einverständnis des Patienten über die Weitergabe seiner persönlichen Daten vorliegen. Der Patient oder sein gesetzlicher Vertreter muss die Erklärung persönlich unterschreiben und datieren.

Jedem eingeschlossenen Patienten wird eine eindeutige Patienten-Identifikationsnummer zugewiesen, die über die gesamte Projektlaufzeit unverändert gültig ist. Diese Nummer dient dazu, den Patienten

während des gesamten Projekts zu identifizieren und muss auf allen projektbezogenen Dokumenten, die sich auf diesen Patienten beziehen, angegeben werden.

Die einzigartige Patienten-ID ist eine 11-stellige Zahl. Die ersten drei Stellen geben die firmeninterne Projektnummer (312), die Stellen 4-8 die Zentrumsnummer und die Stellen 9-11 die Nummer des Patienten an diesem Zentrum wieder. Zum Beispiel wäre der erste eingeschlossene Patient an Zentrum 26001 Patient 31226001001.

5.3 Sammlung von Patientendaten

Nach Aktivierung des Zentrums werden die Daten aus den Krankenakten entnommen und in einen elektronischen, web-basierten Dokumentationsbogen (eCRF) erfasst.

5.4 Formular für die Patientenregistrierung

Die Patienten werden online im web-basierten Dokumentationsbogen (eCRF) registriert.

5.5 Datenerhebungsbogen

Es werden in dieser Anwendungsbeobachtung sowohl retrospektiv als auch prospektiv Daten zur Therapie mit Denosumab (XGEVA®) erhoben. D. h., es werden auch die Daten von maximal 2 Denosumab (XGEVA®)-Applikationen dokumentiert, die vor der Entscheidung zur Teilnahme an dieser Beobachtung verabreicht wurden (siehe 5.5.2).

Diese Angaben beinhalten Folgendes (sofern verfügbar und im Rahmen der klinischen Standardversorgung erfasst):

5.5.1 Beobachtungsbeginn

Nach Einschluss eines Patienten werden die Angaben zu Beobachtungsbeginn (vor der Behandlung mit Denosumab (XGEVA®)) aus seinen Krankenunterlagen durch den teilnehmenden Arzt oder einen Beauftragten in einem elektronischen CRF (eCRF) dokumentiert. Als Werte zu Beobachtungsbeginn gelten die zuletzt eingeholten Werte vor Beginn der Behandlung mit Denosumab (XGEVA®).

Diese Angaben beinhalten Folgendes (sofern verfügbar und im Rahmen der klinischen Standardversorgung erfasst):

- Spezialgebiet des Arztes und Art des Zentrums (Klinik/Praxis, Anzahl der behandelten Knochenmetastasen-Patienten pro Jahr)
- Bestätigung und Datum der schriftlichen Zustimmung des Patienten zur Weitergabe persönlicher Daten
- Stammdaten und Anamnese
    - Geburtsjahr, Geschlecht
    - Tumorerkrankung mit Datum und Staging bei Erstdiagnose(TNM)
    - Datum der Erstdiagnose einer Metastasierung und Lokalisation aller Metastasen (incl. Knochen)
    - Bei Mammakarzinom-Patientinnen: Hormonrezeptor-Status, Her-2/neu-Status zum Zeitpunkt der Erstdiagnose der **metastasierten** Erkrankung
    - Bei Bronchialkarzinom-Patienten: Histologie (NSCLC, SCLC) zum Zeitpunkt der Erstdiagnose der **metastasierten** Erkrankung
    - Skelettale Komplikationen oder Hyperkalzämie in der Anamnese

        - Therapie skelettaler Komplikationen (Strahlentherapie, chirurgischer Eingriff, antiresorptive Therapie, etc.; Anzahl der Zyklen, Regime, Beginn und Ende, bestes Ansprechen)
    - Vorangegangene antineoplastische Behandlungen (ausschließlich für die **metastasierte** Erkrankung)
        - Tumortherapie (Strahlentherapie, chirurgischer Eingriff, Chemotherapie, antihormonelle Therapie, etc.; Anzahl der Zyklen, Regime, Beginn und Ende, bestes Ansprechen)
    - Allgemeinzustand nach ECOG (siehe 11.2)
    - Relevante Begleiterkrankungen, Charlson-Score für Komorbiditäten
- Kalzium- und Kreatininspiegel im Serum (ggf. Kalkulation der Kreatinin-Clearance)
- Vitamin D-Gabe und Kalziumapplikation
- Schmerzscore mittels VAS-Fragebogen (siehe 11.4.1)
- Schmerzmedikation mittels AQA-Fragebogen (siehe 11.4.2)
- Patientenbezogene Endpunkte: Lebensqualität mittels Gesundheitsfragebogen (EQ-5D) (siehe 11.4.3)

5.5.2 Beobachtungsphase

Die Daten, die nach der ersten Behandlung mit Denosumab (XGEVA®) und jeder nachfolgenden Behandlung mit Denosumab (XGEVA®) eingeholt werden, werden ebenfalls in einem elektronischen CRF erfasst. Die Beobachtungsphase beschränkt sich auf höchstens 52 Wochen.

Es werden in dieser Anwendungsbeobachtung sowohl retrospektiv als auch prospektiv Daten zur Therapie mit Denosumab (XGEVA®) erhoben, d. h., dass auch die Daten von maximal 2 Denosumab (XGEVA®)-Applikationen dokumentiert werden müssen, die vor der Entscheidung zur Teilnahme an dieser Beobachtung verabreicht wurden (siehe 4.1).

Diese Angaben beinhalten Folgendes und gelten jeweils für jedes Therapieintervall (sofern verfügbar und im Rahmen der klinischen Standardversorgung erfasst):

- Applikation
    - Dosis von Denosumab (XGEVA®) und Datum der Applikation
    - Applizierende Person (d.h. medizinisches Fachpersonal (im behandelnden Krankenhaus), Hausarzt (in seiner Praxis), medizinisches Fachpersonal, andere)
- Grund (Gründe) für die Nicht-Verabreichung, die Dosisänderung oder ein Absetzen von Denosumab (XGEVA®)
- Informationen zu meldepflichtigen Ereignissen (siehe 6.)
- Labor: Kalziumspiegel, Kreatinin im Serum
- Tumortherapie (Strahlentherapie, chirurgischer Eingriff, Chemotherapie, antihormonelle Therapie, etc.; Anzahl der Zyklen, Regime, Beginn und Ende, bestes Ansprechen)
- Begleitmedikation
    - Vitamin D-Gabe und Kalziumapplikation

- Schmerzscore mittels VAS-Fragebogen bei jeder Denosumab (XGEVA®)-Applikation bis max. 24 Wochen nach der ersten Behandlung mit Denosumab (XGEVA®) (siehe 11.4.1)
- Schmerzmedikation mittels AQA-Fragebogen bei jeder Denosumab (XGEVA®)-Applikation bis max. 24 Wochen nach der ersten Behandlung mit Denosumab (XGEVA®) (siehe 11.4.2)
- Patientenbezogene Endpunkte: Lebensqualität mittels Gesundheitsfragebogen (EQ-5D) jeweils zur 4., 7. und 10. Denosumab (XGEVA®)-Applikation bis max. 52 Wochen nach der ersten Behandlung mit Denosumab (XGEVA®) (siehe 11.4.3)

5.5.3 Beobachtungsende

Zusätzlich zur den oben beschriebenen Datenerhebungen der Beobachtungsphase ist zum Ende des Beobachtungszeitraums eine spezifische Dokumentation erforderlich.

- Datum der Beendigung der Beobachtung und Grund:
    - Abschluss des 52-Wochen Beobachtungszeitraums
    - Tod (mit Datum und primäre Todesursache)
    - „Lost-to-Follow-up“
    - Widerruf des Einverständniserklärung zur Datenweitergabe
    - Informationen zu meldepflichtigen Ereignissen (siehe 6.)
    - administrative Entscheidung
    - Sonstige
- aktuelle antineoplastische Therapie
- Kalzium- und Kreatininspiegel im Serum
- Nach 52 Wochen bzw. Beendigung der Denosumab (XGEVA®) Therapie: Patientenbezogene Endpunkte: Lebensqualität mittels Gesundheitsfragebogen (EQ-5D) (siehe 11.4.3)

5.6 Beendigung der Teilnahme von Patienten

Die Patienten haben das Recht, ihr Einverständnis zur Datenweitergabe jederzeit und gleichgültig aus welchem Grund zu widerrufen, ohne dass sich daraus nachteilige Auswirkungen auf ihre medizinische Versorgung durch den Arzt oder in der Einrichtung ergeben.

