CLINICAL STUDY REPORT RA0027

Title:	A Multicenter, Observational, Noninterventional Study to Evaluate the Safety and Efficacy of Anti-TNF Alpha Therapy with Certolizumab Pegol Observed in Daily Practice in Adult Rheumatoid Arthritis (RA) Patients FαsT: TNFα: Observation of Treatment with Certolizumab Pegol in Daily Practice RA0027
Version identifier of the final study report	Version 1.0
Date of last version of the final study report	Not applicable
Clinical Trial Registry Identifier:	NCT01069419
EU PAS Register Number:	Not applicable.
Active substance:	Certolizumab pegol (CDP870), ATC code L04AB05
Medicinal product:	Certolizumab pegol
Product reference:	Cimzia®
Procedure number:	EMEA/H/C/001037
Marketing authorization holder:	UCB Pharma GmbH
Joint PASS	No
Research question and objectives:	*Primary Objective:* The primary objective of this study was to assess the clinical efficacy of Certolizumab pegol (CZP) in achieving clinical remission (DAS28 [Disease Activity Score 28] of <2.6) after 2 years of therapy in adult patients with RA. *Secondary Objective:* The secondary objective was to assess the effect of treatment with CZP on patients' arthritis pain, physical function, and disease activity after 2 years of therapy. *Safety Objective:* The safety objective of this study was to assess safety data collected in a real life setting in a defined patient population (age, gender, etc.) treated with CZP. Identified and potential risks are specified in the current version of the Summary of Product Characteristics (SmPC).

Country of study:	Germany
Author:	[redacted]
GxP compliance statement:	This study was conducted in compliance with legal requirements for noninterventional studies (NIS).

Marketing Authorization Holder

Marketing authorization holder:	UCB Pharma GmbH. Allée de la Recherche 60 B-1070 Bruxelles BELGIUM
MAH contact person:	[redacted]

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1 ABSTRACT

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Title:

Short study title: FαsT: TNFα: Observation of treatment with certolizumab pegol in daily practice

Title of study: A multicenter, observational, noninterventional study to evaluate the safety and efficacy of anti-TNF alpha therapy with certolizumab pegol observed in daily practice in adult rheumatoid arthritis (RA) patients.

Date of abstract: 02 Mar 2016

Main author and affiliation: [redacted], PhD, of UCB

Keywords: certolizumab pegol (CZP), RA, noninterventional study (NIS), observational, postauthorization safety study (PASS)

Rationale and Background:

Rheumatoid arthritis is a chronic systemic inflammatory disease that is associated with significant morbidity and mortality.

Certolizumab pegol is approved in the European Union, Switzerland, the United States, and Canada for the treatment of adults with moderate to severe active RA.

This study was a company initiated, noninterventional, observational, PASS designed to assess the efficacy and safety of CZP in long-term use (2 years) in standard clinical practice setting. Since the study patients received CZP in accordance with the summary of product characteristics (SmPC), the risk for the patients was not considered to be increased as a result of their participation in this NIS.

Publication (reference): Emma D. Deeks, Certolizumab Pegol, A review of its Use in the Management of Rheumatoid Arthritis, Springer International Publishing Switzerland 2013.

Burmester, G.R., Müller-Ladner, U., Nüsslein, M., von Hinuber, U., Edelmann, E., Detert, J., Höhle, M., Richter, C., Neeck, G., Kumke, T., Fricke, D. 2011. Über die Hälfte der mit Certolizumab Pegol (CZP) behandelten Patienten erreichte Remission oder niedrige Krankheitsaktivität - erste Interim-Ergebnisse aus dem Praxisalltag der nichtinterventionellen Studie (NIS) Fast. Zeitschrift für Rheumatologie, 70 (Suppl. 1), 91-91.

Burmester, G.R., Muller-Ladner, U., Nusslein, H., von Hinuber, U., Edelmann, E., Detert, J., Höhle, M., Richter, C., Klopsch, T., Kumke, T., Fricke, D. 2012. Rapid achievement of remission with certolizumab pegol was maintained for one year: interim results from Fast, a

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German non-interventional study in rheumatoid arthritis real life patients. Annals of Rheumatic Diseases, 71 (Suppl. 3), 664-664.

Burmester, G., Müller-Ladner, U., Nüsslein, H., von Hinüber, U., Edelmann, E., Detert, J., Höhle, M., Richter, C., Klopsch, T., Kumke, T., Fricke, D. 2012. Schnelles Erreichen und Aufrechterhaltung der Remission mit CERTOLIZUMAB PEGOL über ein Jahr: 2. Interim-Analyse der nicht-interventionellen Studie (NIS) FαsT. Zeitschrift für Rheumatologie, 71 (Suppl.2), ….

Burmester, G., Müller-Ladner, U., Nüsslein, H., von Hinüber, U., Edelmann, E., Detert, J., Höhle, M., Richter, C., Klopsch, T., Kumke, T., Fricke, D. 2013. Wirksamkeit und Verträglichkeit von Certolizumab pegol zur Behandlung der rheumatoiden Arthritis in der klinischen Praxis in Deutschland: 3. Interimanalyse der nichtinterventionellen Studie Fast. Zeitschrift für Rheumatologie, 72 (Suppl.2), 100-100.

Burmester, G., Müller-Ladner, U., Nüsslein, H., von Hinüber, U., Edelmann, E., Detert, J., Höhle, M., Richter, C., Klopsch, T., Kumke, T., Fricke, D. 2014. Nicht-interventionelle Studie FαsT: Schnelle Verbesserung der Patienten relevanten Outcomes (PRO) mit CERTOLIZUMAB PEGOL zur Behandlung der rheumatoiden Arthritis im deutschen Praxisalltag. 42. Kongress der Deutschen Gesellschaft für Rheumatologie (DGRh), 17-20 September 2014; Heidelberg/Mannheim, Germany.

Kumke, T., Fricke, D., Burmester, G., Andreas, J.-O. 2013. The Performance of Mixed Model with Repeated Measures (MMRM) and Last Observation Carried Forward (LOCF) in an Observational Study – Results from Interim Data. Oral presentation at the European Statistical Forum, November 18, 2013, Amsterdam, The Netherlands.

First subject enrolled: 07 Oct 2009 (First Patient First Visit)

Last subject completed: 17 Dec 2014

Research question and Objectives:

Primary Objective: The primary objective of this study was to assess the clinical efficacy of CZP in achieving clinical remission (DAS28 [Disease Activity Score-28 joint count] of <2.6) after 2 years of therapy in adult patients with RA.

Secondary Objective: The secondary objective was to assess the effect of treatment with CZP on patients' arthritis pain, physical function, and disease activity after 2 years of therapy.

It is noted that the term "efficacy" is used in this study; in the context of this study, UCB understands this term to mean "effectiveness," which is the term generally used for observational studies.

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Safety Objective: The safety objective of this study was to assess safety data collected in a real life setting in a defined patient population (age, gender, etc) treated with CZP.

Study design:

All patients were prescribed CZP by their treating physician, and the doses were determined by the treating physician during routine clinical practice.

The observational nature of the study left the therapeutic decision exclusively within the discretion of the treating physician. The decision to treat the patient with CZP had to be taken before the treating physician could enroll the patient into this study. A patient was allowed to enroll in the study after starting CZP treatment (after Visit 1) if he/she met all inclusion and exclusion criteria at the start of CZP treatment. Management of adverse events (AEs) was handled according to drug safety regulations in Germany and the European Union.

Setting:

The study duration per patient was intended to be 116 weeks. After the Baseline Visit, visits occurred at around Weeks 6, 12, 24, 36, 52, 64, 76, and 104. The Safety Follow-Up Visit was at around Week 116. All patients who discontinued CZP (except those who withdrew consent or were lost to follow up) were followed up for 84 days to analyze which treatments were commonly used after treatment failure of CZP.

The end of the study was defined as the date of the last visit of the last patient in the study.

Subjects and study size, including dropouts

Number of subjects (planned and analyzed):

Planned: 1068

Enrolled: 1117

Safety Set (SS): 1111

Full Analysis Set (FAS): 851

Discontinued: 696 (from SS), 510 (from FAS)

Where SS was defined as all patients who took at least 1 dose of CZP, and FAS was defined as all patients with a DAS28≥2.6 at Baseline who took at least 1 dose of CZP, and had at least 1 valid post-Baseline DAS28 value (either derived using erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP]).

Diagnosis and main criteria for inclusion: Any patient (male or female) ≥18 years of age diagnosed with moderate to severe active RA, who provided written data consent along with being considered reliable and capable of adhering to the observational plan, and eligible for

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treatment with CZP therapy was included in the study. The decision to prescribe CZP had to be made by the treating physician independently of his/her decision to include the patient in the study. A patient was not permitted to enroll in the study if he/she had previously (before Visit 1) been treated with CZP or had known hypersensitivity for any components of CZP.

Test product, dose and mode of administration, batch number: Certolizumab pegol was provided upon prescription of the treating physician (commercially available Cimzia®) and according to the SmPC.

Variables and data sources:

Efficacy:

The primary efficacy variable for the study was clinical remission (defined as DAS28 of <2.6) at Visit 9 (around Week 104).

The secondary efficacy variables were:

- Change from Baseline in patient's arthritis pain as measured by Patient's Assessment of Arthritis Pain (PAAP) visual analogue scale (VAS) at Visit 9 (around Week 104)
- Change from Baseline in patient's physical function as measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI) (by Lautenschläger et al, 1997; Fries et al, 1980) at Visit 9 (around Week 104)
- Change from Baseline in disease activity measured by Clinical Disease Activity Index (CDAI) at Visit 9 (around Week 104)

The other variables were PAAP VAS, Patient's Global Assessment of Disease Activity Using a VAS (PtGADA), Physician's Global Assessment of Disease Activity Using a VAS (PhGADA), Fatigue Assessment Scale, CDAI, HAQ-DI, DAS28, swollen joint count (SJC) and tender joint count (TJC), American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) remission criteria, Euro Quality of Life-5 Dimensions (EQ-5D), CRP and ESR, collection of information on sick leave, employment status and employability due to RA, duration of morning stiffness, and presence of rheumatoid factor (RF) or anti-cyclic citrullinated peptide antibodies (aCCP).

Safety: Safety was assessed following company and local regulations on an observational basis, based on the incidence of treatment-emergent AEs (TEAEs).

Statistical methods:

All variables were analyzed in an explorative manner using descriptive statistics only. Summary

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statistics consisted of frequency tables for categorical variables. For continuous variables, descriptive statistics (number of available observations; mean and median; standard deviation [SD]; minimum; and maximum) were tabulated unless specified otherwise.

Missing values of binary variables were imputed using the nonresponder imputation (NRI), while missing values of multinomial variables or continuous variables were imputed using a mixed model with repeated measures (MMRM). For the primary efficacy endpoint, the number and percentage of patients with DAS28<2.6 at Week 104 were computed (using NRI) alongside their 95% confidence intervals (CIs) and tabulated. Other endpoints were presented using descriptive statistics and MMRM imputation, if appropriate.

Safety analysis was performed on the SS. The most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) dictionary was used (version 17.1). Incidence rates including 95% CIs, exposure-adjusted event rate (EAER), and exposure-adjusted incidence rate (EAIR) were calculated for TEAEs.

Results:

The percentage of remitters using nonmissing observations, MMRM imputation, and NRI was 120/240 patients (50%), 168/851 patients (19.7%), and 120/851 patients (14.1%), respectively. The higher remission rates of all patients with nonmissing observations are likely to be biased due to the higher probability that more responders complete the study and are therefore to be interpreted with care.

The secondary objective for the study was explored by analyzing mean change from Baseline at Week 104 in PAAP (MMRM imputation: -16.43), HAQ-DI (MMRM imputation: -0.26), and CDAI (MMRM imputation: -14.57) values and the mean change observed for all the 3 variables, demonstrates that the CZP treatment had a positive effect on the patient's arthritis pain, physical functioning, and disease activity after 2 years of therapy.

The benefit of CZP treatment was observed early (ie, up to Week 12) and the treatment continued to be beneficial until Week 104.

Using MMRM imputation for the FAS, the percentage of patients in remission or with low disease activity (LDA) respectively, increased from zero at Baseline to 177/851 patients (20.8%) and 153/851 patients (18.0%) respectively, at Week 12. At Week 104, 168/851 patients (19.7%), and 118/851 patients (13.9%) of the patients were in remission and LDA category, respectively. A higher percentage of DAS28 clinical remitters was observed compared to ACR/EULAR remitters; this is most likely due to the stricter criteria for the ACR/EULAR remission than for DAS28.

Though the absolute values were different, the decreases in the disease activity across the weeks

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were consistent for all the variables of the study.

The mean duration of treatment for the SS was 449.2 days (ranging from 14 to 1821 days), with a total exposure of 1537.8 patient-years, and for the FAS the mean duration of study treatment was 475.8 days (ranging from 14 to 1821 days), with a total exposure of 1239.9 patient-years.

In the SS, 745 patients (67.1%) reported at least 1 TEAE, 212 patients (19.1%) reported serious TEAEs, and 253 patients (22.8%) reported TEAEs leading to the discontinuation of CZP. There were 485 patients (43.7%) with drug-related TEAEs, 135 patients (12.2%) with severe TEAEs, 9 deaths (0.8%), and 440 patients (39.6%) with TEAEs requiring dose change.

Out of the 9 fatal TEAEs (0.8%) during the study, a majority was due to Infections and infestations (3 patients [0.3%]) and Neoplasms benign, malignant and unspecified (incl cysts and polyps) (3 patients [0.3%]).

The TEAEs of interest like tuberculosis, neoplasms, and serious infections were reported in 4 patients (0.4%), 10 patients (0.9%), and 43 patients (3.9%), respectively.

Incidences of these events of interest were not higher compared to what was seen in the clinical development program of Cimzia.

In the SS, out of 485 patients (43.7%) who reported at least 1 drug-related TEAE, 85 patients (7.7%) reported at least 1 drug-related serious TEAEs, 205 patients (18.5%) reported discontinuations due to drug-related TEAEs, 83 patients (7.5%) reported severe drug-related TEAEs, 3 patients (0.3%) had drug-related TEAEs with fatal outcomes, and 327 patients (29.4%) reported drug-related TEAEs requiring dose change.

Discussion:

The results obtained present the assessment of 2 years treatment with CZP in adult patients with RA in daily practice in Germany and describe the benefit and risk associated with the treatment.

- After 2 years treatment with CZP (at Week 104), there was a substantial increase observed in the percentage of DAS28 remitters using nonmissing observations, NRI, and MMRM imputation. The percentage of DAS28 remitters was higher using nonmissing observations.
- The mean change from Baseline at Week 104 values for all 3 secondary variables (PAAP, HAQ-DI, and CDAI) indicated decreased pain and disease activity, and an improvement in physical functioning of the patient. The results support the efficacy of CZP treatment on patients' arthritis pain, physical functioning, and disease activity.
- Overall, the incidence of TEAEs in this large scale NIS was consistent with the known safety profile of CZP and did not reveal any new safety signal for CZP.

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Marketing Authorization Holder: UCB Pharma, S.A.

Names and affiliations of principal investigators:

Principal/Coordinating treating physician:

Prof. Dr. med. [redacted]

[redacted] Germany

[redacted]

Treating physicians: A total of 164 principal treating physicians at active sites (ie, sites that enrolled at least 1 patient) in Germany.

2 LIST OF ABBREVIATIONS

aCCP	anti-cyclic citrullinated peptide
ACPA	antibodies against citrullinized peptide-protein-antigenes
ACR	American College of Rheumatology
AE	adverse event
AJ	assessed joints
ATC	Anatomical Therapeutic Chemical (classification)
CDAI	Clinical Disease Activity Index
CDMS	clinical data management system
CI	confidence interval
CRF	case report form
CRO	Contract Research Organization
CRP	C-reactive protein
CSR	clinical study report
CZP	certolizumab pegol
DAS28	Disease Activity Score-28 joint count
DMARD	disease-modifying antirheumatic drug
DRM	Data Review Meeting
EAER	exposure-adjusted event rate
EAIR	exposure-adjusted incidence rate
EQ-5D	Euro Quality of Life-5 Dimensions
ES	Enrolled Set
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FAS	Full Analysis Set
HAQ-DI	Health Assessment Questionnaire-Disability Index
HLT	high level term
IEC	Independent Ethics Committee
IP	interphalangeal
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
LCL	lower confidence limit

LDA	low disease activity
LPLV	last patient last visit
LS	least squares
MCP	metacarpophalangeal
MCV	mutated citrullinated vimentin
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model with repeated measures
MTX	methotrexate
NIS	noninterventional study
NRI	nonresponder imputation
PAAP	Patient's Assessment of Arthritis Pain
PASS	postauthorization safety study
PhGADA	Physician's Global Assessment of Disease Activity
PIP	proximal interphalangeals
PT	preferred term
PtGADA	Patient's Global Assessment of Disease Activity
QoL	quality of life
RA	rheumatoid arthritis
RF	rheumatoid factor
RR	remission rate
SAE	serious adverse event
SD	standard deviation
SE	standard error
SJ	swollen joints
SJC	swollen joint count
SmPC	Summary of Product Characteristics
SMQ	standardized MedDRA query
SOC	System Organ Class
SOP	standard operating procedure
SS	Safety Set
TEAE	treatment-emergent adverse event
TJ	tender joints
TJC	tender joint count
TNFα	tumor necrosis factor alpha

UCL	upper confidence limit
VAS	visual analog scale
WHO-DD	World Health Organization Drug Dictionary

3 INVESTIGATORS

This NIS was sponsored by UCB Pharma GmbH (hereafter referred to as the Sponsor/UCB) and the Physician involved in the study at the time of this clinical study report (CSR) was as follows:

- Principal/Coordinating Treating Physician: Prof. Dr. med. [redacted] Germany, [redacted]

The details of all study physicians are presented in Annex 1.

4 OTHER RESPONSIBLE PARTIES

The other responsible parties involved in the study at the time of this CSR were as follows:

- Sponsor Study Physician: [redacted] MD, of UCB
- Clinical Monitoring Contract Research Organization (CRO): [redacted] Germany
- Contract Research Organization for statistical analysis and reporting: [redacted] Germany
- Contract Research Organization for Data Management: [redacted] Germany
- Clinical Project Manager: [redacted] of UCB
- Clinical Trial Biostatistician: [redacted] PhD, of UCB
- Central laboratory facility: Not applicable
- Local Medical Affairs Representative [redacted] PhD, of UCB
- Clinical trial supply management: Not applicable
- Interactive Voice Response System (IVRS): Not applicable

5 MILESTONES

The important milestones of the study are indicated in Table 5–1:

Table 5–1: Important study milestones

Milestone	Planned date	Actual date	Comments
Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval dates	Not specified in the protocol	25 Aug 2009	Final protocol vote date of the IEC consulted by the Sponsor of the study.
Start of data collection	Q3 2009	07 Oct 2009	–
End of data collection	Q3 2015	17 Dec 2014	–
Registration in the EU PAS register	NA	NA	NA
Study progress report	NA	NA	NA
Interim analyis 1	Not specified in the protocol	23 Dec 2010	Interim "snapshot" analysis run. No report prepared.
Interim analysis 2	Not specified in the protocol	08 Oct 2011	Interim "snapshot" analysis run. No report prepared.
Interim analysis 3	Not specified in the protocol	31 Aug 2012	Interim "snapshot" analysis run. No report prepared.
Interim analysis 4	Not specified in the protocol	30 Aug 2013 ("snapshot" analysis) 27 Feb 2014 (report date)	Interim "snapshot" analysis run, with interim safety analysis report.
Final report of study results	Not specified in the protocol	02 Mar 2016	–

PAS=postauthorization studies; NA=not applicable; Q=quarter

A listing of all IECs are presented in Annex 1.

6 RATIONALE AND BACKGROUND

6.1 Introduction

Rheumatoid arthritis is a chronic systemic inflammatory disease that is associated with significant morbidity and mortality. The disease is characterized by inflammation of the synovial lined diarthrodial joints that can result in pain, swelling, and joint damage with secondary deformity, progressive disability, and impairment of patient health-related quality of life (QoL). It is estimated that about 1% of the population worldwide has RA.

Certolizumab pegol is a recombinant, humanized antibody Fab′ fragment that is produced in an *Escherichia coli* expression system and is subsequently purified and conjugated with high molecular weight polyethylene glycol (40kDA). Certolizumab pegol has a high affinity for human tumor necrosis factor alpha (TNFα) and binds with a dissociation constant of 90pM. Tumor necrosis factor alpha is a key proinflammatory cytokine with a central role in inflammatory processes. Certolizumab pegol selectively neutralizes TNFα but does not neutralize lymphotoxin α (TNF beta). It was also shown to neutralize membrane associated and soluble human TNFα in a dose-dependent manner. Incubation of monocytes with CZP resulted in a dose-dependent inhibition of lipopolysaccharide induced TNFα and interleukin-1beta (IL1β) production in human monocytes. The fragment crystallizable region normally present in a complete antibody is missing from CZP, and hence it does not fix, complement, or cause antibody-dependent, cell-mediated cytotoxicity nor does it induce apoptosis in human peripheral blood-derived monocytes or lymphocytes, or neutrophil degranulation in vitro.

Certolizumab pegol is approved in the European Union, Switzerland, the United States, and Canada for the treatment of adults with moderate to severe active RA. It can be given as monotherapy, or concomitantly with methotrexate (MTX). In placebo-controlled studies in adult patients with active RA (see SmPC), CZP has been shown to improve signs and symptoms, physical function, fatigue, health-related QoL, and RA-related productivity (at work and within the home), and inhibit the progression of structural damage. The formation of antibodies to CZP is associated with lowered drug plasma concentrations and in some patients reduced efficacy. Approximately 9.6% of patients in Phase 3 trials (see SmPC) had antibodies to CZP, of which one third had antibodies with neutralizing activity in vitro. Patients treated with concomitant immunosuppressants had a lower rate of antibody development than patients who had not been taking immunosuppressants at Baseline.

This study was a noninterventional, PASS study designed to assess the efficacy and safety of CZP in long-term use (2 years) in standard clinical practice according to the instructions for use in patients with RA, as described in the SmPC. Identified and potential risks of CZP treatment are presented in the SmPC. Since the study patients received CZP in accordance with the SmPC guidance, the risk for the patients was not considered to be increased as a result of their participation in this NIS.

The primary efficacy variable was clinical remission at Visit 9 (around Week 104) (defined as DAS28 of <2.6). Other efficacy variables included change from Baseline in the patient's arthritis pain, levels of fatigue, health status, physical functions as assessed by the patient, clinical remission by visit, and pharmacoeconomic information. Management of AEs was handled according to German and European Union drug safety regulations.

6.2 Ethics

6.2.1 Ethical conduct of the study

This study was conducted in compliance with legal requirements for NIS.

7 RESEARCH QUESTIONS AND OBJECTIVES

7.1 Primary objective

The primary objective of this study was to assess the clinical efficacy of CZP in achieving clinical remission (DAS28 of <2.6) after 2 years of therapy in adult patients with RA.

7.2 Secondary objectives

The secondary objective was to assess the effect of treatment with CZP on patients' arthritis pain, physical function, and disease activity after 2 years of therapy.

7.3 Other objectives

The other objectives of the study were as follows:

- Assessment of clinical remission and low disease activity (LDA) for all patients by visit and for different patient populations, based on DAS28 and ACR/EULAR 2011 remission criteria
- Identification of responder/nonresponder to CZP treatment as basis for subgroup classification. A patient was considered to be a responder if the DAS28 decrease was ≥1.2
- Gather information on prescribing habits of the rheumatologists with regards to the concomitant treatment
- Gather information on prescribing habits of rheumatologists with regards to the concomitant RA treatment as well as subsequent treatments in case of CZP discontinuation
- Assess incidence of CZP discontinuation due to remission (DAS28)
- To evaluate and assess the effect of treatment over time with CZP for the following:
  - Arthritis pain (arthritis pain VAS)
  - Fatigue (Fatigue Assessment Scale)
  - Physical function (HAQ-DI) and health-related QoL (EQ-5D)
  - Selected components of the ACR diagnostic and improvement criteria: morning stiffness, TJC, SJC, CRP, or ESR
  - Disease activity (CDAI)
  - Pharmacoeconomic data (missing days at work and employment information)
  - Duration of morning stiffness (in hours)

It is noted that the term "efficacy" is used in this study; in the context of this study, UCB understands this term to mean "effectiveness," which is the term generally used for observational studies.

7.4 Safety objectives

The safety objective of this study was to assess safety data collected in a real life setting in a defined patient population (age, gender, etc) treated with CZP. Identified and potential risks are specified in the current version of the SmPC.

8 AMENDMENTS AND UPDATES

The original protocol approved on 06 Jul 2009 underwent 2 nonsubstantial amendments (Protocol Amendment 1: 12 Oct 2009; Protocol Amendment 2: 21 Oct 2010) and 1 substantial amendment (Protocol Amendment 3: 02 May 2012). Details of the individual amendments are summarized in the following sections, and are included in Annex 1.

Note that the protocol was prepared prior to introduction of the latest guidance on noninterventional PASS (EMA/813938/2011, EMA/48663/2013). Therefore, the structure of the protocol (and amendments) does not follow the format or structure required in that guidance.

8.1 Protocol Amendment 1

Protocol Amendment 1, dated 12 Oct 2009, was implemented to address the following:

- Enrollment of patients into the study was allowed after the start of CZP treatment.
- Study contact information was updated to reflect a change in the Sponsor Study Physician and the addition of a CRO. The serious AE (SAE) reporting telephone and fax numbers were updated and an email address provided to reflect the addition of the CRO.
- The names of the Patient's and Physician's Global Assessment of Arthritis VAS were changed to the Patient's and Physician's Global Assessment of Disease Activity (PtGADA and PhGADA, respectively) using a VAS for internal consistency.
- Vaccination status was removed as a study objective, other efficacy variable, and assessment of efficacy. Instead, information on prior and concomitant vaccinations was collected with prior and concomitant medications and therapies.
- The assessment of concomitant medication was removed as an assessment of efficacy.
- Collection of the incidence of AEs was added as a safety variable.
- Information on prior and concomitant medical procedures was collected at Visit 1 and subsequent visits, respectively.

8.2 Protocol Amendment 2

Protocol Amendment 2, dated 21 Oct 2010, was implemented to address the following:

- The "other efficacy variable" of hospital stays was deleted from the protocol because these data were no longer collected. It was determined by the Sponsor that there was an unreasonable balance between the value of the information and the effort to retrieve it.
- The Cimzia SmPC does not include nor is it foreseen to include a specific DAS28 score to identify moderate to severe, active RA; therefore, the requirement for DAS28>3.2 was deleted from an inclusion criterion.

- Per the request of the German Regulatory Authority, the batch number status was required to be documented on the AE and SAE pages. Therefore, this information was added to the protocol.
- Patients who discontinued CZP due to remission were not followed; therefore, this sentence was deleted.
- The time for follow up of an AE was changed from 21 days to 12 weeks after the patient took the last dose of medication, as this was considered to be a more appropriate amount of time. Guidance on AEs of interest, overdose, and safety signal detection was also added.

8.3 Protocol Amendment 3

Protocol Amendment 3, dated 02 May 2012, was implemented to address the following:

- First interim analyses for data collected in RA0027 showed that the quality of some of the data did not allow for the analyses of some of the originally determined variables. Furthermore, recent scientific evidence (Felson et al, 2011) suggested adding a new criterion for the assessment of clinical remission of RA. In addition, the focus of future interim analyses for RA0027 shifted from Week 104 towards Weeks 12 and 52, due to increased interest of the scientific community in short-term and medium-term response data. The resulting changes in study variables and in the purpose of future interim analyses (as compared to the situation prior to study start) were reflected in this protocol amendment.
- A definition of TEAEs was added to increase the information content of the study protocol. For consistency across the CZP program, injection reaction definitions were added. The AEs of interest (formerly AEs of special interest) section was updated to be consistent with current reporting requirements.
- Several subsections describing the assessment of safety were updated to be consistent with the latest wording used in study protocols for NIS.
- The anticipated date for Last Patient Last Visit (LPLV) was brought forward to account for the promising recruitment status.
- Minor changes were made to make the document more consistent with both the current UCB Submissions Style Guide and the current protocol template for NIS.