Widerruf des Einverständnisses bedeutet, dass die Patientendaten nicht weiter in der Auswertung berücksichtigt werden können. Wenn ein Patient sein Einverständnis vollständig widerruft, werden keine weiteren Daten erhoben.

Bei bereits eingeschlossenen Patienten, bei denen später festgestellt wird, dass sie ein oder mehrere Ausschlusskriterien der Dokumentation erfüllen, wird die Teilnahme an der Beobachtung beendet.

5.7 Festgelegte Patientenzahl

Patienten, die die Beobachtung aus irgendeinem Grund vor dem Abschluss des Beobachtungszeitraums beenden oder als „Lost-to-Follow-up“ gelten, werden nicht ersetzt.

6 SAMMLUNG, DOKUMENTATION UND MELDUNG VON INFORMATIONEN ZUR ARZNEIMITTELSICHERHEIT

Allgemeine Informationen bezüglich des Berichtens von Unerwünschten Ereignissen/ Unerwünschten Arzneimittelwirkungen:

Nur Unerwünschte Arzneimittelwirkungen, andere arzneimittelsicherheitsrelevante Ereignisse und Produktbeschwerden, die ein Amgen-Produkt betreffen, sind zu berichten.

Unerwünschte Arzneimittelwirkungen, die sich vor Verabreichung eines Amgen-Produktes ereigneten, sind nicht zu berichten.

6.1 Definitionen arzneimittelsicherheitsrelevanter Ereignisse

6.1.1 Definition eines Unerwünschten Ereignisses

Ein unerwünschtes Ereignis (UE) ist jedes nachteilige Vorkommnis bei einem Patienten, dem (ein) pharmazeutische(s) Produkt(e) verabreicht wurde(n) und das nicht notwendigerweise mit der Behandlung in Zusammenhang steht.

Ein UE kann somit jedes nachteilige und unbeabsichtigte Anzeichen (einschließlich z.B. eines abweichenden Laborwertes), Symptom oder Erkrankung sein, welches zeitlich mit dem Gebrauch eines Arzneimittels assoziiert ist, unabhängig davon, ob ein Kausalzusammenhang vermutet wird.

Die Definition schließt folgende Ereignisse mit ein:

- Verschlechterung einer bereits vorbestehenden Symptomatik
- Ereignisse, die durch einen Medikationsfehler oder der Überdosierung von Arzneimittel(n), ob unabsichtlich oder absichtlich, zustande kamen,
- Ereignisse, die durch einen Medikamentenmissbrauch bedingt wurden
- Ereignisse, die mit der Unterbrechung der Verabreichung/Einnahme eines Medikaments/ mehrerer Medikamente in Verbindung stehen (z.B. Auftreten neuer Symptome)
- Jedes Ausbleiben oder jeder Verlust der erwarteten Wirkung des Produkts/der Produkte

6.1.1.1 Unerwünschte Arzneimittelwirkungen (UAW)

UE, für die ein Zusammenhang mit der Gabe eines Amgen-Produkts als möglich erachtet wird, werden als Unerwünschte Arzneimittelwirkungen (UAW) klassifiziert.

Es liegt in der Verantwortung des Arztes, vor der Meldung an Amgen zu beurteilen, ob ein Ereignis mit einem Amgen-Produkt im Zusammenhang steht.

6.1.2 Definition eines Schwerwiegenden Unerwünschten Ereignisses

Ein schwerwiegendes Unerwünschtes Ereignis (SUE) ist ein Unerwünschtes Ereignis (entsprechend der obigen Definition), welches eines oder mehrere der folgenden Kriterien erfüllt:

- tödlich
- lebensbedrohend (unmittelbare Gefahr für das Leben des Patienten)
- stationäre Behandlung oder Verlängerung einer stationären Behandlung erforderlich

- bleibende oder schwerwiegende Behinderung/Invalidität
- kongenitale Anomalien/ Geburtsfehler
- „medizinisch bedeutsam“, welches die zuvor genannten Kriterien nicht erfüllt

Eine stationäre Behandlung, die der behördlich festgelegten Definition für „schwerwiegend“ entspricht, ist jede stationäre Aufnahme, die mindestens einen Krankenhausaufenthalt über eine Nacht erforderlich macht.

„Medizinisch bedeutsam“ bezieht sich auf wichtige medizinische Ereignisse, die nicht unmittelbar lebensbedrohend sind oder den Tod oder einen Krankenhausaufenthalt zur Folge haben, die jedoch den Patienten in Gefahr bringen oder eine Intervention zur Vermeidung der oben genannten Ereignisse erforderlich machen. Solche Ereignisse können zum Beispiel allergische Bronchospasmen, Krampfanfälle, Dyskrasien des Blutes, arzneimittelinduzierte Leberschädigung oder Ereignisse, die einen Aufenthalt in der Notaufnahme, einen ambulanten Eingriff oder eine dringende Intervention nötig machen, sein.

In dieser Anwendungsbeobachtung ist die **Kieferosteonekrose (ONJ)** als ein Ereignis von speziellem Interesse definiert. Deshalb sind alle auftretenden Verdachtsfälle von Kieferosteonekrosen wie SUAWs zu dokumentieren, unabhängig von dem Vorhandensein eines „schwerwiegend“-Kriteriums und auch unabhängig von einem Verdacht auf einen Kausalzusammenhang mit der Denosumab (XGEVA®)-Therapie.

6.1.2.1 Schwerwiegende Unerwünschte Arzneimittelwirkungen (SUAW)

SUEs, für die ein Zusammenhang mit der Gabe von Amgen-Produkt(en) als möglich erachtet wird, werden als Schwerwiegende Unerwünschte Arzneimittelwirkungen (SUAW) klassifiziert.

Es liegt in der Verantwortung des Arztes, vor der Meldung an Amgen zu beurteilen, ob ein Ereignis mit einem Amgen-Produkt in Zusammenhang steht.

6.1.3 Definition von anderen arzneimittelsicherheitsrelevanten Ereignissen

Andere arzneimittelsicherheitsrelevante Ereignisse sind unter anderem:

- Medikationsfehler, Überdosierung, Fehlgebrauch, Missbrauch, gleich ob unabsichtlich oder beabsichtigt, die (ein) Amgen-Produkt(e) betreffen, unabhängig davon ob im Zusammenhang mit einem UAW und/oder SUAW
- Exposition während Schwangerschaft und Stillzeit, unabhängig davon ob im Zusammenhang mit einem UAW und/oder SUAW
- Übertragung infektiösen Materials, unabhängig davon ob im Zusammenhang mit einem UAW und/oder SUAW
- Berichte über „nicht-bestimmungsgemäßen“ Gebrauch, Off-label use eingeschlossen, sofern dieser unabhängig davon ob in Zusammenhang mit einem UAW und/oder SUAW steht

6.1.4 Definition einer Produktbeschwerde

Eine Produktbeschwerde bezeichnet jegliche schriftliche, elektronische oder mündliche Kommunikation, die den Vorwurf erhebt, bei einem bereits für den Vertrieb freigegebenen Arzneimittel oder

Medizinprodukt lägen Mängel in Bezug auf Identität, Qualität, Haltbarkeit, Funktionsfähigkeit, Sicherheit, Effektivität oder Wirksamkeit vor. Dies schließt alle Komponenten ein, die gemeinsam mit dem Produkt vertrieben werden, wie die Sekundärverpackung und die Primärverpackung des Produkts, das Verabreichungssystem, die Etikettierung, die Packungsbeilagen etc.

Produktbeschwerden können unter anderem Probleme zu Folgendem beinhalten:

- Äußere Erscheinung (z.B. Brüche, Risse, Farbe, Partikel, Geruch)
- Etikettierung (z.B. fehlend, zerrissen, beschmutzt)
- Haltbarkeit (z.B. Stabilitätsprobleme)
- Geöffnete Umverpackung
- Schädigung des Medizinproduktes (z.B. Fertigspritze mit verbogener Nadel)
- Produktetikettierung für den Kunden nicht verständlich
- Der Kunde kann das Produkt nicht erfolgreich anwenden, inklusive nur teilweiser oder nur unvollständiger Applikation (z.B. defektes System zur Verabreichung (Spritze))

6.2 Meldepflichtige Ereignisse und Berichtszeitraum

Es liegt in der Verantwortung des Arztes, alle UAW, SUAW, Verdachtsfälle von Kieferosteonekrose (ONJ), Produktbeschwerden und anderen arzneimittelsicherheitsrelevanten Ereignissen für Denosumab (XGEVA®), die von ihm im Laufe der Studie beobachtet oder von einem Patienten berichtet wurden und die ab der ersten im Rahmen dieser Anwendungsbeobachtung dokumentierten Denosumab (XGEVA®) Gabe, bis zur letzten Studienvisite aufgetreten sind, in der Patientenakte zu dokumentieren und unter Verwendung der im eCRF eingebundenen Sektion „Meldepflichtige Ereignisse“ an Amgen zu berichten. Im Falle eines technischen Ausfalls des elektronischen Datenerfassungssystem hat die Meldung an Amgen in Papierform zu erfolgen. Ein Beispiel eines Berichtsbogens für Unerwünschte Arzneimittelwirkungen befindet sich unter 11.5.1; unter 11.5.2 und 11.5.3 wurde ein Beispiel eines Meldebogens für Schwangerschaft und Stillzeit angehängt. Meldepflichtige Ereignisse und Berichtszeitraum siehe Tabelle 2:

Tabelle 2. Berichtszeitraum für meldepflichtige Ereignisse

Berichtsart	Beschreibung	Berichtszeitraum
SUAW	Initiale Berichte oder Fallberichte aufgrund von Zusatzinformationen (Follow-up Berichte) für SUAW	Innerhalb eines Arbeitstages nach Bekanntwerden
Andere arzneimittel-sicherheitsrelevante Ereignisse	Initiale Berichte oder Fallberichte aufgrund von Zusatzinformationen (Follow-up Berichte)	Innerhalb eines Arbeitstages nach Bekanntwerden
Verdachtsfälle von Kieferosteo-nekrosen	Initiale Berichte oder Fallberichte aufgrund von Zusatzinformationen (Follow-up Berichte)zu einem Verdachtsfall einer Kieferosteonekrose (ONJ), unabhängig davon ob vom behandelnden Arzt als schwerwiegend oder als im Kausalzusammenhang mit Denosumab (XGEVA®) stehend	Innerhalb eines Arbeitstages nach Bekanntwerden

Berichtsart	Beschreibung	Berichtszeitraum
	beurteilt.	
Produktbeschwerden	Initiale Berichte oder Fallberichte aufgrund von Zusatzinformationen (Follow-up Berichte) für alle Produktbeschwerden	Innerhalb eines Arbeitstages nach Bekanntwerden
Schwangerschaft/ Stillzeit	• Initiale Berichte oder Fallberichte aufgrund von Zusatzinformationen (Follow-up Berichte) bei schwangeren/stillenden Frauen während der Einnahme/Anwendung eines Amgen-Produkts • Initiale Berichte oder Fallberichte aufgrund von Zusatzinformationen (Follow-up Berichte) bei männlichen Partnern von schwangeren/stillenden Frauen, die ein Amgen-Produkt anwenden/einnehmen	Innerhalb eines Arbeitstages nach Bekanntwerden
Weitere UAW	Initiale Berichte oder Fallberichte aufgrund von Zusatzinformationen (Follow-up Berichte) nicht schwerwiegender Ereignisse	Innerhalb von 60 Kalendertagen nach Kenntniserlangung durch den Arzt. Diese Anforderung gilt rückwirkend nur für die ab dem 02. Juli 2012 zur Kenntnis genommenen UAWs, diese sind innerhalb von 60 Kalendertagen nach Gültigkeit der Beobachtungsplanversion Nr. 4 per Berichtsbogen für Unerwünschte Arzneimittelwirkungen (11.5.1) zu melden.

Der Arzt wird unter Umständen gebeten, weitere Informationen zur Verfügung zu stellen, welche Entlassungsbriefe oder Auszüge aus der Patientenakte mit einschließen können.

Jeder Verdachtsfall einer Kieferosteonekrose (ONJ) wird einem unabhängigen „Adjudication Committee“ vorgelegt, um eine möglichst einheitliche Einordnung von Kieferosteonekrose (ONJ) zu gewährleisten. Dazu können gegebenenfalls weitere medizinische Informationen benötigt werden. Sollte dies der Fall sein, hat Amgen die Möglichkeit im jeweiligen Zentrum mittels spezifischer Nachfragen die entsprechenden Informationen einzuholen, um diese dem unabhängigen „Adjudication Committee“ für eine abschließende Beurteilung der Kieferosteonekrose (ONJ) zur Verfügung zu stellen.

Die bereitgestellten, das Ereignis betreffenden Informationen müssen mit den im Fallberichtsbogen der Studie (Case Report Form, CRF), in dem die Daten zur Arzneimittelsicherheit ebenfalls erfasst werden müssen, dokumentierten übereinstimmen (z.B. CRF-Seite „Zusammenfassung Unerwünschte Ereignisse“).

Der Arzt ist für die medizinische Betreuung der Patienten, die ein Unerwünschtes Ereignis erfahren haben, vom Zeitpunkt des Bekanntwerdens bis zum Auskurieren oder bis zur Stabilisierung verantwortlich.

In Übereinstimmung mit den Richtlinien für Pharmakovigilanz und der lokalen Gesetzgebung wird Amgen, wenn erforderlich, UAW und SUAW an Regulierungsbehörden, Ärzte/Einrichtungen, und den zuständigen Ethikkommissionen berichten.

Der Arzt wird in Übereinstimmung mit lokalen Verfahren und Gesetzen allen zuständigen Stellen z.B. (zuständige Ethikkommissionen über (S)UAW, die im Zentrum auftraten und andere UE-Berichte, welche von Amgen zur Verfügung gestellt werden benachrichtigen.

6.2.1 Von der Meldepflicht ausgenommene arzneimittelsicherheitsrelevante Informationen

In dieser Anwendungsbeobachtung werden keine unerwünschten Ereignisse gesammelt, die nicht in einem Zusammenhang mit Denosumab (XGEVA®) stehen.

Denosumab (XGEVA®) besitzt ein etabliertes Sicherheitsprofil mit umfangreicher, mehrjähriger Erfahrung nach der Markteinführung. In dieser Anwendungsbeobachtung ist es daher angemessen, nur unerwünschte Arzneimittelwirkungen zu sammeln, die nach Einschätzung des behandelnden Arztes mit Denosumab (XGEVA®) in Zusammenhang stehen, sowie Produktbeschwerden und andere arzneimittelsicherheitsrelevante Ereignisse zu erfassen (s.o.).

Vor dem Hintergrund des wichtigen identifizierten Risikos der Kieferosteonekrose (ONJ) werden in dieser Anwendungsbeobachtung alle Verdachtsfälle von ONJ unabhängig des vom Arzt eingeschätzten Zusammenhangs mit Denosumab (XGEVA®) erfasst. Alle nicht im Zusammenhang stehenden Todesfälle wurden und werden in der eCRF-Sektion zum Studienende dokumentiert, zudem haben bereits 90% der Patienten die Beobachtungsstudie zum Zeitpunkt dieser Änderung zum Beobachtungsplan (Amendment) abgeschlossen.

7 BIOMETRISCHE PLANUNG UND AUSWERTUNG

7.1 Design

Diese Studie wird als multizentrische, retrospektive und prospektive Anwendungsbeobachtung gemäß § 4(23) Satz 3 des AMG durchgeführt.

Patienten, die die Einschlusskriterien erfüllen, sind für die Beobachtung und Dokumentation im Rahmen dieser Anwendungsbeobachtung geeignet. Die Daten werden bei jedem Patienten ab der ersten Anwendung von Denosumab (XGEVA®) über einen Zeitraum von maximal 52 Wochen erhoben.

7.2 Messparameter für die Ergebnisse der Beobachtung

Primäres Zielkriterium:

- Persistenz (ja/nein) einer Denosumab (XGEVA®)-Therapie nach 24 Wochen – nach 24 Wochen gilt ein Patient dann als „persistent“ unter einer Denosumab (XGEVA®)-Therapie, wenn er mindestens 6 Denosumab (XGEVA®)-Injektionen im Abstand von jeweils nicht mehr als 4 Wochen plus 7 Tagen erhalten hat.