9 RESEARCH METHODS

9.1 Study design

This was an observational, noninterventional, noncomparative, PASS to evaluate efficacy and long-term safety of CZP in adult patients with RA in need of treatment with a biologic.

The observational nature of the study, and the need to reflect the use of CZP in the real life setting in daily practice in Germany, left the therapeutic decision and dose determination exclusively within the discretion of the treating physician. The decision to treat the patient with CZP was taken first before the treating physician enrolled the patient into this study. A patient was allowed to enroll in the study after starting CZP treatment (after Visit 1) if he/she met all inclusion and exclusion criteria at the start of CZP treatment. In addition, patient procedures and assessments were performed in the frame of current standard clinical practice and as directed in

the SmPC. Management of AEs was handled according to drug safety regulations in Germany and the European Union.

Since this was a NIS, CZP was provided upon prescription of the treating physician (commercially available Cimzia).

Physicians treating RA patients with biologic therapies were invited to participate in this PASS. Appropriate selection of the study sites ensured collection of data representative for the general RA population.

The study duration per patient was 2 years to allow collection of both efficacy and safety data after long-term use of CZP.

The study was conducted at approximately 163 sites in Germany. A total of 1068 patients was planned to be enrolled in this study from Q3 2009 to Q4 2014.

Four interim analyses were run during this study, dated 23 Dec 2010, 08 Oct 2011, 31 Aug 2012, and 30 Aug 2013. One interim safety report was prepared, based on database "snapshots" from 30 Aug 2013.

9.2 Setting

The entire study duration per patient was 116 weeks if not prematurely discontinued. The 2 years study duration per patient allowed collection of both efficacy and safety data after long-term use of CZP. Intervals of visits were as follows:

- Baseline Visit at onset of therapy (after the decision to treat the patient with CZP had been taken).
  Note: A patient was enrolled in the study after the start of CZP treatment if he/she met all inclusion and exclusion criteria at the start of CZP treatment. Written data consent had to be obtained no later than the start of Visit 2 and prior to conducting any clinical assessment at Visit 2. Following written data consent (ie, enrollment into the study), all relevant data from original records were entered onto study-specific forms.
- Frequent visits were expected around Weeks 6, 12, 24, 36, 52, 64, 76, and 104: evaluation of efficacy and safety was done by the treating physician.
- Safety Follow-Up Visit around Week 116.

Patients who discontinued CZP for lack of efficacy or safety reasons were followed up for 84 days to analyze which treatments were commonly used after treatment failure of CZP. Patients who discontinued CZP treatment due to personal reasons or as a result of the treating physician's decision were also followed up for 84 days (except for patients who withdrew consent and could not be further followed up).

The end of the study was defined as the date of the last visit of the last patient in the study.

Refer to Section 5 for relevant milestones in this study.

The schedule of study assessments by visit are presented in Table 9–1.

Table 9–1: Study schedule of assessments

Assessments[a]	Treatment period[b]									Safety Follow-Up
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
Week	**0**	**6**	**12**	**24**	**36**	**52**	**64**	**76**	**104**	**116**
Written Data Consent[c]	X	X								
Demographics/Medical history	X									
Presence of rheumatoid factor	X									
Presence of anti-cyclic citrullinated peptide antibodies	X									
RA history	X									
Concomitant medication	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X
Drug administration	X	X	X	X	X	X	X	X	X	
Joint scores (TJC, SJC) (28 joint count)	X	X	X	X	X	X	X	X	X	
Acute phase reactant (CRP or ESR)	X	X	X	X	X	X	X	X	X	
Morning stiffness	X	X	X	X	X	X	X	X	X	
Patient's Global Assessment of Disease Activity (VAS)	X	X	X	X	X	X	X	X	X	
Physician's Global Assessment of Disease Activity (VAS)	X	X	X	X	X	X	X	X	X	

Table 9–1: Study schedule of assessments

Assessments[a]	Treatment period[b]									Safety Follow-Up
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
Week	**0**	**6**	**12**	**24**	**36**	**52**	**64**	**76**	**104**	**116**
Patient's Assessment of Arthritis Pain (VAS)	X	X	X	X	X	X	X	X	X	
Fatigue Assessment Scale	X	X	X	X	X	X	X	X	X	
HAQ-DI	X	X	X	X	X	X	X	X	X	
EQ-5D	X	X	X	X	X	X	X	X	X	
Sick leave	X	X	X	X	X	X	X	X	X	
Employment status and employability due to RA	X	X	X	X	X	X	X	X	X	
Information on subsequent RA treatment										X

CRP=C-reactive protein; EQ-5D=Euro Quality of Life–5Dimensions; ESR= erythrocyte sedimentation rate; HAQ-DI; Health Assessment Questionnaire-Disability Index; RA=rheumatoid arthritis; SJC=swollen joint count; TJC=tender joint count; V=Visit; VAS=visual analog scale

[a] Only if assessed as per current clinical practice. Since this was a noninterventional study, no additional diagnostic or monitoring procedure was applied.

[b] Visits were recommended to be quarterly.

[c] Written data consent was obtained before any data were collected on study-specific forms. Written data consent could be obtained after the start of CZP treatment if the patient met all inclusion and exclusion criteria at the start of CZP treatment. For these patients, written data consent was obtained at the start of Visit 2 and prior to conducting any clinical assessment at this visit.

9.3 Subjects

9.3.1 Inclusion criteria

Patients had to have fulfilled the following inclusion/exclusion criteria at the start of CZP treatment:

- Before any data was collected on study-specific forms for a patient in this noninterventional PASS, written data consent was properly executed and documented. The patient was informed and given ample time and opportunity to think about his/her participation. It was also ensured that the patient had given his/her written consent on the use of data.
  Note: A patient could be enrolled into the study after the start of CZP treatment if he/she met all inclusion and exclusion criteria at the start of CZP treatment. Written data consent was obtained no later than the start of Visit 2 and prior to conducting any clinical assessment at Visit 2. Following written data consent (ie, enrollment into the study), all relevant data from original records was entered onto study-specific forms.
- Patient was considered reliable and capable of adhering to the observational plan (eg, able to understand and complete questionnaires, visit schedule, or medication administration) according to the judgment of the treating physician.
- Patient was male or female ≥18 years of age diagnosed with moderate to severe, active RA and were eligible for treatment with CZP therapy.
  Note: Patients enrolled into the study after the start of CZP treatment had to have a DAS28 score at the start of CZP treatment that was documented in their original records and which indicated moderate to severe RA.
- The decision to prescribe CZP was made by the treating physician independently of his/her decision to include the patient in the study.
- The patient's treatment had to be within the terms of the SmPC.

9.3.2 Exclusion criteria

Patients were not permitted to enroll in the study if any of the following criteria was met:

- Patient had previously (before Visit 1) been treated with CZP.
- Patient had known hypersensitivity to any components of CZP.

9.3.3 Removal of patients from therapy or assessment/withdrawal criteria

Patients were free to withdraw from the study at any time without prejudice to their continued care.

If a patient discontinued for any reason, this reason was recorded on the case report form (CRF). The physician was encouraged to invite the patients who discontinued CZP therapy early to return to the clinic/practice for posttreatment. A Safety Follow-Up Visit was performed 84 days after administration of the last dose of CZP.

In case a patient withdrew his/her data consent no further data was collected or submitted on this patient or caregiver. If a patient was institutionalized, this was recorded on the Medical Update form. Follow up of hospitalized patients was continued during hospitalization. Hospitalization, by itself, did not necessarily constitute a reason for discontinuation.

The treating physician was free to add or withdraw any kind of medication, or to withdraw the patient from the study at his/her own discretion.

9.4 Variables

9.4.1 Measurements for assessment of primary variable

The primary efficacy variable for the study was achieving clinical remission with DAS28 at Visit 9 (around Week 104). The definition of clinical remission was DAS28 value of <2.6. The DAS28 was calculated using the TJC and SJC, CRP, or ESR, and the PtGADA (see Section 9.5.1 and Section 9.9.2.11.1). The DAS28 was not calculated by the treating physician during the course of the study but was computed in the database for analysis purpose.

9.4.2 Measurements for assessment of secondary variables

The secondary efficacy variables were change from Baseline at Visit 9 (around Week 104) in:

- Patient's arthritis pain as measured by PAAP VAS
- Patient's physical function as measured by the HAQ-DI (by Lautenschläger et al, 1997; Fries et al, 1980)
- Disease activity measured by CDAI

9.4.3 Treatments

9.4.3.1 Description of investigational medicinal product

No investigational products were used in this study. Certolizumab pegol was provided on prescription from the treating physician. The dose was determined by the patient's treating physician. The commercially available drug of CZP was used with the trademark Cimzia. It was supplied as a commercially available product and as such was labelled as per the local requirements. It was to be stored in a refrigerator (2-8°C) and was not to be frozen. The prefilled syringe had to be kept in the outer carton in order to be protected from light.

Based on current legislation from the German Regulatory Authority, the batch number had to be documented for a biologic in the case of an AE or an SAE (Section 9.5.4.2.6).

9.4.3.2 Treatments to be administered

Certolizumab pegol was either self-administered or was administered by the physician according to standard clinical practice for the treating physician and as defined by the SmPC.

The patient was instructed to store CZP out of reach and sight of children following the instructions on the label.

9.4.3.3 Method of assigning Patients to treatment

Not applicable. This was an observational, noninterventional, noncomparative study.

9.4.3.4 Concomitant medications/treatments

All concomitant medication and treatment was recorded in the appropriate study documents (ie, CRF and source data).

9.4.3.5 Prior therapy

Patients who underwent prior therapy with CZP were excluded from the study.

9.4.3.6 Permitted concomitant treatments (medications and therapies)

The treating physician was free to add, withdraw, or alter doses of any kind of medication at his/her own discretion based on standard medical practice, and according to the marketing authorization. Physicians were to refer to the treatment label for such prescribing information. The patient was asked at each visit if he/she had had any new vaccinations since last visit.

9.4.3.7 Prohibited concomitant treatments (medications and therapies)

Not applicable.

9.4.3.8 Rescue medications

Not applicable.

9.4.3.9 Treatment compliance

In accordance with standard clinical practice the treating physician or designee assessed compliance of CZP or other RA treatments at each contact with the patient. The information was recorded in the CRF.

9.5 Data sources and measurement

9.5.1 Efficacy measurements

9.5.1.1 Arthritis assessment - TJC and SJC

The joint assessment was carried out on 28 joints. The 28 joints were shoulders; elbows; wrists (included radiocarpal, carpal, and carpometacarpal bones which were to be considered as a single unit); metacarpophalangeal (MCP) I, II, III, IV, and V joints; thumb interphalangeal (IP) joints; proximal interphalangeals (PIP) II, III, IV, and V joints; and the knees.

Artificial and ankylosed joints were excluded from both tenderness and swelling assessments.

The swelling and the tenderness of each joint were graded on a 2-point scale as set out in Table 9–2.

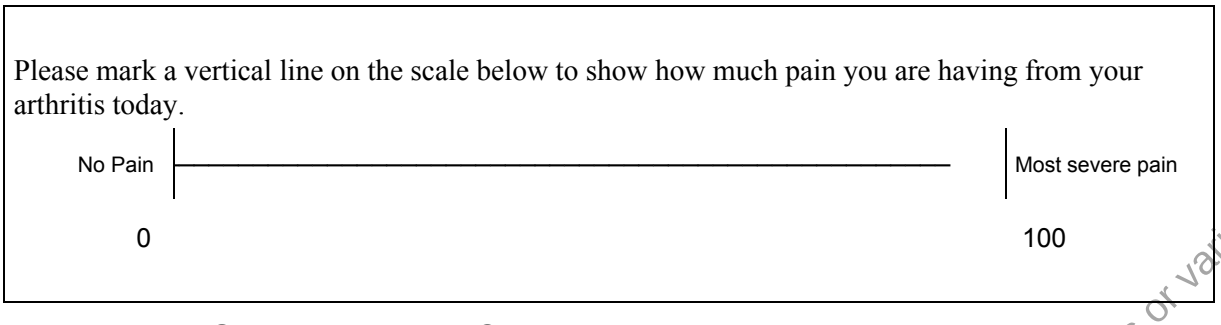
Table 9–2: Grading system for assessment of swelling and tenderness of each joint

Present	Swelling Response (28)	Tenderness Response (28)
No	None	Not tender
Yes	Detectable synovial thickening with or without loss of bony contours, or bulging synovial proliferation with or without cystic characteristics	Positive response to questioning (tender) spontaneous response elicited (tender and winced) or withdrawal by patient on examination (tender, winced, and withdrew)

9.5.1.2 PAAP using a VAS

Patients rated how much pain they were experiencing at the time of the visit caused by their arthritis (ie, my pain at this time is). This was done using the scale system presented in Figure 9-1.

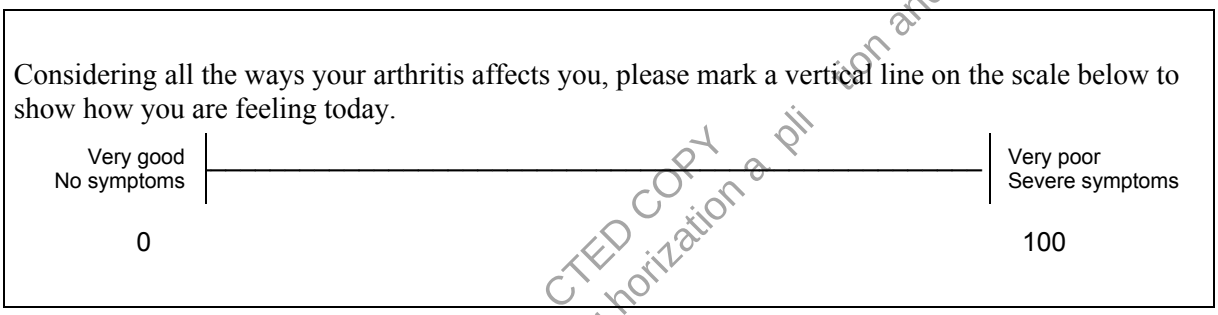
Figure 9-1: PAAP VAS



9.5.1.3 PtGADA using a VAS

Patients scored their global assessment of their arthritis, in response to the question "Considering all the ways your arthritis affects you, how are you feeling today?" using a 100mm VAS. This was done using the scale system presented in Figure 9–2.

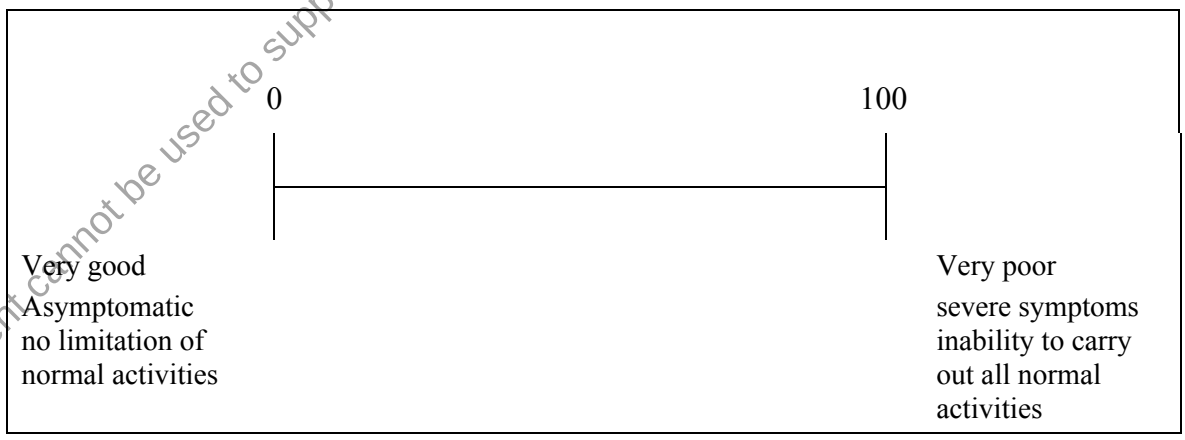
Figure 9–2: PtGADA VAS



9.5.1.4 PhGADA using a VAS

The treating physician assessed the overall status of the patient with respect to the RA signs and symptoms and the functional capacity of the patient using a 100mm VAS. When making this assessment, the physician was blinded to the results of the PtGADA. This was done using the scale system presented in Figure 9–3.

Figure 9–3: PhGADA VAS



9.5.1.5 Fatigue Assessment Scale

Patients were asked to rate their fatigue during the past week on a numeric scale. The scale used is presented in Figure 9–4.

Figure 9–4: Fatigue Assessment Scale

Please rate your fatigue (weariness, tiredness) **during the past 7 days**, on a scale of 0-10.

No Fatigue	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Fatigue as bad as you can imagine**

9.5.1.6 CDAI

The CDAI was calculated using the sum of the TJC and SJC, and the PhGADA and PtGADA.

The CDAI was not calculated by the treating physician during the course of the study, but was computed in the database for analysis purposes.

9.5.1.7 HAQ-DI

The HAQ-DI patient questionnaire (Lautenschläger et al, 1997; Fries et al, 1980), which assesses the degree of difficulty experienced by the patient in 8 categories of daily living activities using 20 questions, was completed by the patient and checked by the treating physician for completeness.

9.5.1.8 DAS28

Descriptions of DAS28 are presented in Section 9.4.1 and Section 9.9.2.11.1.

9.5.1.9 ACR/EULAR remission definition

The ACR and the EULAR suggested a provisional suggestion (Felson et al, 2011) based on a Boolean criterion. At any time point, a patient satisfied all of the following:

2011 ACR/EULAR remission criteria:

- TJC ≤1
- SJC ≤1
- CRP ≤1mg/dL
- PtGADA ≤10mm (on a scale of 0 to 100mm)

9.5.1.10 EQ-5D

Patients were asked to complete the entire document but only the VAS was used to assess the change in health status measured as EQ-5D. The EQ-5D questionnaire consisted of 5 groups to be checked based on the patient's health condition on the day and VAS.

9.5.1.11 CRP and ESR

C-reactive protein levels or ESR were analyzed by a local laboratory. The preferred assessment was CRP; alternatively ESR was also obtained, as long as the assessment was consistent throughout the course of the study.

9.5.1.12 Collection of information on sick leave

If the patient had needed to stay away from work at any time during the course of the study, an accurate record was kept in the patient's medical chart and the Observational form. This record included the duration of and reason for any sick leave.

9.5.1.13 Employment status and employability due to RA

The patient was asked at each visit on the current employment situation and employability due to RA. This record included the type of employment or the reason for unemployment. Responses to each question were reported in the patient's medical file.

9.5.1.14 Assessment of morning stiffness

The patient was asked the duration of morning stiffness by the physician at each visit. Morning stiffness was defined as the time elapsed between the time of usual awakening (even if not in the morning) and the time the patient was as limber as he/she got during a day involving typical activities.

9.5.1.15 Presence of RF or aCCP antibodies

The results of any previously recorded RFs or aCCP antibodies values were collected.

9.5.2 Pharmacokinetic/pharmacodynamic measurements

Not applicable.

9.5.3 Immunologic measurements

Not applicable.

9.5.4 Safety measurements

Safety was assessed following company and local regulations on an observational basis, based on collection of AEs. Safety variables were listed individually for detailed clinical review, when needed.

9.5.4.1 AEs

9.5.4.1.1 Definition of AE

An AE was any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product which did not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Patients were assessed at all study visits including the Withdrawal Visit (if applicable) and at the Safety Follow-Up Visit scheduled 84 days after last dose of study medication. This included all

AEs not present prior to the initial visit and all AEs which recurred or worsened after the initial visit.

Signs or symptoms of the condition/disease for which CZP was being prescribed were recorded as AEs only if their nature changed considerably, or their frequency or intensity increased in a clinically significant manner as compared to the clinical profile known to the treating physician from the patient's history or the Baseline Period.

Changes in scales and questionnaires were not assessed as AEs.

Medical procedures were not assessed as AEs; however, the reason for the procedure could have been assessed as an AE.

9.5.4.1.2 TEAEs

The definition of a TEAE is an AE occurring within 5 half-lives of the last dose, or within 70 days.

9.5.4.1.3 Injection reactions

Injection reactions were also recorded in the Noninterventional Observational form.

Injection reactions were classified as injection site reactions and systemic injection reactions.

An injection site reaction was any untoward medical event occurring at the injection site during or after study drug administration that could be at least possibly attributed to the study drug (ie, the relationship could not be ruled out).

Examples: injection site pain, injection site burning, injection site erythema, injection site itching, injection site swelling.

A systemic injection reaction was any untoward medical hypersensitivity-like event other than injection site reaction, occurring during or after study drug administration that could be at least possibly attributed to the study drug. Systemic injection reactions were further classified as acute and delayed based on timing and presentation of symptoms typical for hypersensitivity reactions.

Acute and delayed reactions to CZP were reported according to the judgment of the treating physician, based on typical features, which included (but were not limited to), the following:

1. Acute injection reactions were usually defined as at least 1 of the following signs or symptoms occurring during or within 2 hours of the CZP infusion:

- Hypotension
- Urticaria
- Flushing
- Facial or hand edema
- Throat tightness, oral cavity or lip edema
- Headache
- Shortness of breath

2. Delayed injection reactions were usually defined as at least 2 of the following 4 signs or symptoms occurring within 1 to 14 days following the infusion:

- Rash
- Fever (more than 100°F [38°C])
- Polyarthralgias
- Myalgias

9.5.4.1.4 Procedures for reporting and recording AEs

The patient was given the opportunity to report AEs spontaneously. A general prompt was also given at each study visit to detect AEs, for example:

"Did you notice anything unusual about your health (since your last visit)?"

In addition, the treating physician reviewed any self-assessment procedures (eg, questionnaires) that were employed in the study.

If an SAE was reported, UCB had to be informed within 24 hours of receipt of this information by the site. The treating physician was to forward to UCB (or its representative) a duly completed Adverse Event Report form provided by UCB, even if the data were incomplete or if it was obvious that more data were needed in order to draw any conclusions. Information recorded on this form was entered into the global safety database.

If clarifications on the AE were necessary, UCB had to request additional information from the treating physician. He/she provided the requested information within a timely manner (maximum 7 calendar days) to allow accurate and timely reporting to the concerned regulatory authorities when applicable.

The Adverse Event Report form was provided in English; all other requested information was provided in German.

Additional information (eg, autopsy or laboratory reports) received by the treating physician had to be provided within 24 hours. All documents in the local language were accompanied by a translation in English, or the relevant information included in the same document was summarized in the Adverse Event Report form. Translations into English were done by the local Drug Safety department of UCB.

UCB performed an assessment of all AEs regarding seriousness and company causality. In case UCB upgraded a case to serious (death, life threatening, medically important event, hospitalization, significant/persistent disability, congenital anomaly), the physician was informed. UCB also assessed a company causal relationship to CZP, independent of the treating physician's causal relationship.

The treating physician was specifically requested to collect and report to UCB (or its representative) any AEs, and also informed participating patients of the need to inform the treating physician of any AE during the study.

9.5.4.1.5 Description of AEs

When recording an AE, the treating physician used an overall diagnosis or syndrome using standard medical terminology, rather than recording individual symptoms or signs. The

Observational form and source documents were consistent. Any discrepancies between the patient's own words on his/her own records (eg, questionnaires) and the corresponding medical terminology were clarified in the source documentation.

9.5.4.1.6 Follow up on AEs

An AE was followed until it was resolved, had a stable sequelae, the treating physician determined that it was no longer clinically significant, or the patient was lost to follow up (ie, could not be contacted).

If an AE was still ongoing at the end of the study for a patient, follow up was requested by the Drug Safety department of the Sponsor, depending on the nature of the AE. It was provided until resolution/stable level of sequelae, the treating physician no longer deemed that it was clinically significant, or until the patient was lost to follow up (ie, could not be contacted).

9.5.4.1.7 Rule for repetition of an AE

Increases in the intensity of an AE led to the repetition of the AE being reported with:

- The outcome date of the first AE that was not related to the natural course of the disease being the same as the start date of the repeated AE, and the outcome of "worsening."
- The AE verbatim term being the same for the first and repeated AE, so that the repeated AE was easily identified as the worsening of the first one.

9.5.4.1.8 Pregnancy

If a patient became pregnant after the administration of CZP during the course of the study, UCB's local Drug Safety department was informed immediately. The treating physician had to inform the patient about the potential risk of malformations and about available alternatives, eg, voluntary termination with medical indication.

The pregnancy and the outcome (birth, miscarriage, or abortion) were documented on the Pregnancy Report and Outcome form provided to the treating physician. The progression of the pregnancy and the eventual birth (if applicable) had to be followed up using the Pregnancy Report and Outcome form in which the treating physician had to report on the health of the mother and of the child. The health of the child and the mother was followed for 30 days after birth for any significant medical issues.

Based on the child's condition UCB could request that follow up was to be continued for a longer period even after end of the study.

In cases where the partner of a male patient enrolled in a NIS became pregnant and especially in case of suspected exposure via semen, UCB asked the treating physician or designee to contact the patient and his partner to request consent via the Partner Pregnancy Consent form to contact the pregnant woman's treating physician. If she agreed to provide additional information, the Pregnancy Report and Outcome form was forwarded to the patient's partner for completion.

9.5.4.1.9 Overdose of Cimzia

Excessive dosing (beyond that allowed according to marketing authorization) was reported on the Adverse Event Report form. Any AE associated with excessive dosing was followed as any other AE. These events could be symptomatic, in that the excessive dosing results in clinical signs and symptoms, or the excessive intake could itself be a symptom.

9.5.4.1.10 Safety signal detection

Selected data from this study were reviewed periodically to detect as early as possible any safety concern(s) related to Cimzia so that treating physicians, patients, regulatory authorities, and Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) were informed appropriately and as early as possible.

The Study Physician or medically qualified designee/equivalent conducted an ongoing review of SAEs, and performed ongoing SAE reconciliations in collaboration with the Global Clinical Safety and Pharmacovigilance (GCSP) representative.

As appropriate for the stage of development and accumulated experience with Cimzia, medically qualified personnel at UCB identified additional safety measures based on the safety review.

9.5.4.2 SAE

9.5.4.2.1 Definition of SAE

Once it was determined that a patient experienced an AE, the seriousness of the AE was determined. An SAE had to meet 1 or more of the following criteria:

- Resulted in death
- Was life threatening (Life threatening did not include a reaction that might have caused death had it occurred in a more severe form)
- Resulted in significant or persistent disability/incapacity
- Was a congenital anomaly/birth defect (including that occurring in a fetus)
- Was an important medical event that, based upon appropriate medical judgment, may jeopardize the patient, and may require medical or surgical intervention to prevent 1 of the other outcomes listed in the definition of serious
- Required initial inpatient hospitalization or prolongation of hospitalization
- A patient admitted to a hospital, even if released on the same day, met the criteria for the initial inpatient hospitalization. An emergency room visit that resulted in admission to the hospital also qualified for the initial inpatient hospitalization criteria. However, emergency room visits that did not result in admission to the hospital did not qualify for this criteria and, instead, were evaluated for 1 of the other criteria in the definition of serious (eg, life-threatening adverse experience, important medical event). Hospitalization for reasons not associated with the occurrence of an AE (eg, preplanned surgery or elective surgery for a pre-existing condition that had not worsened or manifested in an unusual or uncharacteristic manner) did not qualify for reporting. For example, if a patient had a condition recorded on his/her medical history and later had a preplanned surgery for this condition, it was not appropriate to record the surgery or hospitalization as an SAE since there was no AE upon which to assess the serious criterion. Please note that, if the pre-existing condition had worsened or manifested in an unusual or uncharacteristic manner, this then qualified as an AE and, if necessary, the seriousness of the event was to be determined.

- Important medical event:

  An important medical event was defined as an AE that might not have resulted in a serious outcome (ie, resulted in death, was life-threatening, required hospitalization, resulted in a significant or persistent disability/incapacity, or resulted in a congenital anomaly/birth defect), but might be considered serious when, based upon appropriate medical judgment, jeopardized the patient or required medical or surgical intervention to prevent 1 of the serious outcomes listed above.

  Important medical events included allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias that did not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

9.5.4.2.2 Procedures for reporting SAE

If an SAE was reported, UCB Pharma had to be informed within 24 hours of receipt of this information by the site. The physician had to forward to UCB Pharma (or its representative) a duly completed physician SAE Report form provided by UCB Pharma, even if the data were incomplete, or if it was obvious that more data were needed in order to draw any conclusions. Information recorded on this form was entered into the global safety database.