Sekundäre Zielkriterien:

- Persistenz (ja/nein) einer Denosumab (XGEVA®)-Therapie nach 48 Wochen – nach 48 Wochen gilt ein Patient dann als „persistent“ unter einer Denosumab (XGEVA®)-Therapie, wenn er mindestens 12 Denosumab (XGEVA®)-Injektionen im Abstand von jeweils nicht mehr als 4 Wochen plus 7 Tagen erhalten hat.
- Die Zeit bis zur Nicht-Persistenz wird ermittelt als die Zeit in Tagen zwischen der ersten Injektion und dem Tag der letzten Injektion im Zeitraum, in dem der Patient noch als persistent klassifiziert wurde, plus 4 Wochen (max. 28 Tage).
- Primäre und sekundäre Persistenz-Endpunkte nach Tumorart – die Auswertung der Endpunkte wird für jede Tumorart separat durchgeführt.
- Patientencharakteristika vor Patienteneinschluss zur Beschreibung des Patientenkollektives, das mit Denosumab (XGEVA®) in der klinischen Routine behandelt wird, und der Bezug zur Persistenz/Nicht-Persistenz
- Begleitende Tumor-Therapie, die unerwünschten Arzneimittelwirkungen von Denosumab (XGEVA®) und die Krankengeschichte von Patienten, die in der klinischen Routine mit Denosumab (XGEVA®) behandelt werden, und der Bezug zur Persistenz/Nicht-Persistenz
- Dosis und Frequenz der Einnahme von Kalzium- und Vitamin D-haltigen Präparaten vor und während der gesamten Behandlungszeit mit Denosumab (XGEVA®)

Explorative Zielkriterien:

- Veränderung des Schmerz-Scores auf einer 10-Punkte Visuellen Analog Skala (VAS) im Therapieverlauf, beginnend mit der ersten Denosumab (XGEVA®)-Applikation und jeder weiteren bis zu 24 Wochen lang (oder bis zum Ende des Beobachtungszeitraums, je nachdem was früher eintritt)
- Veränderungen der Schmerzmedikation mittels einer 8-Punkte Skala (AQA) im Therapieverlauf, beginnend mit der ersten Denosumab (XGEVA®)-Applikation und jeder weiteren Applikation bis zu 24 Wochen lang (oder bis zum Ende des Beobachtungszeitraums, je nachdem was früher eintritt)
- Messung der Lebensqualität mittels eines präferenzbasierten Gesundheitsfragebogen (EQ-5D) beginnend mit der ersten Denosumab (XGEVA®)-Applikation und jeweils zur 4., 7. und 10. Denosumab (XGEVA®)-Applikation bis zur Woche 52 (oder bis zum Ende des Beobachtungszeitraums, je nachdem was früher eintritt)

Unerwünschte Arzneimittelwirkungen beginnend mit der ersten Denosumab (XGEVA®)-Applikation und nach jeder weiteren Applikation von Denosumab (XGEVA®) bis zur Woche 52 (oder bis zum Ende des Beobachtungszeitraums, je nachdem was früher eintritt.

7.3 Subgruppen/Kovariate

Folgende Subgruppen (Tumorarten) werden im Rahmen der Studie untersucht:

- Patienten mit Prostatakarzinom
- Patienten mit Mammakarzinom
- Patienten mit Bronchialkarzinom
- Patienten mit anderen malignen soliden Tumoren

7.4 Überlegungen zum Stichprobenumfang

In dieser Studie werden keine formalen Hypothesen statistisch getestet. Das Ziel ist es, statistische Schätzer für Persistenzraten nach 24 und 48 Wochen (primäres und sekundäres Zielkriterium) bei Patienten mit malignen, soliden Tumoren und Knochenmetastasen zu bestimmen, die gemäß klinischer Routine mit Denosumab (XGEVA®) behandelt werden.

Insgesamt sollen ca. 1 400 Patienten in ca. 80 Zentren in Deutschland in die Studie eingeschlossen werden. Durch eine repräsentative Auswahl der Zentren und ohne Ausschluss bestimmter schwieriger Patienten soll ein möglicher Selektionsbias minimiert werden und die Genauigkeit der Schätzung sichergestellt werden.

Die Rekrutierungszeit wird voraussichtlich 3 Jahre betragen und jeder Patient wird für maximal 52 Wochen nachbeobachtet.

Die primäre Analyse wird deskriptiv sein, die Fallzahl basiert daher nicht auf Powerüberlegungen, sondern auf einer angenommenen Präzision für die Inzidenzrate von Patienten mit fortdauernder Denosumab (XGEVA®) Behandlung, insgesamt und stratifiziert nach Tumorart.

Es wird erwartet, dass die Tumorarten Mammakarzinom, Prostatakarzinom, Bronchialkarzinom und andere maligne, solide Tumoren ca. jeweils 35%, 35%, 20% bzw. 10% aller eingeschlossenen Patienten ausmachen. Für die verschiedenen Tumorarten werden unterschiedliche Drop-out-Raten nach 24 und 48 Wochen angenommen: Für Patientinnen mit einem Mammakarzinom wird eine Drop-out Rate von 15% nach 24 Wochen und 30% nach 48 Wochen angenommen, für Patienten mit einem Prostatakarzinom von 25% bzw. 50% und für Patienten mit einem Bronchialkarzinom und anderen soliden Tumoren von 50% bzw. 90%.

Die vorgeschlagene Fallzahl basiert auf dem Ansatz, das 95% Konfidenzintervall (KI) zur geschätzten Persistenzrate mit einer vorgegebenen Breite (= Präzision) angeben zu können. Die Anzahl persistierender Patienten wird unter Ausschluss der Drop-out- Patienten berechnet. Eine Präzision (die halbe Breite des 95% KI) von 3,1% für das primäre Zielkriterium in der Gesamtpopulation wird als angemessen angesehen und resultiert in einer Fallzahl von ca. 1 400 Patienten bei einem angenommenen Punktschätzer von 60% für die Anzahl Patienten, die nach 24 Wochen noch mit XGEVA® behandelt werden (siehe Tabelle 1).

Diese Fallzahl erlaubt eine Schätzung des sekundären Zielkriteriums - Patienten, die nach 48 Wochen noch mit Denosumab (XGEVA®) behandelt werden – mit einer Präzision von 3,6% bei einem angenommenen Punktschätzer von 30% und einer Drop-out-Rate von insgesamt 55% (siehe Tabelle 2).

Tabelle 1 Anzahl Patienten nach Tumortypen für die 24 Wochen-Persistenzrate von Denosumab (XGEVA®) (Normalapproximation)

	Erwartete Prävalenz in der eingeschlossenen Patienten Population (%)	Erwartete Fallzahl	Erwartete Drop-out Rate nach 24 Wochen (%)	Erwartete Anzahl auswertbarer Patienten nach 24 Wochen	Approximative Präzision(%) (halbe Breite des 95% Konfidenzintervalls bei einer 60%igen Persistenzrate)	Approximatives 95% Konfidenz-intervall
Prostatakarzinom	35	490	25	365	5,0	(55,0, 65,0)
Mammakarzinom	35	490	15	415	4,7	(55,3, 64,7)
Bronchialkarzinom	20	280	50	140	8,1	(51,9, 68,1)
Andere solide Tumoren	10	140	50	70	11,5	(48,5, 71,5)
Gesamt	100	1400	29	990	3,1	(56,9, 63,1)

Tabelle 2 Anzahl Patienten nach Tumortypen für die 48 Wochen-Persistenzrate von Denosumab (XGEVA®) (Normalapproximation)

	Erwartete Prävalenz in der eingeschlossenen Patienten Population (%)	Erwartete Fallzahl	Erwartete Drop-out Rate nach 48 Wochen (%)	Erwartete Anzahl auswertbarer Patienten nach 48 Wochen	Approximative Präzision(%) (halbe Breite des 95% Konfidenzintervalls bei einer 30%igen Persistenzrate)	Approximatives 95% Konfidenz-intervall
Prostatakarzinom	35	490	50	245	5,7	(24,3, 35,7)
Mammakarzinom	35	490	30	340	4,9	(25,1, 34,9)
Bronchialkarzinom	20	280	90	22	19,1	(10,9, 49,1)
Andere solide Tumore	10	140	90	22	19,1	(10,9, 49,1)
Gesamt	100	1400	55	629	3,6	(26,4, 33,6)

7.5 Zugang zu den Behandlungszuordnungen der einzelnen Patienten

Randomisierung und Entblindungsmaßnahmen treffen für dieses Design nicht zu. Die elektronischen Prüfbögen (eCRFs) werden ausschließlich mit Hilfe einer eindeutigen Patientennummer identifiziert.

7.6 Zwischenanalyse und Leitlinien für eine vorzeitige Beendigung

Die Durchführung einer Zwischenauswertung ist geplant, wenn 25% der eingeschlossenen Patienten 24 Wochen im Rahmen der Anwendungsbeobachtung beobachtet wurden. Die erste Zwischenauswertung wird auf der Basis vollständig geprüfter und bereinigter Daten durchgeführt. Die weitere Studiendurchführung wird durch die Zwischenauswertung nicht beeinflusst.

Sollte die Datenqualität bei der Zwischenauswertung gering sein, wird ein Corrective and Preventive Action (CAPA) Plan erstellt.