An SAE Report form was provided to the physician. The physician SAE Report form was completed in German and was translated in English by the monitoring CRO.

The physician was specifically requested to collect and report to UCB Pharma (or its representative) any SAEs (even if the physician was certain that they were in no way associated with CZP), up to 84 days from the end of the study for each patient, and to also inform participating patients of the need to inform the physician of any AE within this period. Adverse events that the physician thought may be associated with CZP were reported to UCB Pharma regardless of the time between the event and the end of the study.

The reference document for the assessment of the expectedness of the AEs was the SmPC.

9.5.4.2.3 Follow up of SAE

If required, UCB Pharma (or its representative) contacted the physician to receive follow-up information on reported SAEs.

9.5.4.2.4 Adverse events of interest

An AE of interest was any AE which was listed in the European Risk Management Plan, or met another commitment requiring nonstandard expedited reporting, even if the AE did not fulfill the expedited reporting criteria of "serious," and "associated with the use of the drug." Adverse events of interest included:

- Serious infections including opportunistic infections
- Malignancies including lymphoma
- Congestive heart failure
- Demyelinating-like disorders
- Aplastic anemia, pancytopenia, thrombocytopenia, neutropenia, and leucopenia

- Serious bleeding events
- Lupus and lupus-like illness
- Serious skin reactions (eg, Stevens Johnson syndrome, toxic epidermal necrosis, and erythema multiforme)

9.5.4.2.5 Immediate reporting of AEs

The following AEs had to be reported immediately, within 24 hours:

- SAE: AEs that the physician classified as serious by the above definitions regardless of causality
- Suspected transmission of an infectious agent via a medicinal product
- AE of interest (as detailed in Section 9.5.4.2.4)

9.5.4.2.6 Documentation of batch number

Based on current legislation from the German Regulatory Authority, the batch number had to be documented for a biologic in the case of an AE or an SAE.

The batch number status ("batch number" or "batch number: unknown") was documented on the AE page beside the handwritten notice.

The documentation of the batch number status ("batch number" or "batch number: unknown") was to be in the appropriate field on the SAE page for SAEs.

9.5.4.3 Clinical laboratory measurements

Clinical laboratory values for CRP levels or ESR were collected as part of the efficacy variables (see Section 9.5.1.11).

9.5.4.4 Other safety measurements

There were no other safety measurements planned during the study.

9.6 Bias

9.6.1 Blinding

Not applicable.

9.7 Study size

A total of 1068 patients across 160 sites in Germany were planned to be enrolled in the study. The maximum duration of participation for individual patients was 116 weeks.

9.7.1 Determination of sample size

As no information on the expected remission rate (RR) for a 2-year study under real life conditions was available, an overall RR of 50%, which was the worst case scenario for sample size calculation, was used for determination of sample size. Assuming the above RR, a total of 1068 patients were considered to be sufficient to estimate with 95% confidence the overall RR with a precision of ±3.0%. Furthermore, subgroups of about 500 patients were considered to be sufficient to estimate the RR for each subgroup separately with an adequate precision (±4.5%).

In case the overall RR was much lower or higher (15% / 85%), a total of 1068 patients were considered to be sufficient to estimate with 95% confidence the overall RR with a precision of ±2.1%.

9.8 Data transformation

The physician was responsible for the prompt reporting of accurate, complete, and legible data in the Observational forms and in all required reports.

Any change or correction to the Observational forms were dated, initialed, and explained (if necessary), and did not obscure the original entry. Use of correction fluid was not permitted.

Corrections made after the physician's review and signature of the completed Observational forms were resigned and dated by the physician.

The physician maintained a list of personnel who were authorized to enter data into the Observational forms.

Detailed instructions were provided in the Observational forms completion guidelines.

Observational form/external electronic data were entered/loaded into a validated electronic database using a clinical data management system (CDMS). Computerized data cleaning checks were used in addition to manual review in order to check for discrepancies and to ensure consistency of the data.

An electronic audit trail system was maintained within the CDMS to track all data changes in the database once the data was saved initially into the system or electronically loaded. Regular backups of the electronic data were performed.

Details of quality control processes for data management are provided in Section 9.10.

Details of statistical analyses performed on the data are provided in Section 9.9.2.9.

9.9 Statistical methods

Final statistical analysis was performed according to the statistical analysis plan (amendment 1) dated 09 Mar 2015.

9.9.1 Main summary measures

Statistical analysis and generation of tables, figures, and patient data listings were performed using Statistical Analysis System (SAS®) Version 9.1.3 or higher using validated program code according to UCB BIOSCIENCES standard operating procedures (SOPs).

All variables were analyzed in an explorative manner using descriptive statistics only. Summary statistics consisted of frequency tables for categorical variables. For continuous variables, descriptive statistics (number of available observations, mean and median, standard deviation [SD], minimum, and maximum) were tabulated unless specified otherwise.

When reporting relative frequencies or other percentage values the following rules applied:

- For values where all patients fulfilled a certain criterion, the percentage value was displayed as 100
- For values where the absolute frequency was zero, there were no percentages presented at all

- All other percentage displays used 1 decimal place

Decimal places for descriptive statistics always applied the following rules:

- N was an integer
- Mean, SD, and median used 1 decimal place more than the original data

Minimum and maximum were reported using the same number of decimal places as the original value.

9.9.2 Main statistical methods

9.9.2.1 General study level definitions

9.9.2.1.1 Analysis time points

Visits were expected at Baseline (Week 0) and around Weeks 6, 12, 24, 36, 52, 64, 76, and 104 for evaluation of efficacy and safety by the treating physician. For the efficacy analysis, the actual analysis time started when the patient received the first injection of CZP. Analysis days were defined as Day 42 for Week 6, Day 84 for Week 12, Day 168 for Week 24,…, Day 728 for Week 104 after first injection. Data were collected from each patient from a visit at the time nearest to that described in the study schedule.

In order to evaluate the data from all patients who had documented data outside the scheduled visit dates, all analyses were performed at the scheduled weeks including a pre-defined time window:

- Week 0 (Visit 1): +14 days
- Week 6 (Visit 2): ±14 days
- Week 12 (Visit 3): ±14 days
- Week 24 (Visit 4): ±28 days
- Week 36 (Visit 5): ±56 days
- Week 52 (Visit 6): ±42 days
- Week 64 (Visit 7): ±42 days
- Week 76 (Visit 8): ±42 days
- Week 104 (Visit 9): ±56 days
- Safety Follow-Up (Visit 10): ±0 days

The data allocation to weeks rather than to visit had the advantage that only data within a narrow and clinically meaningful time frame were summarized and, hence, minimizing bias of the results.

If a patient had the visit exactly at the midpoint between 2 time windows (eg, Day 406 and Day 490), the patient was allocated to the preceding window. If a patient had more than 1 visit within a specific time window, the following rules were applied:

- If there were n_{tw} preceding time windows with missing visits, the n_{tw}+1 visit within the time window was allocated.

- If there were n_{tw} preceding time windows with missing visits and the number of available visits within the time window was $\leq n_{tw}$, the last visit within the time window was allocated.
- If there were no preceding time windows with missing visits, the first visit within the time window was allocated.

9.9.2.1.2 Relative day

The relative day was included in AE data, medical history, and concomitant medication listings, and was calculated as follows:

- If the start (stop) date occurred on or after the first injection, but prior to the final injection, the relative day was calculated as start (stop) date minus first injection date +1.
- If the start (stop) date occurred after the final injection, the relative day to the final injection was calculated as start (stop) date minus final injection date +1. The relative day in this situation was preceded by a "+."
- If the start (stop) date occurred before the first injection, the relative day was calculated as start (stop) date minus first injection date. The relative day in this situation was preceded by a "–."

Relative days for start and stop dates were calculated as number of days since the first/final injection of the medication. For non-TEAEs, relative day of onset was negative if the event started and stopped before the first dose.

9.9.2.1.3 Study duration and time to discontinuation

For each patient, the number of days in the treatment period of the study was calculated using the date of study termination for dropout patients or the date of last administration of medication for completed patients, the date of data consent and the date of Visit 1 as follows:

$$N_{trial} = \left(date_{Term/Last} - \min\left[date_{Cons}, date_{Vis1}\right]\right)$$

The maximum number of days in the treatment period of the study was 784 (Day 728+56). Additionally, the total number of days on treatment was calculated using the dates of last and first medication applied:

$$N_{treat} = date_{Last} + 14 - date_{First}$$

The total exposure to treatment in patient-years was then calculated using the total number of days on treatment and the Safety Follow-Up Period:

$$N_{Exp} = \left(date_{Last} - date_{First} + 70\right)/365.25$$

where 70 days represent 5 times the terminal elimination phase half-life of CZP. For the calculation of total exposure to treatment, the nominator was censored to Day 728 (±56 days) and the Safety Follow-Up Period of 70 days.

The time to discontinuation for any premature study terminations due to AE or lost to follow up was calculated as number of days using the dates of termination and first dose:

$$N_{Dis} = \left(date_{Term} - date_{First}\right)$$

9.9.2.1.4 RA duration

The RA duration of each patient was calculated using the dates of Visit 1 and the date of RA diagnosis:

$$Dur_{RA} = \left(date_{V1} - date_{RAdiag}\right) / 365.25$$

9.9.2.2 Definition of Baseline values

The Baseline value for all analyzed variables was the measured value at Visit 1 in Week 0. If a patient had Visit 1 later than a maximum of 14 days after receiving the first dose of CZP, the data was not analyzed as Baseline data.

The change from Baseline was calculated as the difference between post-Baseline value and Baseline value (ie, Visit 1).

9.9.2.3 Analysis sets

All data from any enrolled patient were listed with all available data. Patient disposition was based on the ES. The analysis set for the efficacy variables was the Full Analysis Set FAS. In general, all safety analyses were based on the SS.

9.9.2.3.1 ES

All patients who signed a data consent form were included in the ES.

9.9.2.3.2 SS

All patients who took at least 1 dose of CZP were included in the SS.

9.9.2.3.3 FAS

The FAS was defined as all patients with a DAS28≥2.6 at Baseline who took at least 1 dose of CZP and had at least 1 valid post-Baseline DAS28 value (either derived using ESR or CRP).

Note: The FAS was defined in this way because patients who had a Baseline DAS28<2.6 would already be in remission. Therefore, the primary efficacy variable to reach clinical remission would not be defined.

9.9.2.4 Treatment assignment and treatment groups

Not applicable.

9.9.2.5 Center pooling strategy

Due to the small number of patients per site, it was planned to pool all patients within the study.

9.9.2.6 Coding dictionaries

Adverse events and diseases were coded using the Medical Dictionary for Regulatory Activities (MedDRA®) Version 17.1. Medication was coded using the World Health Organization Drug Dictionary (WHO-DD) (Version September 2013). The coding was performed prior to the database lock of the study.

9.9.2.7 Definitions of study-specific derived variables

Not applicable.

9.9.2.8 Statistical/analytical issues

9.9.2.8.1 Interim analyses and data monitoring

All 4 interim analyses of this study have been described in separate interim statistical analysis plans.

9.9.2.8.2 Use of an efficacy subset of patients

No efficacy subset was defined for this study.

9.9.2.8.3 Examination of subgroups

For the analysis of the primary efficacy variable, evaluation of the following subgroups was planned:

- Early DAS28 response as defined in Section 9.9.2.11.3.3.
- Presence of relevant auto-antibodies at Baseline (cut-off depends on test used, eg, immunoglobulin M-RF enzyme linked immunosorbent assay: ≥0.110 optimetric density; Latex test: ≥20IU)
- Presence of anticytoplasmatic antibodies (aCCP antibodies or anti-mutated citrullinated vimentin [MCV]); threshold for aCCP positive patient at Baseline >50Units; threshold for anti-MCV positive patient at Baseline >50Units/mL
- Pretreatments with other anti-TNFα agents
- Pretreatments with other biologics
- Duration of RA disease (<2 years vs ≥2 years)

For the analysis of the other efficacy variables DAS28(CRP), DAS28(ESR), DAS28 overall, PAAP, HAQ-DI, CDAI, duration of morning stiffness, and patient's health-related QoL as measured on a VAS, including changes from Baseline, descriptive statistics were computed and tabulated by visit and each of the following subgroups:

- Prior treatment with anti-TNFα medication
- No prior treatment with anti-TNFα medication
- Prior treatment with other biologics
- Prior treatment with MTX
- Prior treatment with other synthetic disease-modifying antirheumatic drug (DMARD)

The number and percentage of patients in the DAS28 categories were computed and tabulated by visit and each of the following subgroups:

- Prior treatment with anti-TNFα medication
- No prior treatment with anti-TNFα medication
- Prior treatment with other biologics
- Prior treatment with MTX
- Prior treatment with other synthetic DMARDs

The number and percentage of DAS28 responders were computed and tabulated by visit and each of the following subgroups:

- Prior treatment with anti-TNFα medication
- No prior treatment with anti-TNFα medication
- Prior treatment with other biologics
- Prior treatment with MTX
- Prior treatment with other synthetic DMARDs

In addition, for the variables PAAP, CDAI, HAQ-DI, duration of morning stiffness, and patient's health-related QoL as measured on a VAS including changes from Baseline, descriptive statistics were computed and tabulated by visit and each of the following subgroups:

- Early DAS28 response
- No early DAS28 response

9.9.2.9 Study population analyses

9.9.2.9.1 Patient disposition

Among enrolled patients, the number and percentage of patients in each analysis set, the total number of patients completing Visit 9, and the summary of reasons for prematurely terminating before Visit 9 were presented.

9.9.2.9.2 Deviations from the observational plan

The number of patients excluded from the FAS was listed alongside with the primary reason for exclusion. The details regarding deviations from the observational plan can be found in Section 9.10.4 and the final statistical analysis plan amendment 1 (09 Mar 2015).

9.9.2.9.3 Demographics

Patient demographics (gender, age, and race) were summarized for the ES, SS, and the FAS. The number and percentage of patients in age categories were presented, and age was summarized with descriptive statistics.

9.9.2.9.4 Medical history and concomitant diseases

Medical history (including prior and/or concomitant diseases) was listed and summarized by MedDRA System Organ Class (SOC) and preferred term (PT). It included the number and percentage of patients in the SS with such histories present.

Summaries (number of patients and percentages) were presented separately for the status of the RF, the status of the antibodies against citrullinized peptide-protein-antigenes (ACPA), the duration of RA (descriptive statistics), and the duration of RA as categorical analysis (ie, <2 years, ≥2 years) for all patients in the SS and FAS. Any partially missing dates of RA diagnosis were imputed as specified in Section 9.9.3.3.

9.9.2.9.5 Prior and concomitant medications

Medications with a start date prior to the first dose of CZP at study onset were considered prior medications. Medications with a start date prior to, at, or after the first dose of CZP were

considered as concomitant medications if the duration overlapped at least 1 day with the treatment period. Medications with a missing start date whose stop date was either unknown or after the date of the first injection of CZP were considered concomitant.

Non-RA medications were summarized (frequency of patients) using the 1-level (1 digit) and the 2-level (2 digits) Anatomical Therapeutic Chemical (ATC) Classification code of the WHO-DD dictionary. Medications for RA were summarized (frequency of patients) using the 3-level and the 4-level ATC code of the WHO-DD dictionary. Summary tables of both, medications by excluding RA medications and RA medication only, were prepared for prior and concomitant medication for all patients in the SS. Prior and concomitant medications by excluding RA medications and RA medication only were also listed. Any missing or partially missing start or stop dates were imputed according to Section 9.9.3.3.

In addition, the number and percentage of patients with prior treatment of anti-TNFα inhibitors, other biologics, MTX, and other synthetic DMARDs were tabulated for all patients in the SS and FAS, where available.

9.9.2.10 Treatment compliance

In accordance with standard clinical practice, the treating physician or designee assessed compliance of CZP or other RA treatments at each contact with the patient. The information was recorded in the Observational form. A listing was provided that included all patients who had taken and who had not taken CZP according to the SmPC.

9.9.2.11 Efficacy analyses

Analyses for efficacy variables were performed on the patients in the FAS.

9.9.2.11.1 Primary efficacy analyses

9.9.2.11.1.1 Confidence intervals for the RR

Clinical remission based on the DAS28 was defined as a patient achieving a value of DAS28<2.6. The RR was the proportion of those patients who had reached clinical remission at any given visit. The 95% CI of the clinical RR was constructed from an approximation to the Normal distribution. The standard error (SE) of the clinical RR was calculated using:

$$SE = \sqrt{RR \cdot (1 - RR)/n}$$

The 95% CI was then constructed using:

$$RR - 1.96 \cdot SE \leq RR \geq RR + 1.96 \cdot SE$$

where the left-hand side of the inequality was the 95% lower confidence limit (LCL) and the right-hand side was the 95% upper confidence limit (UCL).

9.9.2.11.1.2 Calculation of DAS28

Depending on whether the CRP or the ESR was measured, the DAS28 was calculated using the equation:

$$DAS28(CRP) = 0.56 \cdot \sqrt{TJC} + 0.28 \cdot \sqrt{SJC} + 0.014 \cdot PtGADA + 0.36 \cdot \ln(CRP + 1) + 0.96$$

or

$$DAS28(ESR) = 0.56 \cdot \sqrt{TJC} + 0.28 \cdot \sqrt{SJC} + 0.014 \cdot PtGADA + 0.70 \cdot \ln(ESR)$$

where TJC and SJC were calculated as described in Section 9.5.1.1, PtGADA (mm) was the Patient's Assessment of Disease Activity on a VAS ranging from 0 to 100, the CRP was measured in mg/L, and the ESR was measured in mm/h. If any individual term was missing, then the DAS28 was set to missing.

If CRP and ESR measurements were available for a patient at a given visit, the DAS28(CRP) was preferred. However, if only ESR measurements were available for a patient at other visits, the DAS28(ESR) was preferred for consistency. If the available Baseline DAS28 was based on a different measurement than at other visits, no variables were derived (ie, change from Baseline). Change from Baseline in DAS28 was only derived if the DAS28 at both visits was based on the same measurement, ESR or CRP.

For the analysis, DAS28 values were categorized into the following groups (Aletaha and Smolen, 2005; Pincus et al, 2008):

- DAS28<2.6: clinical remission
- DAS28 from 2.6 to ≤3.2: LDA
- DAS28 from >3.2 to 5.1: moderate disease activity
- DAS28>5.1: high disease activity

9.9.2.11.1.3 Presentation of the clinical RR

The number and percentage of patients with DAS28<2.6 at Week 104 were computed alongside their 95% CIs and tabulated. Missing data were imputed using NRI (see Section 9.9.3).

The analysis was repeated for all subgroups, as defined in Section 9.9.2.8.3.

9.9.2.11.1.4 Supportive and sensitivity analyses of the primary efficacy variables

To evaluate the robustness of the imputation method, the number and percentage of patients with DAS28<2.6 at Week 104 were computed alongside their 95% CIs and tabulated using MMRM imputation and using nonmissing observations. The MMRM imputation was performed on the individual DAS28 components (see Section 9.9.3). The RR was then calculated using the imputed DAS28 values at Week 104.

Both analyses were repeated for all subgroups as defined in Section 9.9.2.8.3.

9.9.2.11.2 Secondary efficacy analyses

9.9.2.11.2.1 Calculation of CDAI and change from Baseline in CDAI

The CDAI was calculated with the equation:

$$CDAI = TJC + SJC + PtGADA/10 + PhGADA/10$$

where PtGADA (mm) was the Patient's Global Assessment of Disease Activity using a VAS ranging from 0 to 100 and PhGADA (mm) was the Physician's Global Assessment of Disease

Activity using a VAS ranging from 0 to 100. Thus, the CDAI ranges from 0 to 76. If any individual term was missing, then the CDAI was set to missing.

Descriptive statistics for the CDAI, including changes from Baseline at Week 104, were computed and displayed. Missing data were imputed using MMRM imputation (see Section 9.9.3).

The MMRM imputation was performed on the individual CDAI components. Descriptive statistics for the CDAI including changes from Baseline at Week 104 were also computed and displayed for patients with nonmissing observations.

The analysis was repeated for all subgroups, as defined in Section 9.9.2.8.3.

9.9.2.11.2.2 Change from Baseline in PAAP

Descriptive statistics for the PAAP, including changes from Baseline at Week 104, were computed and tabulated. Missing data were imputed using MMRM imputation (see Section 9.9.3). Descriptive statistics for the PAAP, including changes from Baseline at Week 104, were also computed and displayed for patients with nonmissing observations.

The analysis was repeated for all subgroups, as defined in Section 9.9.2.8.3.

9.9.2.11.2.3 Change from Baseline in HAQ-DI

Derivation of the HAQ-DI:

The HAQ-DI contains 20 items on a 4-point scale ranging from zero (without any difficulty) to 3 (unable to do). The 20 items are grouped in 8 categories with 2 to 3 items each. The categories are: Dressing and Grooming (2 items), Arising (2), Eating (3), Walking (2), Hygiene (3), Reach (2), Grip (3), Activities (3).

In addition to that, there is a question for checking any aids or devices used, and a question for help from other persons related to each category.

If the patient provided at least 1 item within a category, the score was calculated for that category. If no items were provided, aids/devices and help from other persons were ignored in this category as well.

The HAQ-DI was calculated using the traditional method:

- Scores for each category were derived by using the highest scored item within a category.
- If the score for a category was ≤1 and an aid/device was used or help from other persons was needed, the score was adjusted to 2.
- If the score for a category was ≥2 and an aid/device was used or help from other persons was needed, the score remained unchanged.
- The index was calculated by summing up the adjusted scores for each category and dividing the sum by the number of evaluated categories.

The patient had to have a score for at least 6 of the 8 categories; otherwise a HAQ-DI was not calculated. Scores were set to missing if any of the items in a category, the aid/device, or help from other persons allocated to the category was missing. Aids and devices specified in the "Other" field were not to be used in the calculations.

Presentation of the HAQ-DI:

Descriptive statistics of the HAQ-DI, including changes from Baseline at Week 104, were computed and tabulated. Missing data was imputed using MMRM imputation (see Section 9.9.3). Descriptive statistics for the HAQ-DI, including changes from Baseline at Week 104, were also computed and displayed for patients with nonmissing observations.

The analysis was repeated for all subgroups, as defined in Section 9.9.2.8.3.

9.9.2.11.3 Other efficacy analyses

9.9.2.11.3.1 Presentation of DAS28

Descriptive statistics for the DAS28(CRP), DAS28(ESR), and DAS28 overall, including changes from Baseline, were computed and tabulated by visit using nonmissing observations and missing data imputation. Missing data was imputed using MMRM imputation (see Section 9.9.3).

A table displaying the number and percentage of patients in the DAS28 categories alongside their 95% CIs was tabulated by visit.

9.9.2.11.3.2 Clinical remission and ACR/EULAR remission

Definition of ACR/EULAR remission:

The ACR and EULAR suggested a provisional definition (Felson et al, 2011) based on Boolean criteria. At any time point, a patient had to satisfy all of the following:

- TJC≤1
- SJC≤1
- CRP≤1 in mg/dL (ie, ≤10mg/L)
- PtGADA≤10mm

Presentation of the clinical RR:

The number and percentage of patients in clinical remission (ie, DAS28<2.6) were computed alongside their 95% CIs and tabulated by visit using nonmissing observations and missing data imputation. Missing data were imputed using NRI and MMRM imputation (Section 9.9.3).

The number and percentage of patients in remission according to the ACR/EULAR 2011 remission criteria were computed alongside their 95% CIs and tabulated by visit using nonmissing observations and missing data imputation. Missing data were imputed using NRI and MMRM imputation (Section 9.9.3)

9.9.2.11.3.3 DAS28 clinical response

DAS28 response definition:

The DAS28 response was defined as a decrease in DAS28≥1.2 at post-Baseline when compared with the Baseline value.

An early DAS28 responder was defined as a patient whose DAS28 decrease was ≥1.2 for at least 1 of the Visits 2 or 3 (ie, Week 6 or Week 12) when compared with the Baseline value.

Presentation of DAS28 response:

The number and percentage of DAS28 responders were computed alongside their 95% CIs and tabulated by visit using nonmissing observations and missing data imputation. Missing data were imputed using NRI and MMRM imputation (Section 9.9.3). Percentage of patients with DAS28 response by visit was graphically displayed.

9.9.2.11.3.4 Change from Baseline in TJC and SJC

Scores of swollen and tender joints:

The number of tender joints (TJ) and the number of swollen joints (SJ) was counted on 28 joints (Section 9.5.1.1)

Artificial and ankylozed joints were excluded from both tenderness and swelling assessments. Single joints that were recorded as not available were excluded from the analysis.

Swelling and tenderness received a score of either zero (none or no response, respectively) or 1 (visible or positive, respectively). The TJC and SJC were calculated using the sum of all 28 joints, weighted by the number of the assessed joints (AJ):

$$SJC = 28 \cdot \sum_{i=1}^{n} SJ \Big/ \sum_{i=1}^{n} AJ$$

and

$$TJC = 28 \cdot \sum_{i=1}^{n} TJ \Big/ \sum_{i=1}^{n} AJ$$

The weighting accounted for any missing observations. If a joint could not be assessed at Baseline, then that joint was set to missing throughout the study. If a joint could not be assessed for either tenderness or swollenness, then that joint was set to missing for both. If more than 50% of joints were not assessable for either tenderness or swelling, then no imputation was performed and the total TJC or SJC was set to missing.

Change from Baseline in TJC and SJC:

Descriptive statistics for TJC and SJC, including changes from Baseline, were computed and displayed by visit using nonmissing observations and missing data imputation. Missing data were imputed using MMRM imputation (Section 9.9.3).

9.9.2.11.3.5 Change from Baseline in ESR and/or CRP

Descriptive statistics for ESR and CRP, including percent change from Baseline and ratio to Baseline, were computed and displayed by visit using nonmissing observations and missing data imputation. For ratio to Baseline, the geometric mean, the coefficient of variation of the geometric mean, the first and the third quartile, median, minimum, and maximum were presented.

Missing data were imputed using MMRM imputation (Section 9.9.3).

9.9.2.11.3.6 Change from Baseline in CDAI, PtGADA, PhGADA, PAAP, Fatigue Assessment Scale, HAQ-DI, duration of morning stiffness

For all these variables, descriptive statistics, including changes from Baseline, were computed and displayed by visit using nonmissing observations and missing data imputation. Missing data were imputed using MMRM imputation (Section 9.9.3).

9.9.2.11.3.7 Change from Baseline in EQ-5D VAS

Descriptive statistics for the patient's health-related QoL as measured on a VAS, including changes from Baseline, were computed and tabulated by visit using nonmissing observations and missing data imputation. Missing data were imputed using MMRM imputation (Section 9.9.3).

The percentage of patients reporting problems in the 5 domains was tabulated by visit and graphically displayed for Baseline, Week 12, Week 52, and Week 104.

9.9.2.11.3.8 Changes of concomitant DMARDs and corticosteroids

The patient's number of concomitant DMARDs (eg, MTX) and oral or parenteral corticosteroids (eg, prednisone) was summarized categorically as change during treatment (ie, number and percentage of patients with changes during treatment).

Three categories were defined:

- Increase under treatment: all patients with an increase in the number of DMARDs or corticosteroids since Baseline.
- No change under treatment: all patients with no change in the number of DMARDs or corticosteroids since Baseline. If a concomitant DMARD was temporarily stopped for up to 3 months, it was counted as no change. If a concomitant corticosteroid was temporarily stopped for up to 1 month, it was counted as no change.
- Decrease under treatment: all patients with a decrease in the number of DMARDs or corticosteroids since Baseline.

9.9.2.11.3.9 Incidence of discontinuation of CZP treatment due to DAS28 remission

The number and percentage of patients with discontinuation of CZP treatment due to DAS28 remission were computed alongside their 95% CIs and tabulated by visit using nonmissing observations.

9.9.2.11.3.10 Employment status

The number and percentage of patient's employment status were computed and tabulated by visit using nonmissing observations. In addition, the number and percentage of the reasons for part-time employment or unemployment were computed alongside their 95% CIs and tabulated by visit using nonmissing observations.

9.9.2.11.3.11 Employability of patients

Employability was defined as all patients who were full-time employed, part-time employed, or unemployed and seeking work. The number and percentage of patients who were employable were computed alongside their 95% CIs and tabulated by visit using nonmissing observations.