7.7 Geplante Analysemethoden

Das grundlegende Ziel dieser retrospektiven und prospektiven Beobachtungsstudie ist es, die Persistenz der Behandlung mit XGEVA® gemäß der Fachinformation in der ärztlichen Praxis in Deutschland zu zeigen. Aus diesem Grund sind alle statistischen Analysen in dieser Studie als deskriptiv anzusehen und basieren auf dem Full Analysis Set (FAS). Es werden keine formalen Hypothesen statistisch getestet. Schätzung der Persistenzraten schließen solche Patienten aus, die vor dem Erreichen von 24 bzw. 48 Wochen Beobachtungszeit gestorben sind. Der Einfluss auf die Persistenz von Patienten, die ihr Einverständnis zurückgenommen oder Lost to follow up sind, wird in einer Sensitivitätsanalyse geklärt.

Das primäre Zielkriterium der Studie ist die Schätzung (95% KI) der Anzahl Patienten, die nach 24 Wochen persistent in Bezug auf die Behandlung mit Denosumab (XGEVA®) sind, wobei ein Patient dann als persistent in Bezug auf die Behandlung mit Denosumab (XGEVA®) nach 24 Wochen gilt, wenn er mindestens 6 Denosumab (XGEVA®) -Injektionen in einem Abstand von nicht mehr als 4 Wochen plus 7 Tage erhalten hat.

Der sekundäre Endpunkt der Studie ist die Schätzung (95% KI) der Anzahl Patienten, die nach 48 Wochen persistent in Bezug auf die Behandlung mit Denosumab (XGEVA®) sind, wobei ein Patient dann als persistent in Bezug auf die Behandlung mit Denosumab (XGEVA®) nach 48 Wochen gilt, wenn er mindestens 12 Denosumab (XGEVA®)-Injektionen in einem Abstand von nicht mehr als 4 Wochen plus 7 Tage erhalten hat.

Deskriptive statistische Auswertungen werden für alle Parameter erstellt, sowohl für das Gesamtkollektiv als auch stratifiziert nach Subgruppen bzw. Kovariaten.

Als Subgruppen bzw. Kovariate sind definiert:

- Tumorart (Mammakarzinom, Prostatakarzinom, Bronchialkarzinom, andere solide Tumoren)
- Vorherige antiresorptive Therapie (ja/nein)
- Art der systemischen antineoplastischen Therapie

Die metrischen Parameter werden mit folgenden deskriptiven Kennzahlen dargestellt: Anzahl der Beobachtungen, arithmetischer Mittelwert, Median, Standardabweichung, unteres und oberes 25% Quartil, Minimum und Maximum. Nominale und ordinale Größen werden mit ihren absoluten und relativen (prozentualen) Häufigkeiten angegeben. Konfidenzintervalle und Kaplan Meier Analysen für zeitabhängige Endpunkte werden berechnet, soweit dieses sinnvoll erscheint.

8 MEDIKATION

Denosumab (XGEVA®) – eine Durchstechflasche enthält 120 mg Denosumab.

Bei der Behandlung mit Denosumab (XGEVA®) ist die jeweils aktuelle Fachinformation zu beachten.

9 ADMINISTRATIVE UND GESETZLICHE VORGABEN

9.1 Vertraulichkeit der erhobenen Patientendaten (Geheimhaltung)

Vom Arzt muss die vertrauliche Behandlung der Patientendaten stets gewährleistet werden. In den eCRF und sonstigen AMGEN zugehenden Unterlagen dürfen die Patienten stets nur anhand ihrer

Patienten-ID-Nr. ausgewiesen werden. Nicht zur Vorlage bei AMGEN bestimmte Unterlagen sind vom teilnehmenden Arzt streng vertraulich zu behandeln.

9.2 Dokumentation und Archivierung

Quelldokumente sind Originaldokumente, Daten und Unterlagen, aus denen die Daten für den eCRF des Patienten entnommen werden. Sie beinhalten u.a. Krankenhausunterlagen, Grafiken aus Klinik und Praxis, Labor- und Apotheken-Aufzeichnungen, Tagebücher, Mikrofiches, Röntgenbilder und Schriftverkehr.

Der teilnehmende Arzt und die im Projekt involvierten Mitarbeiter sind dafür verantwortlich, ein umfassendes und zentralisiertes Ablagesystem der gesamten projektrelevanten (wesentlichen) Dokumentation zu pflegen, das für eine jederzeitige Inspektion durch Vertreter von AMGEN und/oder der maßgeblichen Aufsichtsbehörden geeignet ist. Die einzelnen Bestandteile sollten Folgendes beinhalten:

- Patientenakten, die die ausgefüllten Patientenfragebögen, Einverständniserklärungen und die Patientenidentifikationsliste enthalten

- Projektordner, der den Beobachtungsplan mit allen Amendments, Kopien der Dokumentation vor der Beobachtung sowie den gesamten Schriftverkehr mit der Ethikkommission und mit AMGEN enthält

Außerdem müssen alle Original-Quelldokumente, die als Belege für Einträge in den eCRFs dienen, aufbewahrt werden.

Ohne vorherige schriftliche Abstimmung zwischen AMGEN und dem teilnehmenden Arzt darf kein projektrelevantes Dokument vernichtet werden. Sollte der teilnehmende Arzt wünschen, dass die Projektunterlagen einer anderen Partei übertragen oder an einen anderen Standort verbracht werden, muss er AMGEN schriftlich über die neue zuständige Person und/oder den neuen Standort informieren.

9.3 Datenerfassung

Die Daten werden im jeweiligen Zentrum aus den Krankenakten entnommen und in einen elektronischen, web-basierten Dokumentationsbogen (eCRF) übertragen.

Der Vertreter von AMGEN und die Inspektoren der Aufsichtsbehörde sind dafür verantwortlich, mit dem teilnehmenden Arzt in Kontakt zu treten und ihn für Zwecke der Inspektion der Einrichtungen und - auf Verlangen - der verschiedenen projektspezifischen Unterlagen (z.B. eCRFs und andere einschlägige Daten) aufzusuchen, sofern die Vertraulichkeit der Patienten respektiert wird.

Die von AMGEN beauftragte CRO (Metronomia) ist dafür verantwortlich, die eCRFs regelmäßig während der Beobachtung zu verifizieren, um Folgendes zu überprüfen: Einhaltung der Vorgaben; Vollständigkeit, Richtigkeit und Folgerichtigkeit der Daten sowie Einhaltung der Bestimmungen hinsichtlich der Durchführung von Anwendungsbeobachtungen. Den autorisierten Monitoren ist Zugang zu den Krankenakten der Patienten und anderen projektbezogenen Unterlagen zu gewähren, die zur Verifizierung der Einträge in den eCRFs benötigt werden.

Der teilnehmende Arzt stimmt einer Kooperation mit den autorisierten Monitoren zu, um sicherzustellen, dass Probleme (einschließlich Verzögerungen beim Ausfüllen der eCRFs) gelöst werden.

Entsprechend ICH GCP und den Auditplänen des Sponsors kann diese Beobachtung durch Vertreter der Abteilung Klinische Qualitätssicherung („Clinical Quality Assurance“) von AMGEN (oder Beauftragte) für ein Audit ausgewählt werden. Die Inspektion von Einrichtungen des teilnehmenden Zentrums und die Überprüfung von projektbezogenen Unterlagen finden statt, um die Durchführung der Beobachtung und die Einhaltung von Beobachtungsplan, sowie der anzuwendenden regulatorischen Bestimmungen zu beurteilen.