9.9.2.11.3.12 Sick leave

The number and percentage of patients with sick leave days per month including their reasons were computed alongside their 95% CIs and tabulated by visit using nonmissing observations. Descriptive statistics of the number of sick leave days per month due to RA, and in total, were calculated and tabulated by visit using nonmissing observations.

9.9.2.11.3.13 RA treatment following discontinuation of CZP

The number and percentage of patients who continued with RA treatment following discontinuation of CZP were computed alongside their 95% CIs and tabulated by visit using nonmissing observations. The percentage of those patients was based on the number of patients who discontinued from CZP treatment.

The number and percentages of patients on RA treatment with anti-TNFα medication, MTX, DMARDs, and other biologics following discontinuation of CZP were calculated.

9.9.2.12 Safety analyses

All analyses for safety variables were performed using the patients in the SS.

9.9.2.12.1 Extent of exposure

The extent of exposure is defined in Section 9.9.2.1.3. Summary statistics on the number of days of CZP exposure were tabulated. The summary table was repeated for all patients in the FAS.

The number and percentage of where the injections were performed (ie, at home or at the study site) and who administered the injections were computed and displayed by visit. In addition, the number and percentage of patients who did not take the CZP dose as planned according to the SmPC were computed and displayed by visit.

9.9.2.12.2 Analysis of AEs

9.9.2.12.2.1 Definitions and derived variables for AEs

Treatment-emergent AEs were defined as AEs which occurred after CZP was injected up to a period of 70 days after the last injection.

The duration of AE (AE_{Durat}) was calculated as the difference between AE resolution date (AE_{Stop}) and onset date of the AE (AE_{Start}), and was reported in days:

$$AE_{Durat} = AE_{Stop} - AE_{Start} + 1$$

The exposure-adjusted event rate (EAER) for specific TEAEs was scaled to 100 patient-years and calculated using:

$$EAER = 100 \cdot N_{AE} \Big/ \sum_{i=1}^{n} N_{Exp,i}$$

where N_{AE} was the total number of TEAEs.

The exposure-adjusted incidence rate (EAIR) was defined as the number of patients (n) with a specific TEAE adjusted for the total exposure:

$$EAIR = 100 \cdot n \Big/ \sum_{i=1}^{n} N_{Exp,i}$$

If a patient had multiple events, the total exposure was calculated to the first event. If a patient had no events, the total exposure was censored at the last follow up time for the patient.

Exact Poisson 95% CIs for incidence rates were calculated using the relationship between the Poisson and the Chi-square distribution (Fay and Feuer, 1997):

$$LCL = \chi^2_{2n,\alpha/2} / 2$$

$$UCL = \chi^2_{2(n+1),1-\alpha/2} / 2$$

where n was the number of a specific TEAE (or the number of patients with a specific TEAE) for the incidence rate of interest and was the basis for the number of the degrees of freedom for the Chi-square quantile for the upper tail probability χ^2.

9.9.2.12.2.2 Presentation of AEs

Adverse events that occurred during this study were presented by SOC, high level term (HLT), and PT in a frequency table, giving the number of events, the number of patients, and the percentage of patients who experienced the event. Patients with multiple AEs were only counted once within each PT and within each SOC.

A listing of all adverse events was provided. Any missing or partially missing start or stop dates was imputed according to Section 9.9.3.3.

An overall summary table of all AEs was presented.

Tables for TEAEs displayed the following information:

- TEAEs overview including EAERs and incidence rates including their exact 95% CIs.
- Serious TEAEs.
- Nonserious TEAEs.
- TEAEs of interest.
- TEAEs leading to permanent discontinuation of CZP medication.
- TEAEs leading to death.
- TEAEs causing local reactions at the injection site.
- Systemic injection reaction TEAEs by time response (immediate, delayed).
- Drug-related TEAEs.
- Drug-related serious TEAEs.
- Drug-related TEAEs causing local reactions at the injection site.
- Individual patient numbers experiencing a given TEAE, grouped SOC, HLT, PT, intensity, and relation to CZP medication.
- A glossary of all treating physician-reported terms, grouped by coded SOC, HLT, and PT. This listing served as a glossary of PTs, showing which reported terms were summarized under each PT.

Drug-related TEAEs were reported as the sum of all TEAEs in the categories related, possibly related, or those with missing response according to the company's causality assessment.

Nonrelated TEAEs were all TEAEs in the categories unlikely related and not related.

All frequency tables were sorted alphabetically by SOC then by HLT. Within HLT, it was sorted by decreasing frequency of PT.

9.9.3 Missing values

9.9.3.1 Handling of dropouts or missing data

For the analysis of the patients in the FAS, missing values of binomial variables (eg, DAS28 remission) were imputed using the NRI. A patient who had withdrawn prematurely from the study for any reason or who had a missing assessment at a given visit was counted as nonresponder or nonremitter for that visit.

For the analysis of the patients in the FAS, missing values of multinomial variables or continuous variables (eg, change from Baseline in DAS28) were imputed using a MMRM. The MMRM analysis was a special case of the mixed-effects regression model (Siddiqui et al, 2009) and generally written as:

$$Y = \mathbf{X}\beta + \mathbf{Z}\nu + \varepsilon$$

where Y was the continuous or multinomial variable of which the missing value was estimated; X was the n×p matrix of fixed effects in the model; Z was the n×r matrix of variables related to the random component in the model; β was the p×1 vector of regression coefficients for the fixed effects; ν was the r×1 vector of random patient effects; and ε was the n×1 vector of the random residuals in the model.

The MMRM imputation of missing values of a variable because of patient withdrawal or of missing assessment at a given visit was based on a mixed model with Visit (categorical Visit 1, 2, 3, etc), gender (male, female), disease duration (≤2 years, >2 years), patient status at termination (completed, AE, lack of efficacy, lost to follow up, disease remission, consent withdrawn, other reasons), and RF (positive, negative). If the variable was change from Baseline, then the Baseline values of the variable was included as covariate. The multiple visits for each patient were the repeated measures as random effect within each patient. Missing data at Baseline was not imputed.

The covariance structure of the within-patient errors was assumed to be unstructured. Since the unstructured covariance assumption required fitting a lot of parameters, it led to either nonconvergence of the model fit or to zero estimates of the random model term and its SE. If one of those, or related problems occurred, it was assumed that measurements between visits were correlated. The preferred assumption was that the correlation was dependent on time. For this the covariance structure was assumed to be autoregressive first order. If that led to numerical problems, the more general case, the Toeplitz covariance structure was used. If both methods failed to produce a solution, then the covariance structure Compound Symmetry was used. All 3 methods had the advantage of being simple, but also were based on sound assumptions in terms of the data.

The resulting estimates of the regression model were used for replacing the missing values of a variable. If 1 of the regressor variables was missing or if 1 of the estimates was out of range (eg,

outside the VAS scale), then the adjusted least squares (LS) mean at the given visit was used for replacing the missing value. The imputed value for a composite variable was based upon the imputed values of the individual components for that variable.

9.9.3.2 Specific rules for patient-reported outcomes

The following rules were applied for analysis of out of range and ambiguous answers (ie, invalid or unable to interpret answers) to the HAQ-DI, EQ-5D, and the Fatigue Assessment Scale and were part of the data cleaning conventions.

9.9.3.2.1 Out of range answers

In case of an out of range answer (ie, an answer that did not correspond to any possible response proposed in the questionnaire, eg, "?," "I don't know," or any value superior or inferior to the ones specified in the response options), the answer was scored as "missing." However, in case the patient selected 1 of the proposed responses but added a comment (for instance "6 +++" or "5 ?"), the response (ie, "6" or "5") was retained for scoring but not the comment (ie, "+++" or "?").

In the same way, if the patient selected 1 of the proposed responses but added a value superior or inferior to the ones specified in the responses options (for instance "4/5" or "-1/2" on a 5-point scale ranging from 0 to 4), the response corresponding to the possible responses options (ie, "4" or "2") was retained for scoring but not the values superior or inferior to the responses options (ie, "5" or "-1").

9.9.3.2.2 Ambiguous answers

In case of an ambiguous answer (ie, multiple responses to a question allowing only a single response, a response marked between 2 allowed responses), the following rules applied:

- Multiple responses to a question allowing only a single response:
  - If half or more responses were marked (ie, 4 responses marked on a 7-point scale, 3 responses marked on a 5-point scale, 2 responses to a Yes/No item…): the answer was scored "missing."
  - If less than half responses were marked:
    - if the responses were NOT adjacent to each other: the answer was scored "missing."
    - if the responses were adjacent to each other ("2/3" or "2/3/4," for instance), the more severe score was retained.
- If a response was marked between 2 allowed responses (for instance, the patient marked his/her response between 2 and 3 on a 4-point scale allowing only responses 1, 2, 3, and 4), the nearest more severe score was retained.

9.9.3.3 Handling of missing or partially missing dates

In case of missing or partially missing dates, the following rules for AEs and concomitant medication data applied:

- Missing start day, but month and year present: If CZP had been taken in the same month as the occurrence of the AE/concomitant medication, then the start day of the event was

assigned to the day on which CZP was taken for the first time. Otherwise the start day was set to the first day of that month and year.

- Missing start day and month, but year present: If CZP had been taken in the same year as the occurrence of the AE/concomitant medication, then the start day and month was assigned to the day and month on which CZP was taken for the first time. Otherwise the start day and month was set to the first of January of that year.
- Missing start day, month, and year: The start day, month, and year was assigned to the earliest day, month, and year on which CZP was taken. If the event end date preceded the start date of first study medication, the start date was set to the first of January of the year of the end date.
- Missing stop day, but month and year present: Regardless of the timing of dosing, the stop day was set to the last day of the month.
- Missing stop day and month, but year present: The stop day and month was set to the 31st of December of that year or, in case of the current year, to the date of the last known visit.
- Missing stop day, month, and year: The stop date was set to the date of the last visit. If the start date of the event was recorded as after the last known visit, the stop date was set to the event start date.

If a start date was partially missing or completely missing and the stop date was known or partially known, the start date was assigned no later than the stop date.

Missing or partially missing dates of RA diagnosis were imputed to the most recent feasible date (ie, last day of the month if only day was missing, or the last day of the year if day and month were missing).

9.9.4 Sensitivity analysis

9.9.4.1 Multicenter studies

The effect of site (regions) was not evaluated for this study.

9.9.4.2 Multiple comparisons/multiplicity

Only exploratory analyses were performed for this study.

9.9.5 Amendments to the statistical analysis plan

Further subgroups were added for analysis of secondary and other efficacy variables (see Section 9.9.2.8.3). These analyses were necessary to enhance the interpretation of the results.

The variables PtGADA and PhGADA, including their changes from Baseline, were added for analysis (Section 9.9.2.11.3.6), since they were part of the primary and secondary endpoints and their evaluation improve the interpretation of the primary and secondary objectives of the study.

9.10 Quality control

9.10.1 Study monitoring

UCB Pharma (or designee) monitored the study to meet the Sponsor's monitoring SOPs and to ensure that study initiation, conduct, and closure were adequate. Monitoring of the study was delegated by UCB Pharma to a CRO.

The physician and his/her staff were expected to cooperate with UCB Pharma (or designee) and to be available during the monitoring visits to answer questions sufficiently and to provide any missing information. The physicians/institutions permitted direct access to source data/documents for study related monitoring, audits, IRB/IEC review, and regulatory inspections.

The physician allowed UCB Pharma (or designee) to periodically review all Observational forms and corresponding source documents (eg, hospital and laboratory records for each patient). Monitoring visits provided UCB Pharma (or designee) with the opportunity to evaluate the progress of the study, verify the accuracy and completeness of Observational forms, ensure that all observational plan requirements, applicable authorities regulations, and physician obligations were being fulfilled, and to resolve any inconsistencies in the study records.

9.10.2 Source data verification

Source data verification was performed as specified in the monitoring manual to ensure the accuracy and credibility of the data obtained. During monitoring visits, reported data were reviewed and verified with regard to being accurate, complete, and verifiable from source documents (eg, patient files, laboratory notes). All data reported on the Observational forms were supported by source documents, unless otherwise specified.

9.10.3 Database entry and reconciliation

Observational form/external electronic data were entered/loaded into a validated electronic database using a CDMS. Computerized data cleaning plausibility checks were used in addition to manual review in order to check for discrepancies and to ensure consistency of the data.

An electronic audit trail system was maintained within the CDMS to track all data changes in the database once the data had been saved initially into the system or electronically loaded. Regular backups of the electronic data were performed.

9.10.4 Protocol deviations

Information on important protocol deviations and how to identify them (ie, via the clinical database or through review of protocol deviation logs provided by the clinical monitors) was documented in a separate specifications document which was approved prior to the Data Review Meeting (DRM) held prior to database lock.

Where possible, deviations from the observational plan were identified programmatically. The deviations from the observational plan were considered according to the following general categories:

- Data consent procedures
- Inclusion/exclusion criteria
- Withdrawal criteria
- Concomitant medications which affect the efficacy analysis
- CZP administration compliance with the SmPC

Patients, who violated the following criteria, were excluded from the efficacy analysis:

- The patient had a DAS28 ≤3.2 at Baseline.

- The patient had been treated with CZP for >14 days prior to the Baseline visit.
- The patient had taken any anti-TNFα medication other than CZP or anti-inflammatory biological agents during the study.

A list of patients with important deviations from the observational plan was agreed upon during the DRM and was documented in the DRM minutes.

9.10.5 Audits

The physician permitted study-related audits by auditors mandated by UCB Pharma and inspections by domestic or foreign regulatory authorities, after reasonable notice.

The main purpose of an audit or inspection was to confirm that the rights and well-being of the patients enrolled had been protected, that enrolled patients (ie, those signing consent and undergoing study procedures) were appropriate for the study, and that all data relevant for the evaluation of CZP had been processed and reported in compliance with the planned arrangements, the observational plan, physician's site, and IEC SOPs, and applicable regulatory requirements.

The physician provided direct access to all study documents, source records, and source data. If an inspection by a regulatory authority was announced, the physician had to immediately inform UCB Pharma (or designee).

No audits were performed.

10 RESULTS

10.1 Participants

A table with disposition by site is presented in Table 1.2. Disposition and discontinuation reasons are presented for all analysis sets in Table 1.3. Number and percentage of patients with CZP treatment discontinuation due to DAS28(CRP) remission including 95% CIs by visit, using nonmissing observations, is presented in Table 3.11. Number and percentage of patients on RA medication after CZP discontinuation is presented in Table 3.15. By-patient listings of patient disposition and reason for discontinuation from the study are provided in Listing 1.3 and Listing 1.5, respectively, for the ES. A by-patient listing of visit dates is provided in Listing 1.6, for the ES. For the ES, study eligibility criteria text is provided in Listing 1.1, and patients who did not meet study eligibility criteria are provided in Listing 1.2. A listing of comments is presented in Listing 1.7. A listing of procedure history is presented in Listing 2.2.4.

Patient disposition is summarized in Table 10–1.

Table 10–1: Disposition at study entry - Enrolled Set

Disposition	Overall N=1117 n (%)
Enrolled	1117 (100)
Baseline failures	49 (4.4)
Primary reason for Baseline failure	
Inclusion/Exclusion	3 (0.3)
Remission of disease	42 (3.8)
Consent withdrawn	4 (0.4)
Other	1 (0.1)
Valid Baseline	1068 (95.6)

N=total number of patients; n=number of patients with data
Note: Enrolled=Number of patients with signed patient data consent. A Baseline failure was a patient that was not enrolled due to the reasons listed in the table.
Note: Multiple reasons were possible if the treating physician decided to state more than 1 primary reason.
Note: Percentages were based on the number of patients enrolled.
Data source: Table 1.1

A total of 1068 patients were planned to be enrolled in the study. Of the 1117 patients enrolled, 49 patients (4.4%) were failures at Baseline (Table 1.1), the main reason being disease remission (42 patients [3.8%]). The remaining failures at Baseline were due to withdrawn consent (4 patients [0.4%]), inclusion/exclusion criteria not met (3 patients [0.3%]), and other (1 patient [0.1%]) (Table 10–1). A total of 1068 patients had a valid Baseline.

Summary of disposition and discontinuation reasons are presented in Table 10–2, for all analysis sets.

Table 10–2: Disposition and discontinuation reasons

Disposition	ES N=1117 n (%)	SS N=1111 n (%)	FAS N=851 n (%)
Not treated	6 (0.5)	0	0
Treated	1111 (99.5)	1111 (100)	851 (100)
Started study	1117 (100)	1111 (100)	851 (100)
Completed study	402 (36.0)	402 (36.2)	331 (38.9)
Discontinued	702 (62.8)	696 (62.6)	510 (59.9)
Primary reason for discontinuation from the study			
Adverse Event	233 (20.9)	232 (20.9)	156 (18.3)
Lack of efficacy	332 (29.7)	332 (29.9)	263 (30.9)
Lost to follow up	49 (4.4)	49 (4.4)	33 (3.9)
Remission of disease	11 (1.0)	11 (1.0)	8 (0.9)
Consent withdrawn	34 (3.0)	31 (2.8)	19 (2.2)
Other	43 (3.8)	41 (3.7)	31 (3.6)
Other (eg, missing data)	13 (1.2)	13 (1.2)	10 (1.2)

ES=Enrolled Set; FAS=Full Analysis Set; N=total number of patients; n=number of patients with data; SS=Safety Set
Data source: Table 1.3

All 1117 patients were included in the ES, regardless of whether they had a valid Baseline. In the ES, CZP was not given to 6 of the 1117 patients and those patients were excluded from the SS. Therefore, at the start of the study the patient population in ES, SS, and FAS was 1117, 1111, and 851, respectively (Table 10–2).

At study completion, the patient population in ES, SS, and FAS was 402 (36.0%), 402 (36.2%), and 331 (38.9%). In the SS, the majority of discontinuations were due to lack of efficacy (332 patients [29.9%]) and AEs (232 patients [20.9%]), while disease remission led to the discontinuation of 11 patients (1.0%) (Table 1.3, Listing 1.3 and 1.5). The percentage of discontinuations in the ES and FAS due to lack of efficacy and AEs was similar to that in the SS. Due to missing study Observational form termination page for 13 patients (1.2%) in ES and SS; and 10 patients (1.2%) in FAS; the patients were considered as discontinued in the study.

It has been observed that prior treatment with biologics can have an influence on the efficacy of CZP, and a majority of the patients in the study were pretreated with other biologics (see Section 10.2.1.3), (Chatzidionysiou, et al, 2015). Also, the criteria for lack of efficacy were not predefined in the protocol and were dependent on the physician's judgment.

10.2 Descriptive data

10.2.1 Demographic and other Baseline characteristics

10.2.1.1 Patient demographics

A by-patient listing of demographics is provided in Listing 2.1.1, for the ES. Demographics for the ES, SS, and FAS are summarized in Table 2.1.1, Table 2.1.2, and Table 2.1.3, respectively.

A summary of Baseline patient demographics is presented in Table 10–3, for all the analysis sets.

Table 10–3: Demographics at Baseline summary

Variable	Statistic	ES N=1117	SS N=1111	FAS N=851
Age (years)	n	1116	1111	851
	Mean (SD)	55.1 (12.4)	55.0 (12.4)	55.4 (12.1)
	Range	19, 85	19, 85	22, 84
Gender:				
Male	n (%)	247 (22.1)	246 (22.1)	182 (21.4)
Female	n (%)	870 (77.9)	865 (77.9)	669 (78.6)
Missing	n (%)	0	0	0
Racial Group:				
American Indian/Alaskan native	n (%)	0	0	0
Asian	n (%)	4 (0.4)	4 (0.4)	2 (0.2)
Black	n (%)	1 (0.1)	1 (0.1)	1 (0.1)
Native Hawaiian or other Pacific Islander	n (%)	1 (0.1)	1 (0.1)	0
White	n (%)	1097 (98.2)	1091 (98.2)	839 (98.6)
Other/mixed	n (%)	8 (0.7)	8 (0.7)	5 (0.6)
Missing	n (%)	6 (0.5)	6 (0.5)	4 (0.5)

ES=Enrolled Set; FAS=Full Analysis Set; N=number of patients in population; n=number of patients with data; SD=standard deviation; SS=Safety Set
Data sources: Table 2.1.1, Table 2.1.2, Table 2.1.3

In the SS, the mean age of the patients was 55.0 years, and a majority of patients were in the age category >18 to <65 (845 patients [76.1%]) (Table 2.1.2). A majority of the patient population were white (1091 patients [98.2%]) and female (865 patients [77.9%]) (Table 10–3). Similar demography was observed across all datasets (SS, ES, and FAS).

10.2.1.2 History of RA

In the SS, by-patient listing of patient's medical history excluding RA is provided in Listing 2.2.2, and summarized in Table 2.2.1. A by-patient listing of the patient's medical history of RA is provided in Listing 2.2.3, and summarized in Table 2.2.2 for the SS. Medical history glossary for all conditions is provided in Listing 2.2.1.

A summary of patient's medical RA history is presented in Table 10–4 for the SS and FAS.

Table 10–4: Summary of medical rheumatoid arthritis history - Safety Set and Full Analysis Set

Disease status	SS n/N (%)	FAS n/N (%)
Did patient have RF test?	1069/1111 (96.2)	818/851 (96.1)
RF positive[a]	750/1069 (70.2)	575/818 (70.3)
Did patient have ACPA test?	973/1111 (87.6)	747/851 (87.8)
aCCP positive[a]	642/973 (66.0)	500/747 (66.9)
MCV positive[a]	95/973 (9.8)	75/747 (10.0)
Disease duration summary: (years)		
n	1106	851
Mean	9.9	10.1
SD	9.3	9.5
Median	7.1	7.3
Range	0, 66	0, 66
Disease duration categorical:		
<2 years	209/1106 (18.9)	160/851 (18.8)
≥2 years	897/1106 (81.1)	691/851 (81.2)

aCCP=antibodies against cyclic citrullinated peptides; ACPA=antibodies against citrullinized peptide-protein-antigenes; FAS=Full Analysis Set; MCV=mutated citrullinized vimentines; N=number of patients in population; n=number of patients with data; RF=rheumatoid factor; SD=standard deviation; SS=Safety Set

[a] Only if patient had a test result in the past.

Data source: Table 2.2.2

The data in the table indicates that the percentage of patients who had undergone prior RF testing and also the percentage of RF positive patients were similar in the FAS and SS.

The median disease duration in the SS was 7.1 years within a range of 0 to 66 years. The majority of patients (897/1106 patients [81.1%]) had a disease duration of ≥2 years. Data were similar in the FAS. This disease duration observed is longer than in other European noninterventional CZP studies performed by UCB in RA.

10.2.1.3 Other medical history

For the SS, Listing 2.3 presents the by-patient concomitant medical procedures, and Listing 2.5 presents by-patient prior and concomitant vaccinations. Listing 2.4.1 presents the prior and concomitant medications glossary. For the SS, a by-patient listing of prior RA medication is provided in Listing 2.4.4. Prior and concomitant medications excluding RA are presented in Table 2.3.1. Number and percentage of patients with prior treatment with anti-TNFα, other biologics, MTX, and other synthetics DMARDs are presented in Table 2.3.3 and summarized in Table 10–5.

Table 10–5: Number and percentage of patients with prior treatment of anti-TNF alpha, other biologics, MTX, and other synthetic DMARDs - Safety Set and Full Analysis Set

Variable	SS N=1111 n/N (%)	FAS N=851 n/N (%)
Anti-TNF alpha	437/1111 (39.3)	324/851 (38.1)
Other biologics	153/1111 (13.8)	117/851 (13.7)
MTX	809/1111 (72.8)	622/851 (73.1)
Other synthetic DMARDs	895/1111 (80.6)	685/851 (80.5)

CRF=case report form; DMARD=disease-modifying antirheumatic drug; FAS=Full Analysis Set; MTX=methotrexate; N=number of patients in population; n=number of patients with data; SS=Safety Set; TNF=tumor necrosis factor
Note: For percentages (%), the denominator was the number of patients with a nonmissing response at the corresponding visit. The denominator was based on CRF page 3a collecting information over a 10 year period prior to study start (not available for all patients, as it was added 1 year after start of the study).
Data source: Table 2.3.3

A majority of the patients in the SS had prior treatment with other synthetic DMARDs (895/1111 patients [80.6%]) and MTX (809/1111 patients [72.8%]). Data were similar in the FAS.

A by-patient listing of prior and concomitant medications excluding and including DMARDs, corticosteroids is provided in Listing 2.4.2 and Listing 2.4.3, respectively, for the SS. A summary of prior and concomitant medications excluding RA medications is provided in Table 2.3.1 for the SS. A table outlining the changes during treatment with DMARDs and corticosteroids, using nonmissing observations, is presented in Table 3.9.

For all patients, a summary of prior and concomitant RA medications is presented in Table 10–6.

Table 10–6: Prior and concomitant rheumatoid arthritis medications reported in at least 5% of the patients - Safety Set

WHO-DD Sep/2013 Anatomical Main Group, Level 1/ Therapeutic Subgroup, Level 2 Preferred Term	SS N=1111 n (%)
Any prior or concomitant medications	1086 (97.7)
[redacted]	**953 (85.8)**
[redacted]	56 (5.0)
Rituximab	55 (5.0)
[redacted]	952 (85.7)
Methotrexate	600 (54.0)
Leflunomide	446 (40.1)
Etanercept	190 (17.1)
Methotrexate sodium	185 (16.7)
Adalimumab	160 (14.4)
Tocilizumab	87 (7.8)
[redacted]	**915 (82.4)**
[redacted]	915 (82.4)
Prednisolone	757 (68.1)
Prednisone	153 (13.8)
[redacted]	**642 (57.8)**
[redacted]	637 (57.3)
Ibuprofen	192 (17.3)
Diclofenac	163 (14.7)
Etoricoxib	99 (8.9)
Hydroxychloroquine sulphate	93 (8.4)
Celecoxib	62 (5.6)
[redacted]	**227 (20.4)**
[redacted]	208 (18.7)
Metamizole Sodium	58 (5.2)

Table 10–6: Prior and concomitant rheumatoid arthritis medications reported in at least 5% of the patients - Safety Set

WHO-DD Sep/2013 Anatomical Main Group, Level 1/ Therapeutic Subgroup, Level 2 Preferred Term	SS N=1111 n (%)
[redacted]	**204 (18.4)**
[redacted]	189 (17.0)
Sulfasalazine	185 (16.7)

CRF=case report form; CZP=certolizumab pegol; N=number of patients in population; n=number of patients with data; SS=Safety Set; WHO-DD=World Health Organization Drug Dictionary

Note: Medications with a start date prior to the first dose of CZP and with a stop date at study onset were considered as prior medications. Medications with a start date prior to, at, or after the first dose of CZP were considered as concomitant medications if the duration overlapped at least 1day with the Treatment Period. Medications with a missing start date whose stop date was either unknown or after the date of the application of CZP were considered concomitant.

Note: The values in this table were based on prior and concomitant medication page of the CRF, collecting information over 2 months prior to study start.

Data source: Table 2.3.2

During the study, 1086 patients (97.7%) reported at least 1 prior or concomitant medication. The most common medications used were [redacted] (which includes MTX) (953 patients [85.8%]), [redacted] (which includes systemic steroids) (915 patients [82.4%]), and [redacted] (which includes anti-inflammatory drugs) (642 patients [57.8%]).

Regarding previous and ongoing medical history (Listing 2.2.2), 2 patients [redacted] had a prior history of [redacted] and did not receive tuberculosis prophylaxis during the study (Listing 2.4.2, Listing 2.4.3); 1 patient ([redacted]) had a prior history of [redacted] and [redacted] during the study; 1 patient ([redacted]) had ongoing [redacted] and [redacted] during the study; 1 patient ([redacted] had ongoing [redacted] and [redacted] but had no record of receiving tuberculosis treatment during the study; this patient was lost to follow up so it is not possible to provide further details. It is to be noted that, none of these patients developed active tuberculosis during the study (Section 10.6.3.1)

In addition to the above patients, a further 14 patients took concomitant tuberculosis prophylaxis during the study (Listing 2.4.2, Listing 2.4.3). Additionally, 3 patients ([redacted]) received treatment for AEs of tuberculosis and pulmonary tuberculosis, during the study (Listing 2.4.2, Listing 5.3; see also Section 10.6.3.1).

Based on the information in Table 2.3.1, Table 2.3.2, and Table 3.15, the most commonly prescribed prior and concomitant medication can be summarized as follows:

- Based on Table 2.3.1, out of 1111 patients (100%) participating in the study 961 patients (86.5%) were prescribed at least 1 prior or concomitant medication (excluding RA medication).

- Based on Table 2.3.2, out of 1111 patients (100%) participating in the study 1086 patients (97.7%) were prescribed at least 1 prior or concomitant RA medication. The most commonly prescribed medications were antineoplastic and immunomodulating agents (which includes MTX) (953 patients [85.8%]).

In addition, based on Table 3.15, after discontinuation of CZP, 436 out of 510 patients (85.5%) continued to receive RA medication. The majority of patients (413/510 patients [81.0%]) were prescribed other synthetic DMARDs after discontinuation of CZP treatment. The other RA medications prescribed commonly were MTX (377/510 patients [73.9%]), anti-TNFα (221/510 patients [43.3%]), and other biologics (87/510 patients [17.1%]).

10.2.2 Treatment compliance

A by-patient listing, containing details of study medication intake is provided in Listing 4.2, for the SS. A summary of injection administration by visit and location is presented in Table 4.2.1 and also a summary of injection administration by visit and personnel is presented in Table 4.2.2.

At Baseline, the majority of patients (810/1105 patients [73.3%]) were injected at the study center. From Week 6 onwards, the majority of patients (670/810 patients [82.7%]) were injected at home; increasing towards (308/324 patients [95.1%]) Week 104 (Table 4.2.1). At Baseline, injections were most commonly administered by the patient (456/1105 patients [41.3%]) or the nurse (462/1105 patients [41.8%]). The percentage of patients who self-administered the study medication increased (280/324 patients [86.4%]) at Week 104 (Table 4.2.2).

During the entire duration of the study, the maximum treatment noncompliance was observed at Week 36 (84/654 patients [12.8%]), Week 52 (63/502 patients [12.5%]), and Week 104 (46/324 patients [14.2%]) for the SS. For the remaining visits, the number and percentage of patients who did not take study medication as planned are as follows: Week 6 (87/810 patients [10.7%]), Week 12 (57/635 patients [9.0%]), Week 24 (57/602 patients [9.5%]), Week 64 (50/433 patients [11.5%]), and Week 76 (42/404 patients [10.4%]) (Table 4.2.3).

10.3 Outcome data

A by-patient listing of analysis sets, which are defined in Section 9.9.2.3, is provided in Listing 1.4.1, for the ES. A summary of the analysis sets analyzed in this study is provided in Table 1.4 for the ES. A by-patient listing of reasons for exclusion of patients from FAS is presented in Listing 1.4.2.

A summary of patient disposition and discontinuation reasons for all the analysis sets is provided in Table 10–2.

10.4 Main results

10.4.1 Primary efficacy variable: Clinical remission at Week 104 (DAS28 value <2.6)

A summary of clinical remission at Week 104 (DAS28 value <2.6) is presented in Table 10–7 for the FAS. The number and percentage of patients in clinical remission, including 95% CIs, by visit, is provided using nonmissing observations, NRI, and MMRM imputation in Table 3.1.5, Table 3.1.6, and Table 3.1.7, respectively, for FAS. A by-patient DAS28 score listing based on CRP, ESR, and overall including change from Baseline is provided in Listing 3.4, for the FAS. Mean changes from Baseline in DAS28 Versus Visit Using nonmissing observations and

MMRM imputation (FAS) are graphically presented in Figure 1.2. For the FAS, percentages of patients with a DAS28 response versus visit using nonmissing observations and NRI is presented in Figure 1.4.

Table 10–7: Number and percentage of patients in clinical remission based on DAS28 at Week 104, including 95% CIs, using NRI or MMRM imputation, or nonmissing observations - Full Analysis Set

Visit	FAS N=851 n/N (%)	95% LCL	95% UCL
Using NRI:			
Week 104	120/851 (14.1)	11.8	16.4
Using MMRM:			
Week 104	168/851 (19.7)	17.1	22.4
Using nonmissing observations:			
Week 104	120/240 (50.0)	43.7	56.3

CI=confidence interval; DAS28= Disease Activity Score-28 joint count; FAS=Full Analysis Set; LCL=Lower Confidence Limit; MMRM= mixed model with repeated measures; N=number of patients in group; n=number of patients with data; NRI=nonresponder imputation; UCL=Upper Confidence Limit

Note: Clinical remission was defined as DAS28<2.6.

Note: MMRM imputation was based on a mixed model with visit, gender, disease duration, patient status at termination, and rheumatoid factor as fixed effect. If the variable was change from Baseline, the Baseline values of the variable were included as covariate. The multiple visits for each patient were the repeated measures as random effect within each patient. Missing data at Baseline were not imputed.

Note: 95% confidence intervals were constructed based on the approximation to the Normal distribution.

Data sources: Table 3.1.5, Table 3.1.6, Table 3.1.7

At Week 104, a substantial percentage of patients were DAS28 remitters using nonmissing observations (Table 10–7). The percentage of patients in DAS28 remission was higher for nonmissing observations 120/240 patients (50.0%) when compared to NRI and MMRM imputation results (120/851 patients [14.1%] and 168/851 patients [19.7%]), respectively.

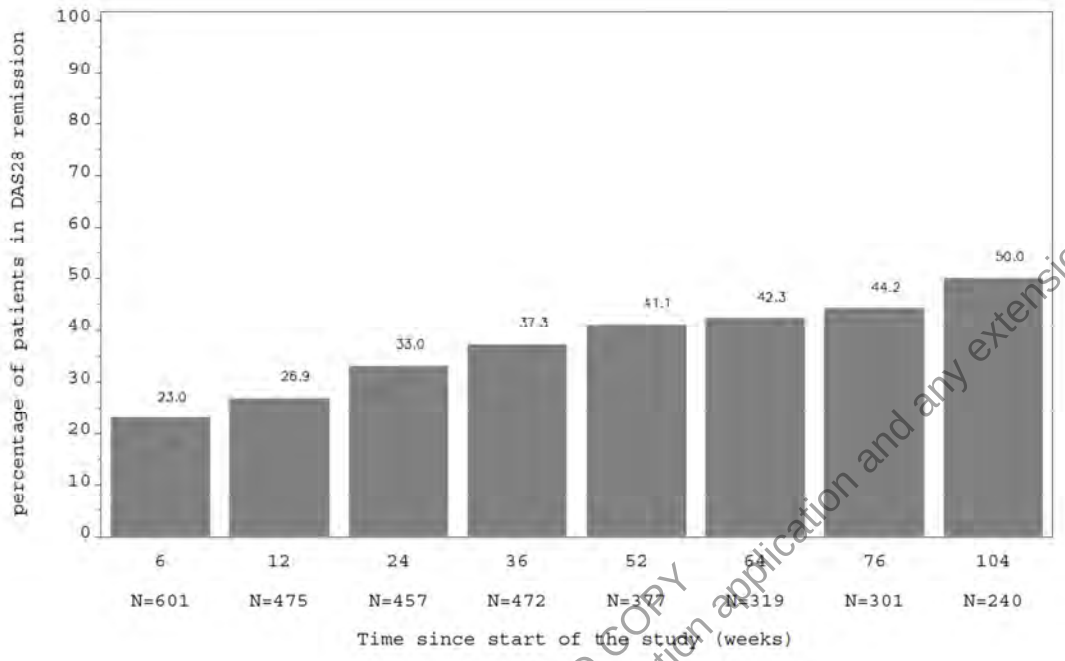
The results for imputed data (N=851) had narrower CIs when compared to the observed data (N=240), due to the larger number of patients. Based on the sample size estimate (Section 9.7.1), analysis of data from 1068 patients was estimated to be sufficient to derive accurate CI values, to allow conclusions regarding clinical remission in the study. Despite not having achieved the estimated sample size, the CI values for the study are still considered sufficient to draw conclusions for clinical remission.

Patients who achieve therapeutic benefit from treatment (eg, responders) are more likely to complete the study than nonresponders, which leads to bias towards a higher percentage of patients in clinical remission in the nonmissing observations analysis. The imputation analysis implemented to account for missing data represents a less biased approach to demonstrate the beneficial effect of CZP in this patient population, where especially the NRI is regarded as a very "conservative" method.

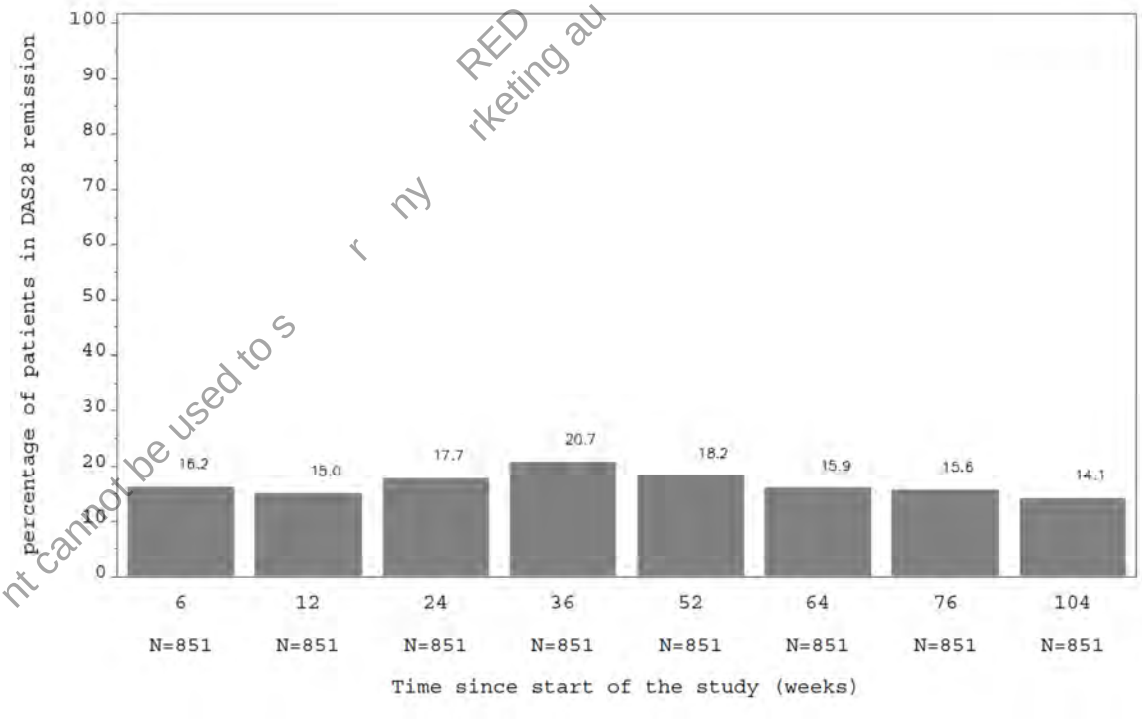
The percentage of patients in DAS28 remission by visit, using nonmissing observations and NRI, is presented in Figure 1.3 and Figure 10–1.

Figure 10–1: Percentage of patients in DAS28 remission by visit using nonmissing observations and NRI – Full Analysis Set

Using nonmissing observations



Using NRI



DAS28= Disease Activity Score-28 joint count; N=number of patients in group; NRI=nonresponder imputation
Note: Clinical remission is defined as DAS28<2.6.
Data source: Figure 1.3

The percentage of patients in clinical remission, using nonmissing observations, showed a steady increase over the weeks as presented in Figure 10–1 demonstrating that CZP continues to show consistent, therapeutic effect during long term treatment. The percentage of patients in clinical remission, using NRI, increased steadily up to Week 36 (176/851 patients [20.7%]) and then decreased towards Week 104.

10.4.2 Secondary efficacy variables

For the FAS, using nonmissing observations and MMRM imputation, all 3 secondary variables demonstrated a consistent effect, ie, decrease from Baseline to Week 104. The benefit of CZP treatment was observed early (ie, up to Week 12) and the treatment continued to be beneficial until Week 104 (Table 3.5.1, Table 3.5.2, Table 3.6.1, Table 3.6.2, Table 3.7.1, and Table 3.7.2). This is an indication of the decreased pain and disease activity, and an improvement in physical functioning of the patient. The results thereby demonstrate the effectiveness of CZP treatment.

10.4.2.1 Change from Baseline in PAAP VAS at Week 104

For the FAS, a by-patient listing of the PAAP is provided in Listing 3.2 and summarized by nonmissing observations and MMRM imputation in Table 3.5.1 and Table 3.5.2, respectively.

The PAAP value at each visit was obtained based on the patient's rating of the pain experienced at the time of visit using a predefined scale system (Figure 9-1).

Summary statistics of the PAAP including change from Baseline, observed values at Baseline and Week 104, using nonmissing observations and MMRM imputation, are presented in Table 10–8.

Table 10–8: Summary statistics of the PAAP including change from Baseline at Baseline and Week 104 using nonmissing observations and MMRM imputation - Full Analysis Set

Visit	Observed value				Change from Baseline value			
	n	Mean (SD)	Min	Max	n	Mean (SD)	Min	Max
Using nonmissing observations:								
Baseline	845	57.87 (21.83)	0.0	100.0	-	-	-	-
Week 104	253	32.40 (23.60)	0.0	98.0	252	-22.77 (28.77)	-89.0	70.0
Using MMRM imputation:								
Baseline	845	57.87 (21.83)	0.0	100.0	-	-	-	-
Week 104	851	40.01 (16.12)	0.0	98.0	845	-16.43 (20.34)	-89.0	70.0

Max=maximum; min=minimum; MMRM=mixed model with repeated measures; n=number of patients with data; PAAP=Patient's Assessment of Arthritis Pain; SD=standard deviation

Note: MMRM imputation was based on a mixed model with visit, gender, disease duration, patient status at termination, and rheumatoid factor as fixed effect. If the variable was change from Baseline, the Baseline values of the variable were included as covariate. The multiple visits for each patient were the repeated measures as random effect within each patient. Missing data at Baseline were not imputed.

Data sources: Table 3.5.1, Table 3.5.2

For the FAS, using nonmissing observations, a mean change of -22.77 is observed from Baseline to Week 104 (Table 10–8). Also, a steady decrease in the mean PAAP value is observed, along with the decrease in the number of patients, from Baseline until Week 104 (Table 3.5.1).

In the FAS, using MMRM imputation, a mean change of -16.43 is observed from Baseline to Week 104 (Table 10–8). Also, a steady decrease in the mean PAAP value is observed until Week 104 (Table 3.5.2).

10.4.2.2 Change from Baseline in HAQ-DI at Week 104

For the FAS, a by-patient listing of the HAQ-DI is provided in Listing 3.5 and summarized by nonmissing observations and MMRM imputation in Table 3.7.1 and Table 3.7.2, respectively.

Summary statistics of the HAQ-DI including change from Baseline, observed values at Baseline and Week 104, using nonmissing observations and MMRM imputation, are presented in Table 10–9.

Table 10–9: Summary statistics of the HAQ-DI including change from Baseline at Baseline and Week 104 using nonmissing observations and MMRM imputation – Full Analysis Set

Visit	Observed value				Change from Baseline value			
	n	Mean (SD)	Min	Max	n	Mean (SD)	Min	Max
Using nonmissing observations:								
Baseline	845	1.38 (0.70)	0.0	3.0	-	-	-	-
Week 104	257	0.88 (0.74)	0.0	3.0	255	-0.40 (0.56)	-2.8	0.9
Using MMRM imputation:								
Baseline	845	1.38 (0.70)	0.0	3.0	-	-	-	-
Week 104	851	1.13 (0.58)	0.0	3.0	845	-0.26 (0.39)	-2.8	1.0

HAQ-DI=Health Assessment Questionnaire-Disability Index; max=maximum; min=minimum; MMRM=mixed model with repeated measures; n=number of patients with data; SD=standard deviation.
Note: MMRM imputation was based on a mixed model with visit, gender, disease duration, patient status at termination, and rheumatoid factor as fixed effect. If the variable was change from Baseline, the Baseline values of the variable were included as covariate. The multiple visits for each patient were the repeated measures as random effect within each patient. Missing data at Baseline were not imputed.
Data sources: Table 3.7.1, Table 3.7.2

For the FAS, using nonmissing observations, a mean change of -0.40 is observed from Baseline to Week 104 (Table 10–9). Also, a steady decrease in the mean HAQ-DI value is observed, along with decrease in the number of patients, from Baseline till Week 104 (Table 3.7.1).

For the FAS, using MMRM imputation, a mean change of -0.26 is observed from Baseline to Week 104 (Table 10–9). Also, a steady decrease in the mean HAQ-DI value is observed till Week 104 (Table 3.7.2).

10.4.2.3 Change from Baseline in CDAI at Week 104

For the FAS, a by-patient listing of the CDAI is provided in Listing 3.2 and summarized by nonmissing observations and MMRM imputation in Table 3.3.1 and Table 3.3.2, respectively.

Summary statistics of the CDAI including change from Baseline, observed values at Baseline and Week 104, using nonmissing observations and MMRM imputation, are presented in Table 10–10.

Table 10–10: Summary statistics of the CDAI including change from Baseline at Baseline and Week 104 using nonmissing observations and MMRM imputation - Full Analysis Set

Visit	Observed value				Change from Baseline value			
	n	Mean (SD)	Min	Max	n	Mean (SD)	Min	Max
Using nonmissing observations:								
Baseline	846	29.65 (12.61)	4.0	73.8	-	-		-
Week 104	249	9.87 (9.01)	0.0	48.3	249	-17.91 (12.47)	-56.9	13.7
Using MMRM imputation:								
Baseline	846	29.65 (12.61)	4.0	73.8	-	-	-	-
Week 104	851	14.65 (7.47)	0.0	48.3	846	-14.57 (10.24)	-56.9	13.9

CDAI=Clinical Disease Activity Index; max=maximum; min=minimum; MMRM=mixed model with repeated measures; n=number of patients with data; SD=standard deviation.
Note: MMRM imputation was based on a model with visit, gender, disease duration, patient status at termination, and rheumatoid factor as fixed effect. If the variable was change from Baseline, the Baseline values of the variable were included as covariate. The multiple visits for each patient were the repeated measures as random effect within each patient. Missing data at Baseline were not imputed.
Data sources: Table 3.3.1, Table 3.3.2

For the FAS, using nonmissing observations, a mean change of -17.91 is observed from Baseline to Week 104 (Table 10–10). Also, a steady decrease in the mean CDAI value is observed, along with decrease in the number of patients, from Baseline till Week 104 (Table 3.3.1).

For the FAS, using MMRM imputation, a mean change of -14.57 is observed from Baseline to Week 104 (Table 10–10). Also, a steady decrease in the mean CDAI value is observed till Week 104 (Table 3.3.2).

10.4.3 Other efficacy variables

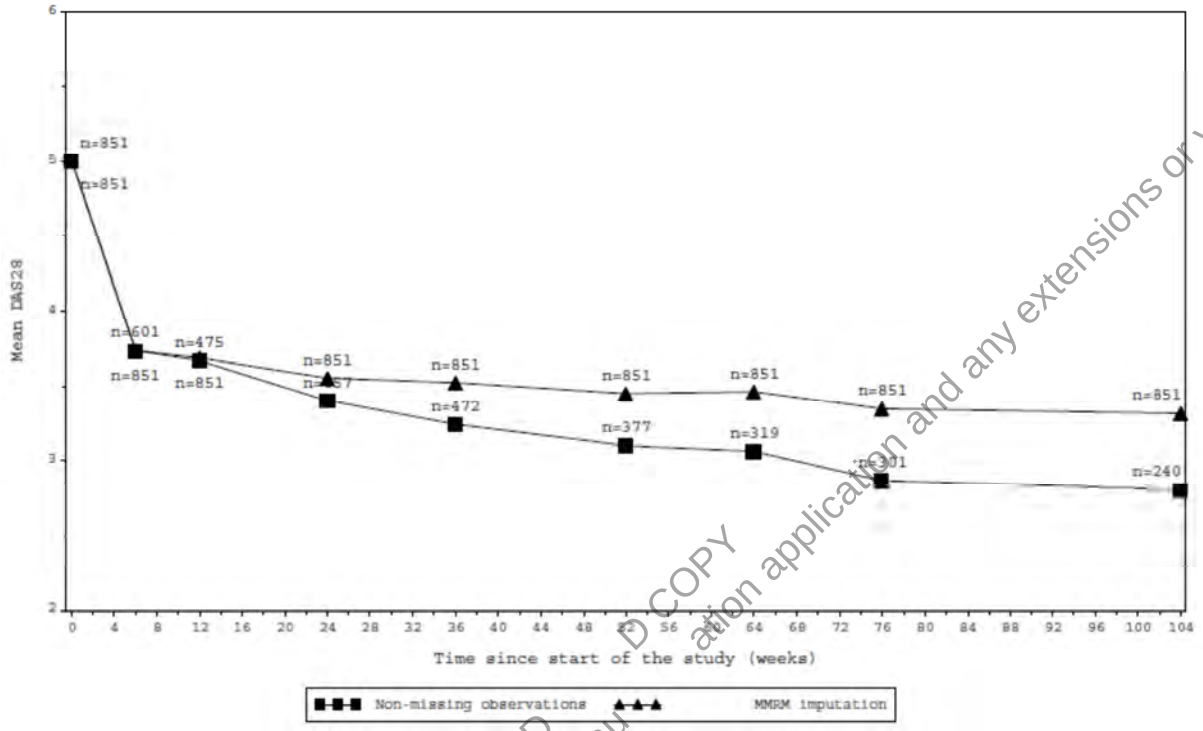
10.4.3.1 Presentation of DAS28

10.4.3.1.1 DAS28 over time

For the FAS, a by-patient listing of DAS28, based on CRP and ESR, is provided in Listing 3.4 and summarized by nonmissing observations and MMRM imputation in Table 3.1.1 and Table 3.1.2, respectively. Several analyses were conducted using CRP and ESR and are tabulated in Table 3.2.3, Table 3.2.4, Table 3.2.5, and Table 3.2.6. Mean DAS28 by visit using nonmissing observations and MMRM imputation is graphically presented in Figure 1.1 and Figure 10–2. Mean change from Baseline in DAS28 by visit is graphically presented in Figure 1.2 and Figure 10–3. A by-patient listing of the CRP and ESR laboratory values is presented in Listing 3.3. Summary statistics of the DAS28 (CRP, ESR, and Overall) including change from

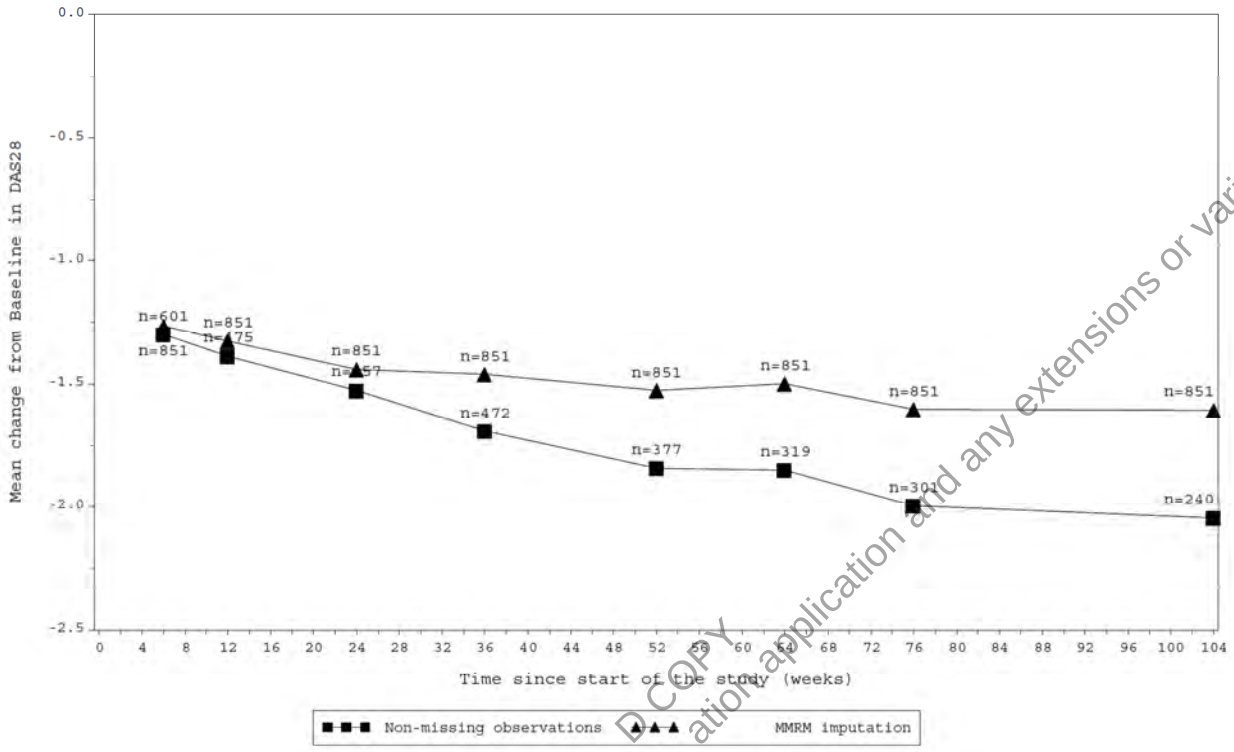
Baseline, at Baseline and Week 104, using nonmissing observations and MMRM imputation are presented in Table 10–11.

Figure 10–2: Mean DAS28 (overall) by visit using nonmissing observations and MMRM imputation – Full Analysis Set



DAS28= Disease Activity Score-28 joint count; MMRM=mixed model with repeated measures; n=number of patients with data
Data source: Figure 1.1

Figure 10–3: Mean change from Baseline in DAS28 (overall) by visit using nonmissing observations and MMRM imputation – Full Analysis Set



DAS28= Disease Activity Score-28 joint count; MMRM=mixed model with repeated measures; n=number of patients with data
Data source: Figure 1.2

Table 10–11: Summary statistics of the DAS28 (CRP, ESR, and Overall) including change from Baseline, at Baseline and Week 104, using nonmissing observations and MMRM imputation - Full Analysis Set

Visit	Observed value				Change from Baseline value			
	n	Mean (SD)	Min	Max	n	Mean (SD)	Min	Max
Using nonmissing observations:								
DAS28 (CRP):								
Baseline	837	5.00 (1.00)	3.2	8.1	-	-	-	-
Week 104	233	2.77 (1.13)	1.0	5.9	229	-2.05 (1.33)	-5.5	1.2
DAS28 (ESR):								
Baseline	786	5.34 (1.13)	2.4	8.9	-	-	-	-
Week 104	208	3.06 (1.40)	0.0	7.3	201	-2.16 (1.44)	-5.4	1.2
DAS28 (overall):								
Baseline	851	5.01 (1.00)	3.2	8.1	-	-	-	-
Week 104	240	2.81 (1.19)	0.9	7.3	240	-2.04 (1.33)	-5.5	1.2
Using MMRM imputation:								
DAS28 (CRP):								
Baseline	837	5.00 (1.00)	3.2	8.1	-	-	-	-
Week 104	851	3.29 (0.83)	1.0	5.9	837	-1.60 (0.97)	-5.5	1.2
DAS28 (ESR):								
Baseline	786	5.34 (1.13)	2.4	8.9	-	-	-	-
Week 104	851	3.61 (0.93)	0.0	7.3	786	-1.61 (1.02)	-5.4	1.2
DAS28 (overall):								
Baseline	851	5.01 (1.00)	3.2	8.1	-	-	-	-
Week 104	851	3.32 (0.86)	0.9	7.3	851	-1.61 (0.97)	-5.5	1.2

CRP=C-reactive protein; DAS28=Disease Activity Score-28 joint count; ESR=erythrocyte sedimentation rate; max=maximum; min=minimum; MMRM=mixed model with repeated measures; n=number of patients with data; SD=standard deviation.

Note: Change from Baseline in DAS28 was only derived if the DAS28 at both visits was based on the same measurement.

Note: MMRM imputation was based on a mixed model with visit, gender, disease duration, patient status at termination, and rheumatoid factor as fixed effect. If the variable was change from Baseline, the Baseline values of the variable were included as covariate. The multiple visits for each patient are the repeated measures as random effect within each patient. Missing data at Baseline were not imputed.