Die Daten für diese Beobachtung werden in eCRFs gemäß folgenden Parametern erfasst:

- Korrekturen auf den elektronischen Formularen werden automatisch durch den „Audit Trail“ der Software dokumentiert

- Zur Sicherstellung der Qualität der klinischen Daten bei allen Patienten und allen Zentren erfolgt eine Überprüfung der Patientendaten, die bei AMGEN eingehen, durch das klinische Datenmanagement („Clinical Data Management“) bei AMGEN oder einem von AMGEN beauftragten Unternehmen. Bei einer solchen Überprüfung werden die Patientendaten im Hinblick auf Folgerichtigkeit, Auslassungen und offensichtliche Abweichungen geprüft. Außerdem werden die Daten hinsichtlich der Einhaltung von Beobachtungsplan überprüft. Zur Klärung von Fragen, die sich bei der Überprüfung durch das klinische Datenmanagement ergeben, werden Nachfragen und/oder Mitteilungen zur Vervollständigung an das Zentrum gesandt und an AMGEN zurückgegeben

- Der für das Projekt verantwortliche Arzt im teilnehmenden Zentrum verifiziert die Daten im eCRF System. Diese Verifizierung besagt, dass der Hauptverantwortliche die Daten auf dem CRF, die Nachfragen und die Mitteilungen an das Zentrum durchgesehen oder überprüft hat und dem Inhalt zustimmt. Nach der Verifizierung können die Eintragungen vom Zentrumspersonal nicht mehr geändert werden. Von den eCRF stehen Papierversionen zur Verfügung, falls der teilnehmende Arzt oder die Ethikkommission diese benötigen

- Die Abteilung klinisches Datenmanagement bei AMGEN oder einem von AMGEN beauftragten Unternehmen korrigiert die Datenbank in folgenden Punkten auf dem eCRF ohne Benachrichtigung des Personals am Zentrum:

    - Orthographische Fehler, durch die sich die Bedeutung des Wortes nicht ändert (mit Ausnahme von Unerwünschte Arzneimittelwirkungen und Medikationen)

    - Stelle der erfassten Daten auf einem fehlerhaften eCRF (z.B. Verschieben der Labordaten von allgemeinen Anmerkungen („General comments“) zur richtigen Laborwert-Tabelle)

    - Fehlerhafte Datumsangaben, die im neuen Jahr gemacht werden

    - Umwandlung von Standardzeitangaben in 24-Stunden-Zeitangaben

    - Falsche Maßeinheit für die Temperatur (Fahrenheit vs. Celsius)

    - Falsche Maßeinheit für das Gewicht (Pfund vs. Kilogramm), wenn ein Gewicht bei Beobachtungsbeginn ermittelt wurde

    - Falsche Maßeinheit für die Größe (in. vs. cm)

    - Administrative Daten (z.B. Bezeichnungen für außerplanmäßige Besuche oder erneute Tests)

    - Bereinigung „sonstige, bitte angeben“ („other, specify“), wenn hier Angaben gemacht werden (z.B. ethnische Herkunft, körperliche Untersuchung)

    - Korrektur oder Eingabe von entweder absoluten Werten oder Prozentangaben („Absolute (A)/Percentage (P)“) bei der Hämatologie, sofern das Feld leer ist; kann anhand unterschiedlicher Daten festgestellt werden

    - Wenn sowohl das Enddatum als auch als Status andauernd („continuing“) angegeben wird (z.B. bei Unerwünschte Arzneimittelwirkungen), erscheint nur das Enddatum

- Löschen von offensichtlich doppelten Angaben (z.B. dieselben Ergebnisse wurden zweimal mit demselben Datum, jedoch bei unterschiedlichen geplanten Klinikbesuchen – Woche 4 und vorzeitige Beendigung - gesandt)

- Bei Unerwünschte Arzneimittelwirkungen, bei denen als Code für die eingeleitete Aktion (action taken) = 01 (none [keine]) eingegeben wird, wird 01 (none [keine]) gelöscht, wenn andere Angaben existieren

- Wenn einander entsprechende Einheiten oder Begriffe anstatt der von AMGEN akzeptierten Standardangaben eingegeben werden (z.B. „cc“ für „mL“, Anwendungsart „SQ“ für „SC“, „Not Examined“ [nicht durchgesehen“ für „Not Done“ [nicht durchgeführt]), werden die bei AMGEN üblichen Einheiten oder Begriffe verwendet

- Wenn die Antwort auf eine JA- oder NEIN-Frage leer oder offensichtlich falsch ist (z.B. die Antworten auf die nachfolgenden Fragen geben nicht die erfassten Angaben wider oder fehlen: „Were there any adverse drug reactions?“ [Sind Unerwünschte Arzneimittelwirkungen aufgetreten?])

9.4 Unabhängige Ethikkommission

Entsprechend der Empfehlungen des Bundesinstituts für Arzneimittel und Medizinprodukte und des Paul-Ehrlich-Instituts zur Planung, Durchführung und Auswertung von Anwendungsbeobachtungen vom 7. Juli 2010 wird der Beobachtungsplan und die jeweiligen Amendments vor Beginn der Studie von AMGEN der Ethikkommission der Bayerischen Landesärztekammer zur Beratung vorgelegt.

9.5 Einverständniserklärung über die Weitergabe von persönlichen Daten

Voraussetzung für die Teilnahme eines Patienten ist die rechtskräftig unterzeichnete Einverständniserklärung zur Verwendung personenbezogener Daten („Datenschutzerklärung“).

9.6 Weitere Verantwortung und Pflichten des teilnehmenden Arztes

Vor Beginn der Beobachtung muss der teilnehmende Arzt folgende Dokumente an das beauftragte Forschungsinstitut senden:

- Unterschriftenseite des Beobachtungsplans, unterzeichnet und datiert
- Unterschriebener Vertrag

10 LITERATUR

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11 ANHANG

11.1 Untersuchungszeitplan

	Beobachtungs-beginn	zu jeder Denosumab (XGEVA®)-Applikation												Beobachtungsende[1]
Woche	1													52
Patienteneinverständniserklärung	x													
Denosumab (XGEVA®) Applikation	1	2	3	4	5	6	7	8	9	10	11	12	13	
Stammdaten und Anamnese	x													
Vitamin D- und Kalziumapplikation	x	x	x	x	x	x	x	x	x	x	x	x	x	x
aktuelle antineoplastische Therapie	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Meldepflichtige Ereignisse (z.B. UAW und SUAW)	x	x	x	x	x	x	x	x	x	x	x	x	x	X[3]
Labor	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Kreatinin-Clearance	x													
Kalzium	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Serum-Kreatinin	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Schmerz-Score (VAS)[2]	x	x	x	x	x	x	x							
Schmerzmittelverbrauch (AQA)[2]	x	x	x	x	x	x	x							
Patientenbezogene Endpunkte (EQ5D)	x			x			x			x				x

[1] Beobachtungsende: nach 52 Wochen, unabhängig von der Anzahl der Denosumab (XGEVA®)-Applikationen, spätestens 4 Wochen nach der letzten Denosumab (XGEVA®)-Applikation; bei vorzeitiger Beendigung der Denosumab (XGEVA®)-Therapie; bei Rückzug der Einverständnis des Patienten; bei Tod und „Lost-to-Follow Up“

[2] Bei jeder Denosumab (XGEVA®)-Applikation bis max. 24 Wochen nach der ersten Denosumab (XGEVA®)-Applikation

11.2 -Allgemeinzustand nach ECOG

Score	
0	Normale uneingeschränkte Aktivität wie vor der Erkrankung.
1	Einschränkung bei körperlicher Anstrengung, aber gehfähig; leichte körperliche Arbeit bzw. Arbeit im Sitzen (z.B. leichte Hausarbeit oder Büroarbeit) möglich.
2	Gehfähig, Selbstversorgung möglich, aber nicht arbeitsfähig; kann mehr als 50% der Wachzeit aufstehen.
3	Nur begrenzte Selbstversorgung möglich; 50% oder mehr der Wachzeit an Bett oder Stuhl gebunden.
4	Völlig pflegebedürftig, keinerlei Selbstversorgung möglich; völlig an Bett oder Stuhl gebunden.
5	Tod

11.3 Common Terminology Criteria for Adverse Events (v.4.0)

11.3.1 Kieferosteonekrose

Musculoskeletal and connective tissue disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Neck soft tissue necrosis	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the neck.					
Osteonecrosis of jaw	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated (e.g., topical agents); limiting instrumental ADL	Severe symptoms; limiting self care ADL; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the bone of the mandible.					
Osteoporosis	Radiologic evidence of osteoporosis or Bone Mineral Density (BMD) t-score -1 to -2.5 (osteopenia); no loss of height or intervention indicated	BMD t-score <-2.5; loss of height <2 cm; anti-osteoporotic therapy indicated; limiting instrumental ADL	Loss of height >=2 cm; hospitalization indicated; limiting self care ADL	-	-
Definition: A disorder characterized by reduced bone mass, with a decrease in cortical thickness and in the number and size of the trabeculae of cancellous bone (but normal chemical composition), resulting in increased fracture incidence.					
Pain in extremity	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the upper or lower extremities.					

CTCAE 4.03 - June 14, 2010 : Musculoskeletal and connective tissue disorders
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11.3.2 Hypokalzämie

Metabolism and nutrition disorders					
	Grade				
Adverse Event	1	2	3	4	5
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of sodium in the blood.					
Hypertriglyceridemia	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	>300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of triglyceride concentration in the blood.					
Hyperuricemia	>ULN - 10 mg/dL (0.59 mmol/L) without physiologic consequences	-	>ULN - 10 mg/dL (0.59 mmol/L) with physiologic consequences	>10 mg/dL; >0.59 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of uric acid.					
Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of albumin in the blood.					
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L; hospitalization indicated	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of calcium (corrected for albumin) in the blood.					