Data sources: Table 3.1.1, Table 3.1.2

For the FAS, using nonmissing observations, based on both CRP and ESR, a mean change of -2.05 and -2.16 was observed from Baseline to Week 104, respectively (Table 3.1.1). For the

FAS, using MMRM imputation, based on both CRP and ESR, a mean change of -1.60 and -1.61 was observed from Baseline to Week 104, respectively (Table 3.1.2).

For the FAS, using nonmissing observations and MMRM imputation, the common pattern observed was a mean decrease in the DAS28 (CRP and ESR) values from Baseline to Week 104.

Table 10–12: Summary statistics of CRP and ESR including percent change from Baseline, by Visit, using nonmissing observations and MMRM imputation - Full Analysis Set

Visit	Statistics	CRP	% Change from Baseline	ESR	% Change from Baseline
Using nonmissing observations:					
Baseline	n	837	-	786	-
	Median	8.00	-	24.00	-
	Min, Max	0.0, 520.0	-	1.0, 120.0	
Week 6	n	591	585	558	537
	Median	5.00	-37.82	17.00	-24.24
	Min, Max	0.0, 284.0	-100.0, 7500.0	0.0, 116.0	-100.0, 1200.0
Week 12	n	460	454	431	419
	Median	4.00	-42.88	18.00	-20.00
	Min, Max	0.0, 130.0	-100.0, 3575.0	1.0, 201.0	-97.0, 1400
Week 24	n	448	440	424	409
	Median	4.20	-31.43	16.00	-23.08
	Min, Max	0.0, 120.0	-100.0, 2425.3	1.0, 102.0	-98.5, 1300.0
Week 36	n	479	470	447	431
	Median	4.00	-43.61	16.00	-25.00
	Min, Max	0.0, 176.0	-100.0, 5066.7	1.0, 123.0	-95.0, 1300.0
Week 52	n	378	370	352	340
	Median	3.95	-45.23	16.00	-25.00
	Min, Max	0.0, 99.5	-100.0, 2627.3	1.0, 98.0	-96.7, 1300.0
Week 64	n	320	314	301	294
	Median	4.00	-49.81	16.00	-29.22
	Min, Max	0.0, 250.0	-100.0, 10445.0	0.0, 110.0	-100.0, 1850.0

Table 10–12: Summary statistics of CRP and ESR including percent change from Baseline, by Visit, using nonmissing observations and MMRM imputation - Full Analysis Set

Visit	Statistics	CRP	% Change from Baseline	ESR	% Change from Baseline
Week 76	n	300	296	276	268
	Median	4.00	-46.38	16.00	-27.43
	Min, Max	0.0, 148.0	-100.0, 2700.0	0.0, 114.0	-100.0, 733.0
Week 104	n	251	246	226	219
	Median	3.14	-50.88	14.50	-28.57
	Min, Max	0.0, 170.0	-100.0, 4122.2	0.0, 95.0	-100.0, 400.0
Using MMRM imputation:					
Baseline	n	837	-	786	-
	Median	8.00	-	24.0	-
	Min, Max	0.0, 520.0	-	1.0, 120.0	-
Week 6	n	851	836	851	786
	Median	6.03	-20.00	18.00	-20.00
	Min, Max	0.0, 284.0	-150.8, 7500.0	0.0, 142.6	-101.7, 1200.0
Week 12	n	851	836	851	786
	Median	6.00	-30.13	19.15	-18.68
	Min, Max	0.0, 130.0	-2720.3, 3772.5	1.0, 201.0	-386.6, 2228.3
Week 24	n	851	836	851	786
	Median	7.00	-18.54	19.71	-18.77
	Min, Max	0.0, 120.0	-2546.6, 5160.7	1.0, 143.2	-379.0, 2604.4
Week 36	n	851	836	851	786
	Median	8.31	-15.55	20.50	-15.77
	Min, Max	0.0, 176.0	-2593.0, 5192.1	1.0, 123.0	-95.0, 1905.3
Week 52	n	851	836	851	786
	Median	9.31	-22.49	23.00	-8.81
	Min, Max	0.0, 99.5	-2898.2, 5429.1	1.0, 98.0	-101.3, 1336.6

Table 10–12: Summary statistics of CRP and ESR including percent change from Baseline, by Visit, using nonmissing observations and MMRM imputation - Full Analysis Set

Visit	Statistics	CRP	% Change from Baseline	ESR	% Change from Baseline
Week 64	n	851	836	851	786
	Median	10.97	-8.95	23.20	-12.44
	Min, Max	0.0, 250.0	-2106.9, 10445.5	0.0, 110.0	-104.4, 1850.0
Week 76	n	851	836	851	786
	Median	10.32	-10.55	23.55	-9.45
	Min, Max	0.0, 148.8	-2450.0, 6334.7	0.0, 114.0	-300.7, 1404.8
Week 104	n	851	836	851	786
	Median	11.93	-3.52	23.69	-9.87
	Min, Max	0.0, 170.0	-1819.7, 7151.2	0.0, 96.1	-102.3, 937.2

CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; max=maximum; min=minimum; MMRM=mixed model with repeated measures; n=number of patients with data

Note: MMRM imputation was based on a mixed model with visit, gender, disease duration, patient status at termination, and rheumatoid factor as fixed effect. If the variable was change from Baseline, the Baseline values of the variable were included as covariate. The multiple visits for each patient are the repeated measures as random effect within each patient. Missing data at Baseline were not imputed.

Data sources: Table 3.2.5, Table 3.2.6

Each individual percentage change from Baseline was calculated and then summary statistics were calculated. The median was the geometric midpoint of the percentage change. The distribution of all percentage changes shift did affect the median values.

For the FAS, using nonmissing observations, the highest median percentage change from Baseline for both CRP and ESR was observed at Week 6 (-37.82% and -24.24%, respectively). The median values from Baseline continued to decrease across the entire study duration for both CRP and ESR up to Week 104 (3.14mg/L and 14.40mm/h, respectively) reflecting a median percentage change from Baseline of -50.88% and -28.57%, respectively (Table 3.2.5).

For the FAS, using MMRM imputation, the median CRP value decreased from Baseline (8.00mg/L) to Week 12 (6.03mg/L), and increased from Week 24 (7.00mg/L) to Week 104 (11.93mg/L), reflecting a median percentage change from Baseline of -3.52%, at Week 104. For the FAS, using MMRM imputation, the median ESR value decreased from Baseline (24.00mm/h) to Week 12 (19.15mm/h), and increased from Week 24 (19.71mm/h) to Week 104 (23.69mm/h), reflecting a median percentage change from Baseline of -9.87%, at Week 104 (Table 3.2.6).

10.4.3.1.2 DAS28 categories

For the FAS, using nonmissing and MMRM imputation, the number and percentage of patients in the DAS28 categories (remission, LDA, moderate disease activity, high disease activity), alongside their 95% CIs were tabulated by visit in Table 3.1.3 and Table 3.1.4.

Using nonmissing observations, the percentage of patients in remission or with LDA, increased from zero at Baseline to 128/475 patients (26.9%) and 76/475 patients (16.0%), respectively, at Week 12. At Week 104, 120/240 patients (50.0%) and 46/240 patients (19.2%) of the patients were in remission and LDA category, respectively.

Using MMRM imputation, the percentage of patients in remission or with LDA, increased from zero at Baseline to 177/851 patients (20.8%) and 153/851 patients (18.0%), respectively, at Week 12. At Week 104, 168/851 patients (19.7%) and 118/851 patients (13.9%) were in remission and LDA category, respectively.

These results reveal that the benefit of CZP treatment was observed early (ie, up to Week 12) and the treatment continued to be beneficial until Week 104.

10.4.3.2 Clinical remission (ACR/EULAR)

For the FAS, the number and percentage of patients in clinical remission (ACR/EULAR 2011) (using nonmissing observations, NRI, and MMRM imputation), including their 95% CIs, by visit, is provided in Table 3.1.8, Table 3.1.9, and Table 3.1.10.

At Week 12 (using nonmissing observations) for the FAS, the percentage of patient population in clinical remission was 18/453 patients (4.0%). A steady increase in percentage of patients achieving clinical remission was observed over the weeks, culminating with 38/233 patients (16.3%) of the patient population in remission at Week 104 (Table 3.1.8).

Using NRI for the FAS, the percentage of patient population in clinical remission increased from 18/851 patients (2.1%) at Week 12 to 44/851 patients (5.2%) at Week 52. From Week 64, there was a rise and fall in the percentage of patients achieving clinical remission, culminating with 38/851 patients (4.5%) of the patient population in remission at Week 104 (Table 3.1.9).

Using MMRM imputation for the FAS, the percentage of patient population in clinical remission increased from 22/851 patients (2.6%) at Week 12 to 47/851 patients (5.5%) at Week 52. From Week 64, there was a rise and fall in the percentage of patients achieving clinical remission, culminating with 41/851 patients (4.8%) of the patient population in remission at Week 104 (Table 3.1.10).

The criteria to be satisfied are more stringent for ACR/EULAR remission when compared to DAS28 remission; hence, a lower percentage of patients in clinical remission were observed based on ACR/EULAR criteria than on the DAS28 criteria (Section 10.4.1).

10.4.3.3 DAS28 clinical response

For the FAS (using nonmissing, NRI, and MMRM imputation), the number and percentage of patients with a DAS28 response are summarized by visit in Table 3.1.11, Table 3.1.12, and Table 3.1.13, respectively.

The DAS28 response was the decrease in DAS28≥1.2 at post-Baseline, when compared with the Baseline value.

The number and percentage of patients with a DAS28 response, using nonmissing observations, NRI, and MMRM imputation, are presented in Table 10-13.

Table 10-13: Number and percentage of patients with a DAS28 response by visit using nonmissing observations, NRI, and MMRM imputation - Full Analysis Set

Visit	Nonmissing observations	NRI	MMRM imputation
	N=851 n/N (%) (95% CI)	N=851 n/N (%) (95% CI)	N=851 n/N (%) (95% CI)
Week 6	290/601 (48.3) (44.3, 52.2)	290/851 (34.1) (30.9, 37.3)	412/851 (48.4) (45.1, 51.8)
Week 12	261/475 (54.9) (50.5, 59.4)	261/851 (30.7) (27.6, 33.8)	457/851 (53.7) (50.4, 57.1)
Week 24	274/457 (60.0) (55.5, 64.4)	274/851 (32.2) (29.1, 35.3)	493/851 (57.9) (54.6, 61.2)
Week 36	302/472 (64.0) (59.7, 68.3)	302/851 (35.5) (32.3, 38.7)	487/851 (57.2) (53.9, 60.6)
Week 52	262/377 (69.5) (64.8, 74.1)	262/851 (30.8) (27.7, 33.9)	515/851 (60.5) (57.2, 63.8)
Week 64	221/319 (69.3) (64.2, 74.3)	221/851 (26.0) (23.0, 28.9)	507/851 (59.6) (56.3, 62.9)
Week 76	217/301 (72.1) (67.0, 77.2)	217/851 (25.5) (22.6, 28.4)	535/851 (62.9) (59.6, 66.1)
Week 104	174/240 (72.5) (66.9, 78.1)	174/851 (20.4) (17.7, 23.2)	548/851 (64.4) (61.2, 67.6)

CI=confidence interval; DAS28=Disease Activity Score-28 joint count; MMRM=mixed model with repeated measures; N=number of patients in group; n=number of patients with data; NRI=nonresponder imputation
Note: A DAS28 responder is defined as a patient whose DAS28 decrease is ≥1.2 in comparison with the Baseline value.
Note: 95% CIs were constructed based on the approximation to the Normal distribution.
Note: MMRM imputation was based on a mixed model with visit, gender, disease duration, patient status at termination, and rheumatoid factor as fixed effect. If the variable was change from Baseline, the Baseline values of the variable were included as covariate. The multiple visits for each patient were the repeated measures as random effect within each patient. Missing data at Baseline were not imputed.
Data sources: Table 3.1.11, Table 3.1.12, Table 3.1.13

For the FAS, using nonmissing observations, the percentage of DAS28 responders increased steadily from 290/601 patients (48.3%) at Week 6 to 174/240 patients (72.5%) at Week 104 (Table 10-13).

For the FAS, using NRI, the percentage of DAS28 responders decreased from 290/851 patients (34.1%) at Week 6 to 274/851 patients (32.2%) at Week 24. The maximum percentage of DAS28 responders was 302/851 patients (35.5%) observed at Week 36, following with the percentage of responders decreasing each visit, culminating with 174/851 patients (20.4%) at Week 104 (Table 10-13).

For the FAS, using MMRM imputation, the percentage of DAS28 responders increased steadily from 412/851 patients (48.4%) at Week 6 to 515/851 patients (60.5%) at Week 52. A slight decrease to 507/851 patients (59.6%) was observed at Week 64. Finally at Week 104, 548/851 patients (64.4%) of the patient population were categorized as DAS28 responders (Table 10-13).

10.4.3.4 Change from Baseline in TJC and SJC

For the FAS, a by-patient listing of the tender and swollen joint counts including change from Baseline is provided in Listing 3.1.2 and these data summarized in Table 3.2.1 and Table 3.2.2, for nonmissing observations and MMRM imputation, respectively. For the FAS, assessment of swelling and tenderness of joints is presented in Listing 3.1.1.

For the FAS, using nonmissing observations, a mean change of -6.64 and -5.67 is observed from Baseline to Week 104 for TJC and SJC, respectively. For TJC and SJC, mean value decreased from 10.27 and 7.35 at Baseline to 2.77 and 1.57 at Week 104, respectively. It is to be noted that the decrease in mean value was rapid from Baseline to Week 6 for TJC and SJC. From Week 12 to Week 104, a slight but constant decrease in the mean value was observed, except for the slight variation observed in the SJC values (Table 3.2.1).

Summary statistics of the TJC and SJC including change from Baseline by visit using MMRM imputation are presented in Table 10–14.

Table 10–14: Summary statistics of the TJC and SJC including change from Baseline by visit using MMRM imputation - Full Analysis Set

Variable Visit	Observed value				Change from Baseline value			
	n	Mean (SD)	Min	Max	n	Mean (SD)	Min	Max
TJC:								
Baseline	851	10.27 (7.02)	0.0	28.0				
Week 6	851	5.61 (6.33)	0.0	28.0	851	-4.65 (6.22)	-28.0	21.0
Week 12	851	5.50 (6.21)	0.0	28.0	851	-4.75 (6.24)	-28.0	16.0
Week 24	851	4.95 (5.60)	0.0	28.0	851	-5.32 (6.00)	-28.0	17.0
Week 36	851	5.14 (5.68)	0.0	28.0	851	-5.11 (5.99)	-27.0	26.0
Week 52	851	5.09 (5.00)	0.0	28.0	851	-5.19 (5.74)	-28.0	22.0
Week 64	851	5.14 (4.80)	0.0	28.0	851	-5.14 (5.59)	-28.0	17.0
Week 76	851	4.73 (4.41)	0.0	28.0	851	-5.61 (5.57)	-27.0	18.7
Week 104	851	4.73 (3.83)	0.0	28.0	851	-5.47 (5.20)	-27.0	9.5
SJC:								
Baseline	851	7.35 (5.67)	0.0	28.0				
Week 6	851	3.84 (4.39)	0.0	24.0	851	-3.55 (4.83)	-24.9	12.0
Week 12	851	3.47 (4.22)	0.0	26.0	851	-3.90 (5.21)	-24.9	16.2
Week 24	851	3.05 (3.75)	0.0	24.0	851	-4.36 (5.19)	-27.0	20.0
Week 36	851	3.04 (3.72)	0.0	25.0	851	-4.38 (5.08)	-24.4	20.0
Week 52	851	2.76 (2.98)	0.0	22.0	851	-4.70 (5.00)	-22.0	18.0
Week 64	851	2.79 (2.88)	0.0	25.8	851	-4.63 (5.00)	-22.0	16.2
Week 76	851	2.57 (2.42)	0.0	18.0	851	-4.85 (4.80)	-22.0	7.2

Variable Visit	Observed value				Change from Baseline value			
	n	Mean (SD)	Min	Max	n	Mean (SD)	Min	Max
Week 104	851	2.61 (2.20)	0.0	18.0	851	-4.75 (4.61)	-22.0	11.0

Max=maximum; min=minimum; MMRM=mixed model with repeated measures; n=number of patients with data; SD=standard deviation; SJC=swollen joint count; TJC=tender joint count

Note: MMRM imputation was based on a mixed model with visit, gender, disease duration, patient status at termination, and rheumatoid factor as fixed effect. If the variable was change from Baseline, the Baseline values of the variable were included as covariate. The multiple visits for each patient were the repeated measures as random effect within each patient. Missing data at Baseline were not imputed.

Data source: Table 3.2.2

For the FAS, the trend observed in TJC and SJC values was similar for MMRM imputation and nonmissing observations. The only exception to the pattern was that slight variations were observed in SJC for nonmissing observations and in TJC for MMRM imputation. As presented in Table 10–14, a mean change of -5.47 and -4.75 was observed from Baseline to Week 104 for TJC and SJC, respectively. For TJC and SJC, mean value decreased from 10.27 and 7.35 at Baseline to 4.73 and 2.61 at Week 104, respectively. It is to be noted that the decrease in mean value was rapid from Baseline to Week 6 for TJC and SJC. From Week 12 to Week 104, a slight but consistent decrease in the mean value was observed, except for the slight variation observed in the TJC values.

10.4.3.5 PtGADA and PhGADA

For the FAS, summary statistics of the PtGADA and PhGADA, including change from Baseline by visit are provided in Table 3.4.1, Table 3.4.2, Table 3.4.3, and Table 3.4.4, for nonmissing observations and MMRM imputation.

For the FAS, using nonmissing observations, a mean change of -23.04 and -34.92 was observed in PtGADA and PhGADA from Baseline to Week 104, respectively. For PtGADA and PhGADA, the mean value decreased from 59.28 and 60.56 at Baseline to 32.96 and 23.69 at Week 104, respectively. It is to be noted that the decrease in mean value was rapid from Baseline to Week 6 for PtGADA and PhGADA. From Week 12 to Week 104, the decrease in the mean value remained steady (Table 3.4.1 and Table 3.4.3).

For the FAS, using MMRM imputation, a mean change of -17.60 and -27.15 was observed in PtGADA and PhGADA from Baseline to Week 104, respectively. For PtGADA and PhGADA, mean value decreased from 59.28 and 60.56 at Baseline to 40.48 and 31.30 at Week 104, respectively. It is to be noted that the decrease in mean value was rapid from Baseline to Week 6 for PtGADA and PhGADA. From Week 12 to Week 104, the decrease in the mean value remained steady (Table 3.4.2 and Table 3.4.4).

It is to be noted that, even though the physician was blinded to the PtGADA values during the assessment of PhGADA, similar patterns in the mean PtGADA and PhGADA values were observed which is supportive of the reliability of the study results.

10.4.3.6 Patient's assessment of fatigue

For the FAS, summary statistics of the patient's assessment of fatigue including change from Baseline by visit are provided in Table 3.6.1 and Table 3.6.2, for nonmissing observations and MMRM imputation, respectively.

For the FAS, using nonmissing observations and MMRM imputation, a mean change of -1.59 and -1.14 was observed from Baseline to Week 104. The mean fatigue value decreased from 5.73 at Baseline to 3.73 (nonmissing observations) and 4.50 (MMRM imputation) at Week 104.

10.4.3.7 Morning stiffness

For the FAS, summary statistics of the patient's duration in morning stiffness including change from Baseline by visit are provided in Table 3.10.1 and Table 3.10.2, for nonmissing observations and MMRM imputation, respectively.

For the FAS, using nonmissing observations and MMRM imputation, a mean change of -0.90 and -0.80 was observed from Baseline to Week 104. A decrease in the mean value was observed

from 1.47 at Baseline to 0.33 (nonmissing observations) and 0.65 (MMRM imputation) at Week 104. The decrease in mean value was steady across the visits for nonmissing observations and MMRM imputation values.

10.4.3.8 Collection of information on sick leave

For the FAS, a by-patient listing of patient's sick leave days is provided in Listing 3.7 and summary statistics of the number of sick leave days per month due to RA are provided in Table 3.14.2, using nonmissing observations. Summary statistics of the patient's sick leave days by reason are presented in Table 3.14.1.

For the FAS, using nonmissing observations, the mean number of patient's sick leave days at Baseline was 4.14, which increased to 17.80 at Week 6. From Week 12 to Week 76, a decrease in the mean value from 11.55 to 3.94 was observed, respectively. At Week 104, the mean value showed a slight increase and concluded at 4.61.

10.4.3.9 EQ-5D

For the FAS, a by-patient listing of EQ-5D dimensions and EQ-5D VAS scale including change from Baseline is provided in Listing 3.6. Summary statistics of the patient's health-related (QoL) VAS scale including change from Baseline by visit, using nonmissing observations and MMRM imputation, are provided in Table 3.8.2 and Table 3.8.3, respectively. Number and percentage of patient's by response category for each dimension of the EQ-5D by visit, using nonmissing observations, is presented in Table 3.8.1. For the FAS, percentage of patients reporting a problem in the EQ-5D dimensions at Baseline, Week 12, Week 52, and Week 104 using nonmissing observations is graphically presented in Figure 2.

As mentioned in Section 9.5.1.10, the EQ-5D questionnaire consisted of 5 questions and a VAS scale. For the FAS, the results in Table 3.8.2 (using nonmissing observations) show a rapid improvement in the mean value, increasing from 46.50 at Baseline to 56.82 at Week 6. The mean value continued to improve steadily across the visits, culminating with a value of 67.58 at Week 104. Similarly, the mean change from Baseline value was 10.89 at Week 6 and culminated with a value of 18.48 at Week 104.

The same improvement was observed in the results obtained using MMRM imputation for the FAS. As seen in nonmissing observations, MMRM imputation results for the FAS, presented in Table 3.8.3, also show a rapid improvement in the mean value, increasing from 46.50 at Baseline to 56.62 at Week 6. The mean value continued to improve steadily across the visits, culminating with a value of 61.97 at Week 104. Similarly, the mean change from Baseline value was 10.40 at Week 6 and culminated with a value of 14.56 at Week 104.

10.4.3.10 Employment status and employability due to RA

For the FAS (using nonmissing observations), a by-patient listing was provided in Listing 2.1.2 for the employment status of the patient. Number and percentage of patient's employment status including 95% CIs by visit, using nonmissing observations, are presented in Table 3.12.1.

For the FAS (using nonmissing observations), Table 3.12.3 summarizes the number and percentage of the reasons for unemployment. As per the results obtained, the percentage of patients unemployed due to RA increased from Baseline (77/463 patients [16.6%]) to Week 12 (58/282 patients [20.6%]). A downward slide in the percentage of unemployed patients is observed from Week 24 (42/261 patients [16.1%]) to Week 104 (22/146 patients [15.1%]). For

the FAS (using nonmissing observations), employability rates were not overly affected by CZP treatment and showed very small fluctuations over the weeks (Table 3.13).

The number and percentage of the reasons for part-time employment by visit are provided in Table 3.12.2, using nonmissing observations.

10.5 Subgroup analyses of efficacy

Subgroup analyses were performed to investigate the potential effect of presence of RF, presence of aCCP antibodies, duration of RA disease, prior anti-TNF treatment, and early DAS28 response on the therapeutic benefit of CZP. Data are presented for the FAS in Table 3.16.1 to Table 3.16.32.

For the FAS, of the 818 patients with RF testing done, 70.3% of patients were RF positive. Of the 747 patients with aCCP testing done, 66.9% of patients were aCCP antibody positive. The majority of patients (81.2%) had disease duration ≥2 years (Table 2.2.2).

A by-patient listing of prior RA medication during the last 10 years is provided in Listing 2.4.4 for the SS. It was found that 38.1% of patients in the FAS had received prior anti-TNFα therapy.

10.5.1 Effect of RF, aCCP antibodies, and disease duration

10.5.1.1 DAS28 remission by RF, aCCP antibodies, and disease duration

Disease Activity Score-28 joint count (DAS28) remission by RF, aCCP antibodies, and disease duration at Baseline, using nonmissing observations, NRI imputation, and MMRM imputation, is provided in Table 3.16.1, Table 3.16.2, and Table 3.16.3, respectively.

Using nonmissing observations, remission at Week 104 occurred in higher proportions of patients who were positive for RF (53.5%), positive for aCCP (58.0%), or had disease duration ≥2 years (52.5%) than in those who were negative for RF (41.3%), negative for aCCP (32.0%), or had disease duration <2 years (37.5%). However, only for aCCP was there no overlap in the 95% CIs for the 2 categories.

Using NRI imputation, similar results were observed. Remission at Week 104 occurred in higher proportions of patients who were positive for RF (16.0%), positive for aCCP (17.4%), or had disease duration ≥2 years (15.2%) than in those who were negative for RF (10.7%), negative for aCCP (7.2%), or had disease duration <2 years (9.4%). However, only for aCCP was there no overlap in the 95% CIs for the 2 categories.

Using MMRM imputation, similar results were observed. Remission at Week 104 occurred in higher proportions of patients who were positive for RF (21.0%), positive for aCCP (23.0%), or had disease duration ≥2 years (20.4%) than in those who were negative for RF (18.5%), negative for aCCP (14.4%), or had disease duration <2 years (16.9%). However, only for aCCP was there no overlap in the 95% CIs for the 2 categories.

10.5.2 Effect of prior RA medication

10.5.2.1 DAS28 by prior RA medication

For the SS, a by-patient listing of prior RA medication during the last 10 years is provided in Listing 2.4.4.

10.5.2.1.1 DAS28 over time

Summary statistics of the DAS28, including change from Baseline, by prior RA medication and visit using nonmissing observations and MMRM imputation are provided in Table 3.16.4 and Table 3.16.5, respectively. An overview of the data is presented in Table 10–15.

Table 10–15: Summary statistics of the DAS28 (overall), including change from Baseline, at Baseline, and Week 104, by prior anti-TNF alpha medication using nonmissing observations and MMRM imputation - Full Analysis Set

Visit	Observed value		Change from Baseline value	
	n	Mean (SD)	n	Mean (SD)
Prior anti-TNF alpha treatment, using nonmissing observations:				
Baseline	324	5.03 (1.05)		
Week 104	73	3.03 (1.32)	73	-1.89 (1.44)
Prior anti-TNF alpha treatment, using MMRM:				
Baseline	324	5.03 (1.05)		
Week 104	324	3.47 (0.81)	324	-1.47 (0.93)
Anti-TNF alpha naïve, using nonmissing observations:				
Baseline	527	5.00 (0.96)		
Week 104	167	2.71 (1.11)	167	-2.11 (1.27)
Anti-TNF alpha naïve, using MMRM:				
Baseline	527	5.00 (0.96)		
Week 104	527	3.22 (0.87)	527	-1.69 (0.98)

DAS28=Disease Activity Score-28 joint count; MMRM=mixed model with repeated measures; n=number of patients with data; SD=standard deviation; TNF=tumor necrosis factor

Note: MMRM imputation was based on a mixed model with visit, gender, disease duration, patient status at termination, and rheumatoid factor as fixed effect. If the variable was change from Baseline, the Baseline values of the variable were included as covariate. The multiple visits for each patient were the repeated measures as random effect within each patient. Missing data at Baseline were not imputed.

Data sources: Table 3.16.4, Table 3.16.5

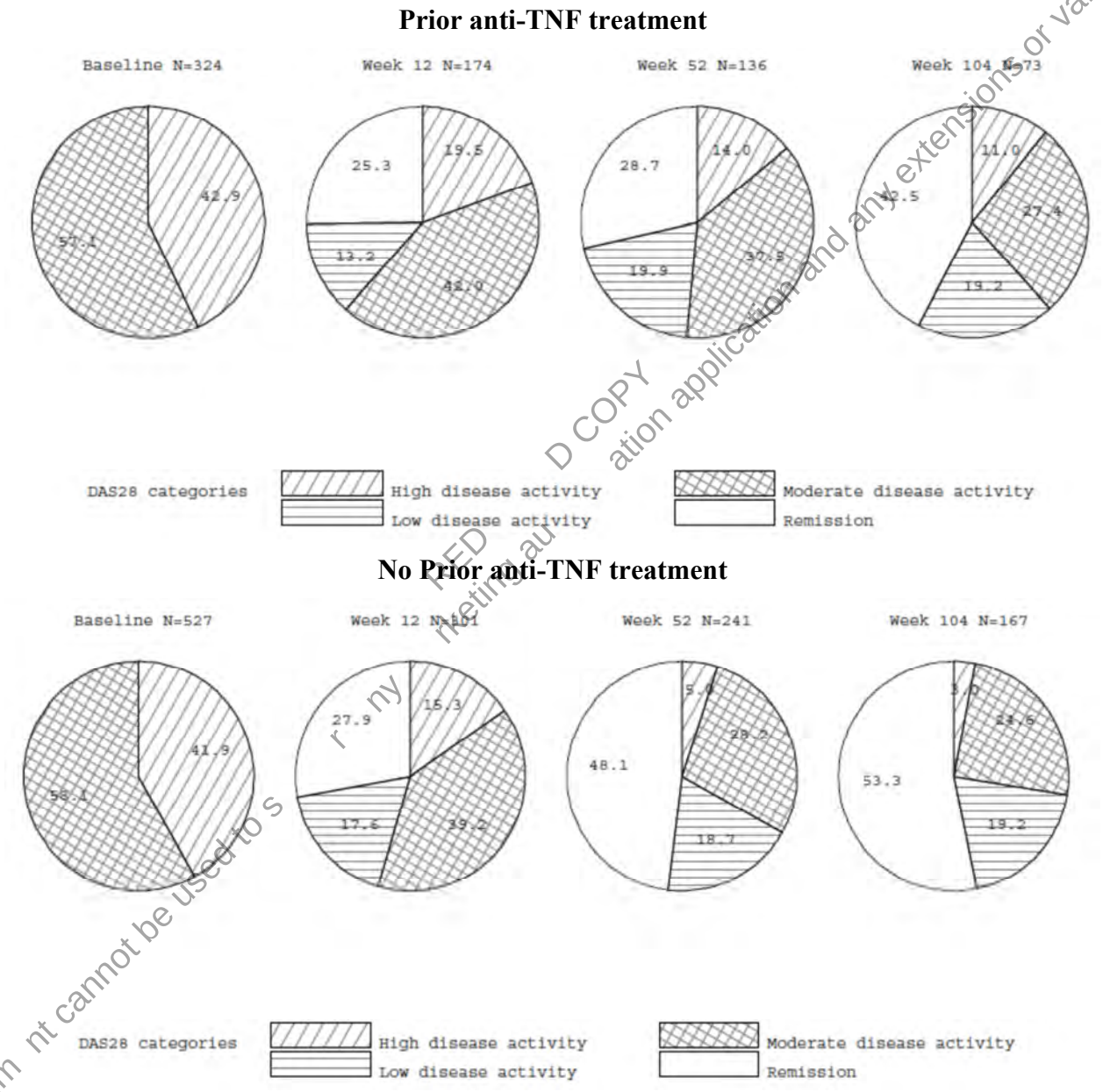
In both anti-TNF pretreated and anti-TNF naïve patients, changes in DAS28 over time followed a similar trend as for the overall population (Section 10.4.3.1.1). Both categories of patients had similar mean DAS28 values at Baseline. However, using both the nonmissing observations and MMRM imputation, patients who were anti-TNF naïve had slightly lower mean values (and slightly greater mean decrease) of DAS28 at all timepoints when compared to anti-TNF pretreated patients (Table 10–15).

Data for patients who had received MTX and other DMARDs were generally consistent with those for patients who had received prior anti-TNF treatment. Patients who had received other biologics had generally slightly higher mean DAS28 values throughout the study and mean changes from Baseline were lower (Table 3.16.4 and Table 3.16.5).

10.5.2.1.2 DAS28 categories

A summary of DAS28 categories by prior RA medication and visit using nonmissing observations and MMRM imputation is provided in Table 3.16.6 and Table 3.16.7, respectively. An overview of the data is presented in Figure 1.5 and Figure 10–4.

Figure 10–4: Percentage of patients in DAS28 categories at Baseline, Week 12, Week 52, and Week 104 by anti-TNF alpha inhibitor pretreatment using nonmissing observations – Full Analysis Set



DAS28=Disease Activity Score-28 joint count; N=number of patients in group; TNF=tumor necrosis factor
Data sources: Figure 1.5, Table 3.16.6

In both anti-TNF pretreated and anti-TNF naïve patients, DAS28 categories followed a similar trend as for the overall population (Section 10.4.3.1.2). Using nonmissing observations, the

percentage of patients in remission or with LDA increased throughout the study (Figure 10–4). At Week 104, the percentage of patients in remission or with LDA was higher for anti-TNF-inhibitor naïve patients (72.5%) than in anti-TNF pretreated patients (61.7%). Using MMRM imputation, results were similar, although, as expected, the absolute values were lower (37.9% and 26.6%, respectively, at Week 104) (Table 3.16.7).

Data for patients who had received MTX and other DMARDS were between those of anti-TNF naïve and pretreated patients. However, the proportion of patients in remission or with LDA was lower for patients who had received other biologics (36.8% using nonmissing observations, 15.4% using MMRM imputation, at Week 104) (Table 3.16.6 and Table 3.16.7).

10.5.2.1.3 DAS28 responders

A summary of DAS28 responders by prior RA medication and visit using nonmissing observations and MMRM imputation is provided in Table 3.16.8 and Table 3.16.9.

In both anti-TNF pretreated and anti-TNF naïve patients, DAS28 responders followed a similar trend as for the overall population (Section 10.4.3.3). Using nonmissing observations, the percentage of responders increased throughout the study. At Week 104, the percentage of responders was higher for anti-TNF-inhibitor naïve patients (74.9%) than in anti-TNF pretreated patients (67.1%). Using MMRM imputation, results were similar, although, as expected, the absolute values were slightly lower (67.0% and 60.2%, respectively, at Week 104).

Data for patients who had received other biologics, MTX, and other DMARDS were between those of anti-TNF naïve and pretreated patients. However, the proportion of responders was lower for patients who had received other biologics using nonmissing observations (42.1% at Week 104).

10.5.2.2 PAAP VAS by prior RA medication

Summary statistics of PAAP VAS, including change from Baseline, by prior RA medication and visit, using nonmissing observations and MMRM imputation are provided in Table 3.16.10 and Table 3.16.11, respectively.

In both anti-TNF pretreated and anti-TNF naïve patients, changes in PAAP VAS over time followed a similar trend as for the overall population (Section 10.4.2.1). Both categories of patient had similar mean PAAP VAS values at Baseline. However, using both the nonmissing observations and MMRM imputation, patients who were anti-TNF naïve had slightly lower mean values (and slightly greater mean decrease) of PAAP VAS at all timepoints when compared to anti-TNF pretreated patients. Using nonmissing observations, mean (SD) PAAP VAS values were 30.5 (22.9) in anti-TNF naïve patients and 36.7 (24.8) in anti-TNF pretreated patients at Week 104. Using MMRM imputation, mean (SD) PAAP VAS values were 38.5 (16.7) in anti-TNF naïve patients and 42.5 (14.8) in anti-TNF pretreated patients at Week 104.

Data for patients who had received MTX and other DMARDS were generally consistent with those for patients who had received prior anti-TNF treatment. Patients who had received other biologics had generally slightly higher mean PAAP VAS values throughout the study and mean changes from Baseline were lower using nonmissing observations (but not using MMRM imputation).

10.5.2.3 HAQ-DI by prior RA medication

Summary statistics of HAQ-DI, including change from Baseline, by prior RA medication and visit, using nonmissing observations and MMRM imputation are provided in Table 3.16.12 and Table 3.16.13.

In both anti-TNF pretreated and anti-TNF naïve patients, changes in HAQ-DI over time followed a similar trend as for the overall population (Section 10.4.2.2). For nonmissing observations, patients who were anti-TNF naïve had slightly lower mean values of HAQ-DI at Baseline when compared to anti-TNF pretreated patients (1.29 versus 1.51). Using both the nonmissing observations and MMRM imputation, these differences at Baseline remained throughout the study, and both categories had similar mean decreases over time. Using nonmissing observations, mean (SD) HAQ-DI values were 0.78 (0.74) in anti-TNF naïve patients and 1.13 (0.70) in anti-TNF pretreated patients at Week 104. Using MMRM imputation, mean (SD) HAQ-DI values were 1.05 (0.60) in anti-TNF naïve patients and 1.27 (0.52) in anti-TNF pretreated patients at Week 104.

Data for patients who had received MTX and other DMARDS were generally consistent with those for patients who had received prior anti-TNF treatment. Patients who had received other biologics had generally slightly higher mean HAQ-DI values throughout the study and mean changes from Baseline were lower using nonmissing observations (but not using MMRM imputation).

10.5.2.4 CDAI by prior RA medication

Summary statistics of CDAI, including change from Baseline, by prior RA medication and visit, using nonmissing observations and MMRM imputation are provided in Table 3.16.14 and Table 3.16.15, respectively.

In both anti-TNF pretreated and anti-TNF naïve patients, changes in CDAI over time followed a similar trend as for the overall population (Section 10.4.2.3). Both categories of patients had similar mean CDAI values at Baseline. However, using both the nonmissing observations and MMRM imputation, patients who were anti-TNF naïve had slightly lower mean values (and slightly greater mean decrease) of CDAI at all timepoints when compared to anti-TNF pretreated patients. Using nonmissing observations, mean (SD) CDAI values were 9.2 (8.7) in anti-TNF naïve patients and 11.4 (9.5) in anti-TNF pretreated patients at Week 104. Using MMRM imputation, mean (SD) CDAI values were 13.8 (7.5) in anti-TNF naïve patients and 16.0 (7.2) in anti-TNF pretreated patients at Week 104.

Data for patients who had received MTX and other DMARDS were generally consistent with those for patients who had received prior anti-TNF treatment. Patients who had received other biologics had generally slightly higher mean CDAI values throughout the study, and mean changes from Baseline were lower using nonmissing observations (but not using MMRM imputation).

10.5.2.5 Duration of morning stiffness by prior RA medication

Summary statistics of duration of morning stiffness, including change from Baseline, by prior RA medication and visit, using nonmissing observations and MMRM imputation are provided in Table 3.16.16 and Table 3.16.17.

In both anti-TNF pretreated and anti-TNF naïve patients, changes in duration of morning stiffness over time followed a similar trend as for the overall population (Section 10.4.3.7). For nonmissing observations, patients who were anti-TNF naïve had slightly lower mean duration of morning stiffness at Baseline when compared to antiTNF pretreated patients (1.40 versus 1.59). Using nonmissing observations, patients who were anti-TNF naïve had slightly lower mean values (and slightly greater mean decrease) at all timepoints when compared to anti-TNF pretreated patients. Using MMRM imputation, mean changes from Baseline were similar in both categories.

10.5.2.6 EQ-5D by prior RA medication

Summary statistics of EQ-5D, including change from Baseline, by prior RA medication and visit, using nonmissing observations and MMRM imputation are provided in Table 3.16.18 and Table 3.16.19, respectively.

In both anti-TNF pretreated and anti-TNF naïve patients, changes in EQ-5D over time followed a similar trend as for the overall population (Section 10.4.3.9). Both categories of patients had similar mean EQ-5D values at Baseline. Using both the nonmissing observations and MMRM imputation, patients who were anti-TNF naïve had slightly higher mean values (and slightly greater mean increase) at all timepoints when compared to anti-TNF pretreated patients.

10.5.3 Effect of early DAS28 response

Early DAS28 response is defined in Section 9.9.2.11.3.3.

10.5.3.1 DAS remission by early DAS28 responders

DAS28 remission by early DAS28 response (yes/no), using nonmissing observations, NRI imputation, and MMRM imputation, is provided in Table 3.16.20, Table 3.16.21, and Table 3.16.22, respectively.

At Week 104, using nonmissing observations, the percentage of patients in DAS28 remission was higher for patients with early DAS28 response (54.8%) than in patients without early DAS28 response (31.1%). Similar results were observed using MMRM and NRI imputation (although with lower percentages in both categories).

10.5.3.2 PAAP VAS by early DAS28 response

Summary statistics of PAAP VAS, including change from Baseline, by early DAS28 response (yes/no) and visit, using nonmissing observations and MMRM imputation are provided in Table 3.16.23 and Table 3.16.24.

In both categories, changes in PAAP VAS over time followed a similar trend as for the overall population (Section 10.4.2.1). Both categories of patients had similar mean PAAP VAS values at Baseline. Using both the nonmissing observations and MMRM imputation, patients with early DAS28 response had slightly lower mean values (and slightly greater mean decrease) at all timepoints when compared to patients without early DAS28 response.

10.5.3.3 HAQ-DI by early DAS28 response

Summary statistics of HAQ-DI, including change from Baseline, by early DAS28 response (yes/no) and visit, using nonmissing observations and MMRM imputation are provided in Table 3.16.25 and Table 3.16.26.

In both categories, changes in HAQ-DI over time followed a similar trend as for the overall population (Section 10.4.2.2). Patients with early DAS28 response had slightly lower mean values of HAQ-DI at Baseline when compared to patients without early DAS28 response. Using both the nonmissing observations and MMRM imputation, patients with early DAS28 response had a greater mean decrease at all timepoints when compared to patients without early DAS28 response.

10.5.3.4 CDAI by early DAS28 response

Summary statistics of CDAI, including change from Baseline, by early DAS28 response (yes/no) and visit, using nonmissing observations and MMRM imputation are provided in Table 3.16.27 and Table 3.16.28, respectively.

In both categories, changes in CDAI over time followed a similar trend as for the overall population (Section 10.4.2.3). Both categories of patients had similar mean CDAI values at Baseline. Using both the nonmissing observations and MMRM imputation, patients with early DAS28 response had slightly lower mean values (and slightly greater mean decrease) at all timepoints when compared to patients without early DAS28 response.

10.5.3.5 Duration of morning stiffness by early DAS28 response

Summary statistics of duration of morning stiffness, including change from Baseline, by early DAS28 response (yes/no) and visit, using nonmissing observations and MMRM imputation are provided in Table 3.16.29 and Table 3.16.30, respectively.

In both categories, changes in duration of morning stiffness over time followed a similar trend as for the overall population (Section 10.4.3.7). Both categories of patients had similar mean duration of morning stiffness at Baseline. Using both the nonmissing observations and MMRM imputation, patients with early DAS28 response had a greater mean decrease at most timepoints when compared to patients without early DAS28 response.

10.5.3.6 EQ-5D by early DAS28 response

Summary statistics of EQ-5D, including change from Baseline, by early DAS28 response (yes/no) and visit, using nonmissing observations and MMRM imputation are provided in Table 3.16.31 and Table 3.16.32, respectively.

In both categories, changes in EQ-5D over time followed a similar trend as for the overall population (Section 10.4.3.9). Both categories of patients had similar mean EQ-5D at Baseline. Using the nonmissing observations and MMRM imputation, patients with early DAS28 response had a greater mean increase at all timepoints when compared to patients without early DAS28 response.

10.6 Adverse Events/adverse reactions

10.6.1 Extent of exposure

A by-patient listing of the patient's exposure to CZP is provided in Listing 4.1 for the SS and these data summarized in Table 4.1. An overview of the incidence of AEs is presented in Table 5.1.1. A glossary of AEs is presented in Listing 5.1.

An overview of the duration of CZP and the patient-years exposure is provided in Table 10–16 for the SS and FAS.

Table 10–16: Summary statistics of CZP duration and patient-years exposure - Safety Set and Full Analysis Set

	SS N=1111	FAS N=851
Study medication duration (days)		
Mean (SD)	449.2 (334.7)	475.8 (330.1)
Range	14, 1821	14, 1821
Total study medication duration (years)	1367.3	1109.4
Total patient-years of exposure	1537.8	1239.9

CZP=certolizumab pegol; FAS=Full Analysis Set; N=number of patients; SD=standard deviation; SS=Safety Set
Note: Calculation of study medication duration=date of last medication – date of first medication +14.
Note: Calculation of patient-years of exposure =(date of last medication – date of first medication +70)/365.25, censored at the date of last clinical contact.
Note: Total study medication duration was the sum of each patient's study medication duration within each country/all patients.
Data source: Table 4.1

In the SS, the mean duration of study treatment was 449.2 days (ranging from 14 to 1821 days), with a total exposure of 1537.8 patient-years. In the FAS, the mean duration of study treatment was 475.8 days (ranging from 14 to 1821 days), with a total exposure of 1239.9 patient-years.

10.6.2 Adverse Events

10.6.2.1 Overall summary of TEAEs

A by-patient listing of the AEs and TEAEs is provided in Listing 5.2 for the SS. A summary of nonserious incidence of TEAEs is presented in Table 5.2.3, for SS.

An Overview of the incidence of TEAEs is provided in Table 5.1.2.1 and Table 10–17 for the SS.

Table 10–17: Overview of TEAEs - Safety Set

Category	N=1111 n (%) [#]
Any TEAEs	745 (67.1) [2000]
Serious TEAEs	212 (19.1) [306]
Discontinuations due to TEAEs	253 (22.8) [319]
Drug-related TEAEs[a]	485 (43.7) [956]
Severe TEAEs	135 (12.2) [212]
Deaths	9 (0.8) [9]
TEAEs requiring dose change	440 (39.6) [740]

#=number of individual TEAE occurrences; N=number of patients in group; n=number of patients reporting at least 1 TEAE in that category; TEAE=treatment-emergent adverse event

[a] Drug-related TEAEs were those with a relationship of related, possibly related, or those with missing response according to the company's causality assessment.

Data source: Table 5.1.2.1

In the SS, 745 patients (67.1%) reported at least 1 TEAE, 212 patients (19.1%) reported serious TEAEs, and 253 patients (22.8%) reported TEAEs leading to the discontinuation of CZP. There were 485 patients (43.7%) with drug-related TEAEs, 135 patients (12.2%) with severe TEAEs, 9 deaths (0.8%), and 440 patients (39.6%) with TEAEs requiring dose change (Table 10–17).

The EAIR and EAER of the TEAEs are presented in Table 5.1.2.2 and Table 10–18.

Table 10–18: Incidence of TEAEs - exposure-adjusted incidence rates and event rates - Safety Set

Category	Number of patients and events n [#]	Exposure for EAIR (years)	EAIR Events per 100 patient-years (95% CI)	EAER Events per 100 patient-years
Any TEAEs	745 [2000]	921.11	80.88 (75.18, 86.90)	130.06
Serious TEAEs	212 [306]	1405.88	15.08 (13.12, 17.25)	19.90
Discontinuations due to TEAEs	253 [319]	1516.74	16.68 (14.69, 18.87)	20.74
TEAEs of serious infections	43 [53]	1514.26	2.84 (2.06, 3.83)	3.45
Drug-related TEAEs[a]	485 [956]	1217.16	39.85 (36.38, 43.56)	62.17
Severe TEAEs	135 [212]	1464.51	9.22 (7.73, 10.91)	13.79
Deaths	9 [9]	1534.75	0.59 (0.27, 1.11)	0.59
TEAEs requiring dose change	440 [740]	1283.79	34.27 (31.15, 37.63)	48.12

#=number of individual TEAE occurrences; CI=confidence interval; EAER=exposure-adjusted event rates; EAIR=exposure-adjusted incidence rates; N=number of patients in group; n=number of patients having at least 1 event in that category; TEAE=treatment-emergent adverse event

Note: EAIR calculated the number of patients having at least 1 event in each category. EAER calculated the number of events in each category, based on total exposure of 1537.8 years.

[a] Drug-related TEAEs were those with a relationship of related, possibly related, or those with missing response according to the company's causality assessment.

Note: 95% CIs were constructed based on the relationship between Poisson and Chi-square distribution.

Data source: Table 5.1.2.2

In the SS, any TEAEs had EAER of 130.06 events per 100 patient-years, serious TEAEs had 19.90 events per 100 patient-years, discontinuations due to TEAEs had 20.74 events per 100 patient-years, TEAEs of serious infections had 3.45 events per 100 patient-years, drug-related TEAEs had 62.17 events per 100 patient-years, severe TEAEs had 13.79 events per 100 patient-years, deaths had 0.59 events per 100 patient-years, and TEAEs requiring dose change had 48.12 events per 100 patient-years (Table 10–18).

In the SS, any TEAEs had EAIR of 80.88 events per 100 patient-years, serious TEAEs had 15.08 events per 100 patient-years, discontinuations due to TEAEs had 16.68 events per 100 patient-years, TEAEs of serious infections had 2.84 events per 100 patient-years, drug-related TEAEs had 39.85 events per 100-patient-years, severe TEAEs had 9.22 events per 100 patient-years, deaths had 0.59 events per 100 patient-years, and TEAEs requiring dose change had 34.27 events per 100 patient-years (Table 10–18).

10.6.2.2 Most commonly reported TEAEs

The incidence of TEAEs is presented in Table 5.2.1 for the SS. Incidence of TEAEs, reported in at least 1% of the patients, is presented by SOC and PT in Table 10–19.

Table 10–19: Incidence of TEAEs reported in at least 1% of patients - Safety Set

MedDRA (Version 17.1) **System Organ Class** Preferred Term	**N=1111** **n (%) [#]**
Any System Organ Class	745 (67.1) [2000]
Infections and infestations	**353 (31.8) [598]**
Gastrointestinal infection	19 (1.7) [20]
Herpes zoster	14 (1.3) [14]
Respiratory tract infection	15 (1.4) [17]
Infection	12 (1.1) [14]
Bronchitis	41 (3.7) [49]
Pneumonia	13 (1.2) [13]
Nasopharyngitis	111 (10.0) [143]
Upper respiratory tract infection	30 (2.7) [36]
Sinusitis	19 (1.7) [21]
Urinary tract infection	27 (2.4) [31]
Cystitis	13 (1.2) [16]
Skin and subcutaneous tissue disorders	**175 (15.8) [196]**
Alopecia	20 (1.8) [20]
Dermatitis allergic	17 (1.5) [17]
Eczema	11 (1.0) [11]
Pruritus	15 (1.4) [17]
Psoriasis	19 (1.7) [19]
Rash	31 (2.8) [34]
Musculoskeletal and connective tissue disorders	**160 (14.4) [229]**
Arthralgia	12 (1.1) [12]
Rheumatoid arthritis	45 (4.1) [51]
Gastrointestinal disorders	**137 (12.3) [171]**
Diarrhoea	22 (2.0) [23]
Nausea	31 (2.8) [34]

Table 10–19: Incidence of TEAEs reported in at least 1% of patients - Safety Set

MedDRA (Version 17.1) **System Organ Class** Preferred Term	**N=1111** **n (%) [#]**
General disorders and administration site conditions	**120 (10.8) [142]**
Fatigue	31 (2.8) [34]
Injection site erythema	11 (1.0) [12]
Oedema peripheral	15 (1.4) [15]
Nervous system disorders	**111 (10.0) [140]**
Headache	30 (2.7) [31]
Dizziness	29 (2.6) [31]
Paraesthesia	11 (1.0) [11]
Respiratory, thoracic and mediastinal disorders	**80 (7.2) [93]**
Dyspnoea	15 (1.4) [15]
Cough	21 (1.9) [22]
Vascular disorders	**49 (4.4) [53]**
Hypertension	19 (1.7) [21]

#=number of individual TEAE occurrences; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients in group; n=number of patients reporting at least 1 TEAE within system organ class/preferred term; TEAE=treatment-emergent adverse event
Data source: Table 5.2.1

The most commonly reported TEAEs were Infections and infestations (353 patients [31.8%]), Skin and subcutaneous tissue disorders (175 patients [15.8%]), Musculoskeletal and connective tissue disorders (160 patients [14.4%]), and Gastrointestinal disorders (137 patients [12.3%]). The most commonly reported TEAE PTs were nasopharyngitis (10.0%); RA (4.1%); bronchitis (3.7%); and fatigue, nausea, and rash (each 2.8%) (Table 10–19). Overall, the incidence of TEAEs was consistent with the known safety profile of CZP and did not reveal any new safety signal for CZP.

A summary of the incidence of nonserious TEAEs above the reporting frequency threshold of 5% of patients is presented in Table 5.2.7 for the SS.

10.6.2.3 Drug-related TEAEs

An Overview of drug-related TEAEs is presented in Table 5.4.1 and Table 10–20.

Table 10–20: Overview of drug-related TEAEs - Safety Set

Category	N=1111 n (%) [#]
Any drug-related TEAEs	485 (43.7) [956]
Serious drug-related TEAEs	85 (7.7) [106]
Discontinuations due to drug-related TEAEs	205 (18.5) [251]
Severe drug-related TEAEs	83 (7.5) [112]
Drug-related deaths	3 (0.3) [3]
Drug-related TEAEs requiring dose change	327 (29.4) [489]

#=number of individual TEAE occurrences; N=number of patients in group; n=number of patients having at least 1 event in that category; TEAE=treatment-emergent adverse event
Drug-related TEAEs were those with a relationship of related, possibly related, or those with missing response according to the company's causality assessment.
Data source: Table 5.4.1

In the SS, 485 patients (43.7%) reported at least 1 drug-related TEAE, 85 patients (7.7%) reported serious drug-related TEAEs, 205 patients (18.5%) reported discontinuations due to drug-related TEAEs, 83 patients (7.5%) reported severe drug-related TEAEs, 3 patients (0.3%) had drug-related TEAEs with fatal outcomes, and 327 patients (29.4%) reported drug-related TEAEs requiring dose change (Table 10–20).

The incidence of drug-related TEAEs is presented in Table 5.4.2 for the SS. The incidence of drug-related TEAEs reported in at least 1% of the patients is presented by SOC and PT in Table 10–21.

Table 10–21: Incidence of drug-related TEAEs reported in at least 1% patients - Safety Set

MedDRA (Version 17.1) System Organ Class Preferred Term	N=1111 n (%) [#]
Any System Organ Class	485 (43.7) [956]
Infections and infestations	**213 (19.2) [354]**
Bronchitis	24 (2.2) [27]
Pneumonia	11 (1.0) [11]
Nasopharyngitis	53 (4.8) [74]
Upper respiratory tract infection	22 (2.0) [26]
Sinusitis	13 (1.2) [15]
Urinary tract infection	13 (1.2) [15]

Table 10–21: Incidence of drug-related TEAEs reported in at least 1% patients - Safety Set

MedDRA (Version 17.1) System Organ Class Preferred Term	N=1111 n (%) [#]
Skin and subcutaneous tissue disorders	**122 (11.0) [132]**
Alopecia	12 (1.1) [12]
Dermatitis allergic	11 (1.0) [11]
Psoriasis	14 (1.3) [14]
Rash	24 (2.2) [27]
General disorders and administration site conditions	**84 (7.6) [99]**
Fatigue	27 (2.4) [29]
Injection site erythema	11 (1.0) [12]
Gastrointestinal disorders	**60 (5.4) [80]**
Diarrhoea	14 (1.3) [14]
Nausea	18 (1.6) [20]
Nervous system disorders	**50 (4.5) [60]**
Headache	18 (1.6) [18]
Dizziness	14 (1.3) [16]
Musculoskeletal and connective tissue disorders	**44 (4.0) [49]**
Rheumatoid arthritis	17 (1.5) [17]
Respiratory, thoracic and mediastinal disorders	**41 (3.7) [47]**
Cough	11 (1.0) [11]

#=number of individual TEAE occurrences; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients in group; n=number of patients reporting at least 1 TEAE within system organ class/preferred term; TEAE=treatment-emergent adverse event

Drug-related TEAEs were those with a relationship of related, possibly related, or those with missing response according to the company's causality assessment.

Data source: Table 5.4.2

The most common drug-related TEAEs reported were Infections and infestations (213 patients [19.2%]), Skin and subcutaneous tissue disorders (122 patients [11.0%]), General disorders and administration site conditions (84 patients [7.6%]), Gastrointestinal disorders (60 patients [5.4%]), and Nervous system disorders (50 patients [4.5%]). The most commonly reported TEAE PTs were nasopharyngitis (4.8%), fatigue (2.4%), bronchitis (2.2%), and rash (2.2%) (Table 10–21).

10.6.3 TEAEs of interest

During analysis, specific PTs relevant to TEAEs of interest (Section 9.5.4.2.4) were identified by use of programmed data interrogation and manual listing review by the study physician.