CTCAE 4.03 - June 14, 2010 : Metabolism and nutrition disorders
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11.4 Patientenfragebögen

11.4.1 Schmerzscore - Visuelle Analogskala

AMGEN

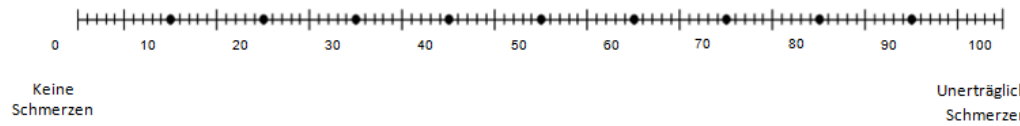
XGEVA® (Denosumab) Studie 20101312, Datum: _____

Patienten ID [redacted]

Visuelle Analogskala (VAS)

Dies ist eine Skala zur Messung der subjektiven Schmerzempfindung. Um Patienten zu helfen anzugeben, wie ausgeprägt ihre Schmerzen sind (kein Schmerz - unerträglicher Schmerz) haben wir eine Skala gezeichnet (ähnlich einem Thermometer), auf der der beste vorstellbare Zustand mit 0 und der schlimmste vorstellbare Zustand mit 100 angegeben ist.

Bitte wählen Sie dazu einen Punkt auf der Skala aus, der angibt, wie stark Ihre Schmerzen heute Ihrer Ansicht nach sind heute sind.



Keine Schmerzen

Unerträgliche Schmerzen

20101312 – Visuelle Analog Skala Version 2.0 14. März 2014

11.4.2 Schmerzmedikation - AQA (Analgesic Quantification Algorithm) Fragebogen

Score	Definition
0	Keine Analgetika
1	Nicht-opioide Analgetika
2	Schwache Opioide (Meperidin, Codein)
3	Starke Opioide ≤ 75 mg OME pro Tag
4	Starke Opioide 76 - 150 mg OME pro Tag
5	Starke Opioide 151 - 300 mg OME pro Tag
6	Starke Opioide 301 - 600 mg OME pro Tag
7	Starke Opioide > 600 mg OME pro Tag

OME = Oral Morphine Equivalent (orale Morphin-Äquivalente)

Quelle Chung et al. *Eur J Can Suppl 2009; 7: 186 (abstr P-3037)*

11.4.3 Lebensqualität – Gesundheitsfragebogen (EuroQol-5 Dimensions) (EQ-5D)

Gesundheitsfragebogen

(Deutsche Version)

(German version)

AMGEN

XGEVA® (Denosumab) Studie 20101312

Patienten ID [redacted]

Bitte geben Sie an, welche Aussagen Ihren heutigen Gesundheitszustand am besten beschreiben, indem Sie ein Kreuz in ein Kästchen jeder Gruppe machen.

Beweglichkeit/Mobilität

Ich habe keine Probleme herumzugehen ❑
Ich habe einige Probleme herumzugehen ❑
Ich bin ans Bett gebunden ❑

Für sich selbst sorgen

Ich habe keine Probleme, für mich selbst zu sorgen ❑
Ich habe einige Probleme, mich selbst zu waschen oder mich anzuziehen ❑
Ich bin nicht in der Lage, mich selbst zu waschen oder anzuziehen ❑

Alltägliche Tätigkeiten *(z.B. Arbeit, Studium, Hausarbeit, Familien- oder Freizeitaktivitäten)*

Ich habe keine Probleme, meinen alltäglichen Tätigkeiten nachzugehen ❑
Ich habe einige Probleme, meinen alltäglichen Tätigkeiten nachzugehen ❑
Ich bin nicht in der Lage, meinen alltäglichen Tätigkeiten nachzugehen ❑

Schmerzen/Körperliche Beschwerden

Ich habe keine Schmerzen oder Beschwerden ❑
Ich habe mäßige Schmerzen oder Beschwerden ❑
Ich habe extreme Schmerzen oder Beschwerden ❑

Angst/Niedergeschlagenheit

Ich bin nicht ängstlich oder deprimiert ❑
Ich bin mäßig ängstlich oder deprimiert ❑
Ich bin extrem ängstlich oder deprimiert ❑

1

AMGEN

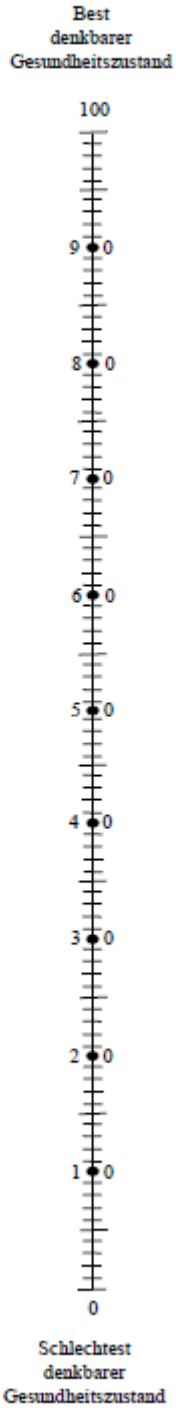
XGEVA® (Denosumab) Studie 20101312

Patienten ID [redacted]

Um Sie bei der Einschätzung, wie gut oder wie schlecht Ihr Gesundheitszustand ist, zu unterstützen, haben wir eine Skala gezeichnet, ähnlich einem Thermometer. Der best denkbare Gesundheitszustand ist mit einer "100" gekennzeichnet, der schlechteste mit "0".

Wir möchten Sie nun bitten, auf dieser Skala zu kennzeichnen, wie gut oder schlecht Ihrer Ansicht nach Ihr persönlicher Gesundheitszustand heute ist. Bitte verbinden Sie dazu den untenstehenden Kasten mit dem Punkt auf der Skala, der Ihren heutigen Gesundheitszustand am besten wiedergibt.

Ihr heutiger Gesundheitszustand



1

Quelle: Brooks R. EuroQol: the current state of play. *Health Policy*. 1996;37(1):53-72.

11.5 Meldungen zur Arzneimittelsicherheit

11.5.1 Beispiel eines Berichtsbogens für Unerwünschte Arzneimittelwirkungen

AMGEN 20101312

Meldebogen für Unerwünschte Arzneimittelwirkungen

Schwerwiegende Unerwünschte Arzneimittelwirkungen und Produktbeschwerden innerhalb eines Arbeitstages an Amgen melden [redacted]

☐ Initial ☐ Follow-up

Art des Ereignisses: ☐ Unerwünschtes Ereignis (UE)/Anderes arzneimittelsicherheitsrelevantes Ereignis (ASE)
☐ UE/ASE mit Produktbeschwerde ☐ nur Produktbeschwerde ☐ Verdachtsfall Kieferosteonekrose (ONJ)

1. Informationen über das Zentrum

Zentrumsnummer	Prüfer	Land

Berichtende Person	Telefonnummer	Faxnummer
	( )	( )

2. Patienteninformation

Patienten ID Nummer	Initialen	Geburtsdatum Tag Monat Jahr **oder** Alter	Geschlecht	Ethnische Herkunft
			☐W ☐M	

3. Unerwünschtes Ereignis, anderes arzneimittelsicherheitsrelevantes Ereignis oder Produktbeschwerde

Unerwünschte Arzneimittelwirkung (Diagnose oder Syndrom) Wenn Diagnose unbekannt, bitte Anzeichen und Symptome eintragen Bei bekannter Abschlussdiagnose diese bitte als Unerwünschte Arzneimittelwirkung eintragen *Bitte ein Ereignis pro Zeile eintragen* *Falls der Patient verstarb, bitte Todesursache eintragen* "Tod" bitte nicht bei Ereignis sondern bei „aktueller Status" eintragen	Datum des ersten Auftretens Tag Monat Jahr	Beendigung des Unerwünschten Ereignisses Tag Monat Jahr	Ist das Ereignis schwerwiegend? Nein✓	Ja✓	Falls schwerwiegend bitte Schwerwiegendheitskriterium eintragen (Code siehe unten)	Kausalzusammenhang Steht dieses Produkt im kausalen Zusammenhang mit den berichteten Ereignissen? Nein✓	Ja✓	Aktueller Status 01 beendet 02 auf dem Weg der Besserung 03 fortbestehend 04 Patient verstorben
							✓	
							✓	
							✓	
							✓	
Hier bitte Verdachtsfall von Kieferosteonekrose (ONJ) eintragen und Kausalzusammenhang angeben:								

Schwerwiegendheitskriterium: 01 Tödlich; 02 Unmittelbar lebensbedrohend; 03 Stationäre Behandlung erforderlich; 04 Verlängerung einer stationären Behandlung erforderlich; 05 bleibende oder schwerwiegende behinderung/Invalidität; 06 kongenitale Anomalien/Geburtsfehler; 07 medizinisch bedeutsam

4. Hospitalisierung

	Aufnahmedatum Tag Monat Jahr	Entlassungsdatum Tag Monat Jahr
Hospitalisiert? ☐Nein ☐Ja; Wenn ja, bitte weitere Angaben →		

5. Amgen Verdachtspräparat

	Erste Verabreichung Tag Monat Jahr	Vor oder zum Zeitpunkt des Ereignisses: Datum der Gabe Tag Monat Jahr	Dosis	Applikationsart	Applikationsfrequenz	Maßnahmen 01 Behandlung fortgesetzt 02 Dauerhaft abgesetzt 03 Zeitweise ausgesetzt
Amgen Produkt: _____ Chargennummer: _____						
Amgen Produkt: _____ Chargennummer: _____						
Amgen Produkt: _____ Chargennummer: _____						

6. Relevante Begleitmedikation (z.B. Chemotherapie) Falls keine, bitte hier ankreuzen: ☐

Produktname(n)	Erste Verabreichung Tag Monat Jahr	Letzte Verabreichung Tag Monat Jahr	Zusammenhang? Nein✓	Ja✓	Fortgesetzt? Nein✓	Ja✓	Dosis	Applikationsart	Applikationsfrequenz	UE-Behandlung? Nein✓	Ja✓

Translation/ adaptation for XTREME of FORM-015478 Adverse Drug Reaction Report Form v5.0 Effective date: 17-Aug-2012 Translation date: 12-Nov-2012
Seite 1 von 2

AMGEN 20101312	Meldebogen für Unerwünschte Arzneimittelwirkungen *Schwerwiegende Unerwünschte Arzneimittelwirkungen und Produktbeschwerden innerhalb eines Arbeitstages an Amgen melden*	☐Initial ☐Follow-up

Zentrumsnummer | Patienten ID Nummer

7. Relevante medizinische Vorgeschichte *(einschließlich Daten, Allergien und relevante Therapien in der Vergangenheit)*

8. Relevante Laborparameter *(einschließlich Ausgangswerten)* Falls keine vorhanden, bitte ankreuzen: ☐

Test											
Einheit											
Datum (Tag Monat Jahr)											

9. Andere relevante Tests *(Diagnostik oder Verfahren)* Falls keine durchgeführt, bitte ankreuzen: ☐

Datum (Tag Monat Jahr)	Zusätzliche Tests	Befunde	Einheit

10. Fallbeschreibung *(Bitte stellen Sie Informationen zu den in Abschnitt 3 aufgeführten Ereignissen bereit)*
*Für jedes Ereignis aus Abschnitt 3, für das ein Kausalzusammenhang für möglich erachtet wird, bitte Begründung angeben

Unterschrift des Prüfers oder seines Stellvertreters	Titel	Datum

Translation/ adaptation for XTREME of FORM-015478 Adverse Drug Reaction Report Form v5.0 Effective date: 17-Aug-2012 Translation date: 12-Nov-2012
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11.5.2 Beispiel eines Fragebogens zur Exposition während der Schwangerschaft

AMGEN Fragebogen zur Exposition während der Schwangerschaft
Ausgefüllten Bogen bitte an die Abteilung für Arzneimittelsicherheit faxen unter [redacted]

1. Administrative Angaben

Protokollnummer/Nummer der Anwendungsbeobachtung: 20101312

Prüfdesign: ☐ Klinische Studie ☒ Beobachtungsstudie (falls Beobachtungsstudie: ☒ prospektiv ☒ retrospektiv)

2. Kontaktinformationen

Name des Prüfers: _____ Nummer des Zentrums:_____

Telefonnummer: (_____)_____ Faxnummer: (_____)_____ Emailadresse: _____

Einrichtung: _____

Adresse: _____

3. Angaben zum Patienten

Patienten ID Nummer: _____ Geschlecht: ☐ weiblich ☐ männlich Geburtsdatum (TT/MM/JJJJ):____/_____/_____

4. Exposition gegenüber einem Produkt von Amgen

Amgen-Produkt	Dosierung zur Zeit der Empfängnis	Applikations-frequenz	Applikationsart	Erste Verabreichung (TT/MM/JJJJ)
Denosumab (XGEVA)				/ /

Wurde die Gabe des Amgen-Produkts unterbrochen? ☐ Ja ☐ Nein

Wenn ja, bitte Datum der letzten Verabreichung des Amgen-Produkts angeben: (TT/MM/JJJJ) ____/____/____

Hat der Patient/die Patientin die Teilnahme an der Anwendungsbeobachtung beendet? ☐ Ja ☐ Nein

5. Angaben zur Schwangerschaft

Datum der letzten Menstruation der Schwangeren: (TT/MM/JJJJ) ____/____/_____ ☐ unbekannt

Voraussichtlicher Entbindungstermin: (TT/MM/JJJJ) ____/____/_____ ☐ unbekannt ☐ nichts zutreffend
Falls „nichts zutreffend" angekreuzt wurde: Datum das Abbruchs (oder geplantes Datum): (TT/MM/JJJJ): ____/____/_____

Hat die Schwangere bereits entbunden? ☐ Ja ☐ Nein ☐ unbekannt ☐ nichts zutreffend
Falls ja, bitte Entbindungsdatum angeben: (TT/MM/JJJJ) ____/____/_____

War das Kind gesund? ☐ Ja ☐ Nein ☐ Unbekannt ☐ nichts zutreffend

Falls bei dem Kind ein Unerwünschtes Ereignis auftrat, bitte kurz erläutern: _____
_____
_____

Ausgefüllt von:

Name (in Druckbuchstaben): _____ Titel: _____

Unterschrift: _____ Datum:_____

Global Version Effective Date: 27-MAR-2011 Translation Effective Date for Xtreme 14-NOV-2012, Version 1

11.5.3 Beispiel eines Fragebogens zur Exposition während der Stillzeit

AMGEN Fragebogen zur Exposition während der Stillzeit

Ausgefüllten Bogen bitte an die Abteilung für Arzneimittelsicherheit faxen unter [redacted]

1. Administrative Angaben

Protokollnummer/Nummer der Anwendungsbeobachtung: 20101312

Prüfdesign: ☐ Klinische Studie ☒ Beobachtungsstudie (falls Beobachtungsstudie: ☒ prospektiv ☒ retrospektiv)

2. Kontaktinformationen

Name des Prüfers: _____ Nummer des Zentrums:_____

Telefonnummer: (_____)_____ Faxnummer: (_____)_____ Emailadresse: _____

Einrichtung: _____

Adresse: _____

3. Angaben zur Patientin

Patienten ID Nummer: _____ Geburtsdatum (TT/MM/JJJJ):_____/_____/_____

4. Exposition gegenüber einem Produkt von Amgen

Amgen-Produkt	Dosierung zur Zeit des Stillens	Applikations-frequenz	Applikationsart	Erste Verabreichung (TT/MM/JJJJ)
Denosumab (XGEVA)				/ /

Wurde die Gabe des Amgen-Produkts unterbrochen? ☐ Ja ☐ Nein

Wenn ja, bitte Datum der letzten Verabreichung des Amgen-Produkts angeben: (TT/MM/JJJJ) ____/____/____

Hat die Patientin ihre Teilnahme an der Anwendungsbeobachtung beendet? ☐ Ja ☐ Nein

5. Angaben zum Stillen

Hat die Mutter, während sie mit einem Amgen-Produkt behandelt wurde, gestillt oder das Kind mit abgepumpter Muttermilch gefüttert?
☐ Ja ☐ Nein Falls Nein, bitte Datum der letzten Verabreichung angeben: (TT/MM/JJJJ) ____/____/_____

Geburtsdatum des Kindes: (TT/MM/JJJJ) ____/____/_____

Geschlecht des Kindes: ☐ weiblich ☐ männlich

Ist das Kind gesund? ☐ Ja ☐ Nein ☐ Unbekannt ☐ Keine Angabe

Falls bei Mutter oder Kind ein Unerwünschtes Ereignis auftrat, bitte kurz erläutern: _____

_____

_____

Ausgefüllt von:

Name (in Druckbuchstaben): _____ Titel: _____

Unterschrift: _____ Datum:_____

Global Version Effective Date: 09-APR-2012, Version 2 Translation Effective Date for Xtreme14-NOV-2012, Version 1