For the SS, a by-patient listing of TEAEs of interest is provided in Listing 5.3 and summarized in Table 5.2.4 and Table 10–22.

Table 10–22: Incidence of TEAEs of interest - Safety Set

MedDRA (V17.1) **System Organ Class** Preferred Term	**SS** **N=1111** **n (%) [#]**
Any System Organ Class	63 (5.7) [78]
Serious Infections and infestations	**43 (3.9) [53]**
Diverticulitis	2 (0.2) [2]
Gastroenteritis	1 (0.1) [1]
Gastrointestinal infection	1 (0.1) [1]
Peritonitis	1 (0.1) [1]
Arthritis bacterial	1 (0.1) [1]
Cellulitis	1 (0.1) [1]
Cellulitis gangrenous	1 (0.1) [1]
Mastitis	1 (0.1) [1]
Cystitis escherichia	1 (0.1) [1]
Escherichia sepsis	1 (0.1) [1]
Gall bladder empyema	1 (0.1) [1]
Liver abscess	1 (0.1) [1]
Herpes zoster	1 (0.1) [1]
Ophthalmic herpes zoster	1 (0.1) [1]
Abscess	1 (0.1) [1]
Abscess limb	1 (0.1) [1]
Localised infection	1 (0.1) [1]
Postoperative wound infection	1 (0.1) [1]
Influenza	1 (0.1) [1]
Pneumonia	10 (0.9) [10]
Bronchopneumonia	2 (0.2) [2]
Bronchitis	1 (0.1) [1]

Table 10–22: Incidence of TEAEs of interest - Safety Set

MedDRA (V17.1) System Organ Class Preferred Term	SS N=1111 n (%) [#]
Epididymitis	1 (0.1) [1]
Muscle abscess	1 (0.1) [1]
Sepsis	4 (0.4) [4]
Erysipelas	2 (0.2) [2]
Pneumonia pneumococcal	1 (0.1) [1]
Pulmonary tuberculosis	2 (0.2) [2]
Tuberculosis	2 (0.2) [2]
Urinary tract infection	3 (0.3) [4]
Cystitis	1 (0.1) [1]
Gastrointestinal viral infection	1 (0.1) [1]
Viral infection	1 (0.1) [1]
Neoplasms benign, malignant and unspecified	**10 (0.9) [10]**
Breast cancer	1 (0.1) [1]
Cervix carcinoma stage 0	1 (0.1) [1]
Endometrial adenocarcinoma	1 (0.1) [1]
Squamous cell carcinoma	1 (0.1) [1]
Bronchial carcinoma	1 (0.1) [1]
Small cell lung cancer	1 (0.1) [1]
Malignant melanoma	1 (0.1) [1]
Basal cell carcinoma	2 (0.2) [2]
Thyroid cancer recurrent	1 (0.1) [1]
Blood and lymphatic system disorders	**3 (0.3) [3]**
Anaemia	2 (0.2) [2]
Thrombocytopenia	1 (0.1) [1]
Cardiac disorders	**5 (0.5) [6]**
Cardiac failure chronic	3 (0.3) [3]
Cardiac failure	2 (0.2) [3]
Gastrointestinal disorders	**3 (0.3) [3]**
Diarrhoea haemorrhagic	1 (0.1) [1]

Table 10–22: Incidence of TEAEs of interest - Safety Set

MedDRA (V17.1) System Organ Class Preferred Term	SS N=1111 n (%) [#]
Non-site specific gastrointestinal haemorrhages	**2 (0.2) [2]**
Gastrointestinal haemorrhage	1 (0.1) [1]
Melaena	1 (0.1) [1]
Injury, poisoning and procedural complications	**1 (0.1) [1]**
Post procedural myocardial infarction	1 (0.1) [1]
Nervous system disorders	**1 (0.1) [1]**
Haemorrhage intracranial	1 (0.1) [1]
Vascular disorders	**1 (0.1) [1]**
Haematoma	1 (0.1) [1]

#=number of individual TEAE occurrences; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients in group; n=number of patients reporting at least 1 TEAE within system organ class/preferred term; SS=Safety Set; TEAE=treatment-emergent adverse event
Data source: Table 5.2.4

The most common TEAEs of interest were classified under MedDRA SOCs Infections and infestations (43 patients [3.9%]), Neoplasms benign, malignant and unspecified (10 patients [0.9%]), Blood and lymphatic system disorders (3 patients [0.3%]), and Cardiac disorders (5 patients [0.5%]). The most commonly reported TEAE of interest PTs were pneumonia (10 patients [0.9%]), sepsis (4 patients [0.4%]), urinary tract infection (3 patients [0.3%]), and cardiac failure chronic (3 patients [0.3%]). (Table 10–22).

The TEAEs of interest like tuberculosis, neoplasms, and serious infections were reported in 4 patients (0.4%), 10 patients (0.9%), and 43 patients (3.9%), respectively. Incidences of these events of interest were not higher compared to what was seen in the clinical development program of Cimzia.

The following sections summarize information relating to events that are listed as important identified and potential risks in the current EU Risk Management Plan. An evaluation is made whether real life data from a large scale NIS provides additional information relevant to the characterization of these risks.

10.6.3.1 Infections

10.6.3.1.1 Serious infections

Serious Infections, as classified in the SOC of Infections and infestations, were reported in 43 patients (3.9%) (Table 10–22). The most commonly reported PTs of serious infections were pneumonia (10 patients [0.9%]), sepsis (4 patients [0.4%]), urinary tract infection (3 patients [0.3%]), diverticulitis (2 patients [0.2%]), bronchopneumonia (2 patients [0.2%]), erysipelas (2 patients [0.2%]), pulmonary tuberculosis (2 patients [0.2%]), and tuberculosis (2 patients [0.2%]). As specified in Table 10–18, the EAIR for serious infections was 2.84 [(2.06; 3.83)]. In

a pooling of RA clinical studies with a cut-off of 31 Dec 2014, the incidence rate for serious infections was 4.20 in the ALL CZP in all studies group. Any comparison between these data sets must, however, be interpreted with caution due to potential differences in study population and differences in individual patient follow-up periods combined with unequal distribution over time for certain events.

10.6.3.1.2 Opportunistic infections (including active tuberculosis)

No serious opportunistic infections were reported. Localized fungal infections were reported but none were serious or considered as opportunistic.

During the study, there were 2 patients with TEAEs of tuberculosis, 2 patients with TEAEs of pulmonary tuberculosis, and 1 patient with latent tuberculosis. Brief summaries are provided below:

- Patient [redacted] was a [redacted]-year-old [redacted]. The first injection of CZP was given on [redacted]. At 714 days after CZP initiation (49 days after the latest administration), [redacted] experienced a serious TEAE of tuberculosis. The action taken with study drug was reported as drug withdrawn. Patient discontinued from the study due to tuberculosis and the final dose of CZP was taken on an [redacted]; the final visit was on [redacted]. The relationship of CZP to the event was reported as related.
- Patient [redacted] was a [redacted]-year-old [redacted]. The first injection of CZP was given on [redacted]. At 219 days after CZP initiation, [redacted] experienced a serious TEAE of tuberculosis. The action taken with study drug was reported as drug withdrawn. The patient took medications for treatment of tuberculosis from [redacted] Patient discontinued from the study due to tuberculosis and the final dose of CZP was taken on an [redacted]; the final visit was on [redacted]. The relationship of CZP to the event was reported as related.
- Patient [redacted] was a [redacted]-year-old [redacted]. The first injection of CZP was given on [redacted]. On an unknown date after CZP initiation, [redacted] experienced a serious TEAE of pulmonary tuberculosis. The action taken with study drug was reported as not applicable. The patient took medications for treatment of tuberculosis of the lung from [redacted]. Patient discontinued from the study due to pulmonary tuberculosis, and the final dose of CZP was taken on an [redacted]; the final visit was on [redacted]. The relationship of CZP to the event of pulmonary tuberculosis was reported as related.
- Patient [redacted] was a [redacted]-year-old [redacted]. The first injection of CZP was given on [redacted]. At 386 days after CZP initiation, [redacted] experienced a serious TEAE of pulmonary tuberculosis. Patient discontinued from the study due to pulmonary tuberculosis, and the final dose of CZP was taken on an [redacted]; the final visit was on [redacted]. The relationship of CZP to the event of pulmonary tuberculosis was reported as related.
- Of note, there was 1 nonserious case of latent tuberculosis. The event was reported in a [redacted]-year-old [redacted] patient ([redacted]). The first injection of CZP was given on [redacted]. In [redacted], patient was diagnosed with latent tuberculosis. The patient took medications for treatment of latent tuberculosis from [redacted]. During the study, the treatment with CZP was interrupted between [redacted] and [redacted]. The patient

then resumed therapy with CZP and continued treatment until [redacted], after which [redacted] dropped out of the study due to lack of efficacy (last contact [redacted]).

All 5 cases had negative tuberculosis test at the start of CZP treatment. On detection of TB, CZP treatment was discontinued. In the case of latent TB, treatment with CZP was resumed while the patient was under prophylactic treatment.

10.6.3.2 Malignancies

Neoplasms, including malignancies, were reported in 10 patients 0.9% (Table 10–22). The only neoplasm reported in more than 1 patient was basal cell carcinoma (2 patients [0.2%]), which was nonserious in 1 patient ([redacted]). All other reports of malignancies were serious (Listing 5.3). There were no reports of lymphoma. In addition, 1 case ([redacted]) of metastatic breast cancer was reported as a post-treatment case 3 months after stop of CZP and therefore not in the list of malignancies reported while on CZP treatment.

CZP was withdrawn after the diagnosis of malignancy was established in all cases except the 2 cases of basal cell carcinoma where CZP was resumed after surgical excision of the lesions.

10.6.3.3 Major cardiovascular events

Although not reported as congestive, 3 patients ([redacted]) reported serious TEAE of cardiac failure chronic and 2 patients ([redacted]) reported SAEs of cardiac failure (Listing 5.2). The event in patient [redacted] was considered possibly related to CZP (the other events were considered unrelated or unlikely related to CZP). One patient ([redacted] had a [redacted] (Listing 2.2.2).

Potential ischemic cardiac events: One patient reported acute myocardial infarction (considered serious), 2 patients reported myocardial infarction (both considered serious, 1 resulting in death), and 1 patient reported angina pectoris (nonserious) (Table 5.2.1, Listing 5.2).

10.6.3.4 Neurologic events

Neurologic events were rare; 1 patient (0.1%; [redacted]) reported a serious TEAE of intracranial hemorrhage (Table 10–22, Listing 5.3). No reports suggestive of new onset or exacerbation of clinical symptoms and/or radiographic evidence of demyelinating disease, including multiple sclerosis, were reported.

One patient reported ischemic cerebral infarction (serious), 1 patient reported cerebrovascular accident (serious), 1 patient reported a cerebrovascular accident (serious) and transient ischemic attack (nonserious), and an additional 4 patients reported a transient ischemic attack (all serious) (Table 5.2.1, Listing 5.2).

10.6.3.5 Autoimmune disorders

Lupus and lupus-like illness: No events of lupus-like illness were included under TEAEs of interest (Table 10–22). However, 1 patient ([redacted]) reported systemic lupus erythematosus (nonserious). This event started 58 days after the first dose of CZP, was considered to be of moderate intensity and possibly related to CZP, and the dose of CZP was not changed (Listing 5.2). The patient had no medical history of autoimmune disease.

There were no reports of other immunogenic events such as sarcoidosis.

10.6.4 Other TEAEs of interest

10.6.4.1 Injection reactions (including hypersensitivity)

Injection reactions were classified as local (Table 5.3.1) or systemic (Table 5.3.2.1 and Table 5.3.2.2) by the physician. Incidence of drug-related TEAEs causing local reactions at the injection site is presented in Table 5.4.4, for SS. Incidence of TEAEs by patient numbers is presented in Table 5.5, for SS.

10.6.4.1.1 Local injection reactions

For the SS, incidence of TEAEs causing local reactions at the injection site is presented in Table 10–23.

Table 10–23: Incidence of TEAEs causing local reactions at the injection site - Safety Set

MedDRA (V17.1) **System Organ Class** Preferred Term	**SS** N=1111 n (%) [#]
Any System Organ Class	28 (2.5) [37]
General disorders and administration site conditions	**24 (2.2) [31]**
Injection site erythema	11 (1.0) [12]
Injection site pain	7 (0.6) [7]
Injection site reaction	4 (0.4) [5]
Injection site pruritus	3 (0.3) [3]
Injection site urticarial	2 (0.2) [2]
Injection site discolouration	1 (0.1) [1]
Injection site macule	1 (0.1) [1]
Skin and subcutaneous tissue disorders	**3 (0.3) [3]**
Skin discolouration	1 (0.1) [1]
Dermatitis allergic[a]	1 (0.1) [1]
Urticaria[a]	1 (0.1) [1]
Immune system disorders	**1 (0.1) [1]**
Hypersensitivity[a]	1 (0.1) [1]
Infections and infestations	**1 (0.1) [1]**
Oral herpes[a]	1 (0.1) [1]
Injury, poisoning and procedural complications	**1 (0.1) [1]**
Injection related reaction	1 (0.1) [1]

#=number of individual TEAE occurrences; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients in group; n=number of patients reporting at least 1 TEAE within system organ class/preferred term; SS=Safety Set; TEAE=treatment-emergent adverse event

[a] The classification is based on physician assessment and does not necessarily match UCB assessments.

Data source: Table 5.3.1

The most commonly reported TEAE SOC which caused local reactions at injection site was General disorders and administration site conditions like Injection site reactions (24 patients [2.2%]). The most commonly reported injection site reactions included Injection site erythema (11 patients [1.0%]) and injection site pain (7 patients [0.6%]). One event of hypersensitivity was reported as a local reaction.

The most commonly reported drug-related TEAEs which caused local reactions at injection site were General disorders and administration site conditions like injection site reactions

(24 patients [2.2%]). The most commonly reported local injection site reactions included injection site erythema (11 patients [1.0%]) and injection site pain (7 patients [0.6%]).

10.6.4.1.2 Systemic injection reactions

For the SS, incidences of systemic injection reaction by time response according to physician's judgment and incidences of systemic injection reactions response according to standardized MedDRA queries (SMQs), is provided in Table 5.3.2.1 and Table 5.3.2.2, respectively. The most commonly reported systemic injection reaction SOCs were Gastrointestinal disorders and Skin and subcutaneous tissue disorders. The most commonly reported systemic injection reaction PTs per SMQs were rash (31 patients), cough (21 patients), dyspnoea (15 patients), pruritus (15 patients), erythema (9 patients), and hypersensitivity (7 patients). The most commonly reported systemic injection reaction PTs per physician's judgment were dermatitis allergic (8 patients), rash (7 patients), hypersensitivity (5 patients).

The most commonly reported systemic injection reactions by time response according to physician's judgment are presented in Table 10–24.

Table 10–24: Incidences of systemic injection reactions by time response according to physician's judgment in at least 1% patients - Safety Set

MedDRA (V17.1) System Organ Class Preferred Term	**Time response**	**SS** N=1111 **n (%) [#]**
Any System Organ Class	Any	75 (6.8) [108]
	Acute	22 (2.0) [31]
	Delayed	55 (5.0) [76]
Gastrointestinal disorders	Any	12 (1.1) [14]
	Acute	5 (0.5) [6]
	Delayed	8 (0.7) [8]
Skin and subcutaneous tissue disorders	Any	31 (2.8) [33]
	Acute	4 (0.4) [5]
	Delayed	27 (2.4) [28]

#=number of individual TEAE occurrences; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients in group; n=number of patients reporting at least 1 TEAE within system organ class/preferred term; SS=Safety Set; TEAE=Treatment-Emergent Adverse Event

Note: The classification, as well as determination of delayed or acute, is based on physician assessment and does not necessarily match UCB assessments.

Data source: Table 5.3.2.1

As presented in Table 10–24, the most commonly reported systemic injection reactions by time response were Gastrointestinal disorders and Skin and subcutaneous tissue disorders. Systemic injection reactions relating to skin and subcutaneous tissue were more commonly delayed than acute.

No events of hypersensitivity (assessed as such by the treating physician) were included under TEAEs of interest (Table 10–22). However, 7 patients (0.6%) reported hypersensitivity (considered serious in 1 patient) and, 1 patient reported anaphylactic reaction (considered serious) (Table 5.2.1). The serious TEAE of hypersensitivity occurred on the first day of CZP administration. Of the patients with nonserious hypersensitivity TEAEs, 5 occurred within 10 days after starting CZP and 1 occurred later. The serious TEAE of anaphylactic reaction occurred 12 days after starting CZP and lasted 1 day (Listing 5.2).

10.6.4.1.3 Serious bleeding events

Serious bleeding events: Six patients reported serious TEAEs relating to bleeding, including gastrointestinal hemorhage [redacted]), diarrhea hemorhagic [redacted]), melaena ([redacted], hematoma [redacted]), contusion ([redacted]), and hemoptysis ([redacted]) (Listing 5.3). In addition, there was 1 case of interest of intracranial hemorhage as mention in Section 10.6.3.4. All other bleeding events, including events of epistaxis, nasal disorders, contusions, and gingival bleeding were mostly of mild and moderate intensity, with only patient [redacted] reporting contusion of severe intensity. Epistaxis resulted in CZP withdrawal in 3 patients.

10.6.4.1.4 Hematopoietic cytopenia

No cases were reported during the study.

10.6.4.1.5 Serious skin reactions

Skin reactions: Severe and potentially drug-related reactions such as Steven Johnson Syndrome, toxic epidermal necrolysis, and eryhtema multiforme are adverse events of interest for CZP. No such skin reactions were reported. Psoriatic conditions were reported in 23 patients (2.1%) (including psoriasis, pustular psoriasis, and dermatitis psoriasiform) (Table 5.2.1); these were considered as serious in 7 patients (0.6%) (Table 5.2.2). Other SAEs relating to skin were dermatitis allergic (3 patients [0.3%]) and drug eruption, erythema, erythema nodosum, rash, and rash vesicular (each in 1 patient [0.1%]) (Table 5.2.2).

10.6.4.1.6 Blood and lymphatic disorders

Blood and lymphatic system disorders: TEAEs of anemia (2 patients [0.4%]; serious in 2 patients), and thrombocytopenia (1 patient [0.1%]; serious) were reported (Table 10–22; Listing 5.3). There were no reports of aplastic anemia, pancytopenia, or neutropenia.

10.6.4.1.7 Hepatobiliary disorders

Hepatobiliary disorders: There were single reports of cholelithiasis, cholecystitis, and autoimmune hepatitis (all considered serious), and hepatitis (nonserious) (Listing 5.2). A total of 20 patients (1.8%) had TEAEs reported relating to liver function analyses (including liver function test abnormal, transaminases increased, gamma-glutamyltransferase increased, and hepatic enzyme increased), only 1 of which was considered serious (liver function test abnormal). No cases of Hepatitis B reactivation, which is a potential risk for CZP were reported.

10.6.5 Deaths

For the SS, incidences of TEAEs leading to death are presented in Table 10–25.

Table 10–25: Incidence of TEAEs leading to death - Safety Set

MedDRA (V17.1) System Organ Class Preferred Term	SS N=1111 n (%) [#]
Any System Organ Class	9 (0.8) [9]
Infections and infestations	**3 (0.3) [3]**
Sepsis	3 (0.3) [3]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**2 (0.2) [2]**
Bronchial carcinoma	1 (0.1) [1]
Small cell lung cancer	1 (0.1) [1]
Cardiac disorders	**1 (0.1) [1]**
Myocardial infarction	1 (0.1) [1]
Gastrointestinal disorders	**1 (0.1) [1]**
Diarrhoea haemorrhagic	1 (0.1) [1]
General disorders and administration site conditions	**1 (0.1) [1]**
Death	1 (0.1) [1]
Injury, poisoning and procedural complications	**1 (0.1) [1]**
Multiple injuries	1 (0.1) [1]

#=number of individual TEAE occurrences; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients in group; n=number of patients reporting at least 1 TEAE within system organ class/preferred term; SS=Safety Set; TEAE=Treatment-Emergent Adverse Event
Data source: Table 5.2.6

Nine patients (0.8%) had TEAEs with fatal outcome. The most commonly reported SOCs were Infections and infestations (3 patients [0.3%]) and Neoplasms benign, malignant and unspecified (including cysts and polyps) (2 patients [0.2%]). Three patients died as a result of sepsis. All other fatal PTs were reported only once (Table 10–25 and Table 5.2.6).

As indicated in Table 10–18, the EAIR for deaths was 0.59 (0.27, 1.11) per 100 patient-years. This is in line with the identified incidence rate of deaths in a pooling of RA studies, with a cut-off date of 31 Dec 2014; ie, 0.53 (0.41-0.67) deaths per 100 patient-years for the ALL CZP in all studies group. However, caution must be applied when comparing real-life data with data from clinical studies, due to differences that might exist like the study population or length of follow up of the patients.

Narratives for deaths are provided below briefly:

- Patient [redacted] was a [redacted]-year-old [redacted]. The first injection of CZP was given on [redacted]. At 3.5 months after CZP initiation (14 days after the final study drug administration), [redacted] experienced severe pneumococcal pneumonia and sepsis ([redacted]

[redacted]). Five days later ([redacted]), the patient died due to sepsis. The relationships of CZP to the events were reported as related.

- Patient [redacted] was a [redacted]-year-old [redacted]. The first injection of CZP was given on [redacted]. On [redacted], approximately 2 years after CZP initiation (77 days after the final administration), [redacted] experienced cerebral toxoplasmosis which was severe in intensity. The final dose of CZP was taken on [redacted]; the final visit was on [redacted]. Certolizumab pegol was permanently discontinued on [redacted]. On [redacted], [redacted] experienced an event of severe myocardial infarction and died on the same day. The patient discontinued from the study due to the fatal events of myocardial infarction and cerebral toxoplasmosis. The relationship of CZP to the events was reported as unlikely related (myocardial infarction), and not related (cerebral toxoplasmosis).
- Patient [redacted] was a [redacted]-year-old [redacted]. The first injection of CZP was given on [redacted]. At 2 months after CZP initiation (37 days after the final administration), [redacted] experienced severe bronchial carcinoma (metastatic). The action take with the study drug was reported as drug withdrawn, and patient discontinued from the study due to the bronchial carcinoma. The final dose of study drug was taken on an [redacted]; the final visit was on [redacted]. Five months (153 days) after onset, the patient died due to the event. The relationship of CZP to the event was reported as not related.
- Patient [redacted] was an [redacted]-year-old [redacted]. The first injection of CZP was given on [redacted]. At 4 months after CZP initiation [redacted] experienced severe cerebral infarction, facial paresis, and flaccid paralysis. At 8 months after CZP initiation (51 days after the final CZP administration), the patient experienced an event of severe haemorrhagic diarrhea and died on the same day ([redacted]. The final dose of study drug was taken on [redacted]; the final visit was on [redacted]. The relationship of CZP to the event was reported as not related.
- Patient [redacted] was a [redacted] year-old [redacted]. The first injection of CZP was given on [redacted]. Starting from 73 days after CZP initiation, [redacted] experienced serious TEAE of cardiac failure, psoriasis, gastrointestinal viral infection, and sepsis. The patient was withdrawn from the study due to the cardiac failure. At 28 days after the final CZP administration, [redacted] experienced sepsis followed by a serious TEAE of ventricular fibrillation 3 days later. The patient died 2 weeks later ([redacted]) as a result of sepsis. The final dose of study drug was taken on [redacted]; the final visit was on [redacted]. The relationship of CZP to the sepsis was reported as possibly related.
- Patient [redacted] was a [redacted]-year-old [redacted]. The first injection of CZP was given on [redacted]. At 5 months after CZP initiation (27 days after the final administration), [redacted] died, due to unknown cause (PT "death"). The final dose of study drug was taken on [redacted]; the final visit was on [redacted]. A causality assessment of CZP for the event was not reported by the treating physician (as per convention the case was databased with a related).
- Patient [redacted] was a [redacted]-year-old [redacted]. The first injection of CZP was given on [redacted]. At 11 months after CZP initiation, the patient experienced serious TEAE of ventricular dilatation and pneumonia. At 18 days after the final CZP administration [redacted]

experienced severe bacterial sepsis as well as serious TEAEs of liver abscess and renal failure acute. The patient discontinued from the study due to liver abscess, renal failure acute, and sepsis; and the action taken with CZP was reported as withdrawn. The events of liver abscess and renal failure acute resolved. The patient died 24 days later ([redacted]) as a result of sepsis. The final dose of study drug was taken on [redacted]; the final visit was on [redacted]. The relationship of CZP to the sepsis was reported as unlikely related.

- Patient [redacted] was a [redacted]-year-old [redacted]. The first injection of CZP was given on [redacted]. At 5 months after CZP initiation, the patient experienced an event of mild transient ischaemic attack. The patient experienced a serious TEAE of severe small cell lung cancer, reported 2 days after the final CZP administration. [redacted] discontinued from the study due to this event; and the action taken with CZP was reported as withdrawn. At 220 days after onset of the event ([redacted]), the patient died. The final dose of study drug was taken on [redacted]; the final visit was on [redacted]. The relationship of CZP to the event was reported as not related.
- Patient [redacted] was a [redacted]-year-old [redacted]. The first injection of CZP was given on [redacted]. At 19 months after CZP initiation (27 days after the final administration), the patient experienced an event of severe multiple injuries due to a "traffic accident." [redacted] discontinued from the study due to the multiple injuries; and the action taken with CZP was reported as not applicable. The patient died on an [redacted]. The final dose of study drug was taken on [redacted]; the final visit was on [redacted]. The relationship of CZP to the event was reported as not related.

10.6.6 Other serious adverse events

For the SS, incidence of serious TEAEs is reported in Table 5.2.2 and also presented in Table 10–26.

Table 10–26: Incidence of serious TEAEs reported in at least 0.5% patients - Safety Set

MedDRA (V17.1) **System Organ Class** Preferred Term	**SS** N=1111 n (%) [#]
Any System Organ Class	212 (19.1) [306]
Infections and infestations	**43 (3.9) [53]**
Pneumonia	10 (0.9) [10]
Musculoskeletal and connective tissue disorders	**59 (5.3) [74]**
Osteoarthritis	7 (0.6) [7]
Rheumatoid arthritis	22 (2.0) [23]

MedDRA=Medical Dictionary for Regulatory Activities; TEAE=Treatment-Emergent Adverse Event
Note: n=number of patients reporting at least 1 serious TEAE within System Organ Class/Preferred Term.
(%)=percentage of patients among total N. [#] is the number of individual occurrences of the serious TEAE.
Data source: Table 5.2.2

As summarized in Table 10–26, the most common serious TEAE were Infections and infestations (43 patients [3.9%]) and Musculoskeletal and connective tissue disorders (59 patients [5.3%]). The most commonly reported serious TEAE PTs were RA (2.0%), pneumonia (0.9%), and osteoarthritis (0.6%).

For the SS, incidence of drug-related serious TEAEs is reported in Table 5.4.3 and also presented in Table 10–27.

Table 10–27: Incidence of drug-related serious TEAEs occurring in at least 0.5% patients - Safety Set

MedDRA (V17.1) **System Organ Class** Preferred Term	**SS** N=1111 n (%) [#]
Any System Organ Class	85 (7.7) [106]
Infections and infestations	**37 (3.3) [42]**
Pneumonia	8 (0.7) [8]
Musculoskeletal and connective tissue disorders	**9 (0.8) [11]**
Rheumatoid arthritis	5 (0.5) [5]

#=number of individual TEAE occurrences; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients in group; n=number of patients reporting at least 1 TEAE within system organ class/preferred term; SS=Safety Set; TEAE=Treatment-Emergent Adverse Event

Note: Drug-related TEAEs are those with relationship related, possibly related, or those with missing response according to the company's causality assessment.

Data source: Table 5.4.3

As summarized in Table 10–27, the most common drug-related serious TEAE were Infections and infestations (37 patients [3.3%]) and Musculoskeletal and connective tissue disorders (9 patients [0.8%]). The most commonly reported serious TEAE PTs were pneumonia (0.7%) and RA (0.5%).

10.6.7 Discontinuation due to adverse events

For the SS, incidence of TEAEs leading to permanent discontinuation of CZP is provided in Table 5.2.5 and summarized in Table 10–28.

Table 10–28: Incidence of TEAEs leading to permanent discontinuation of CZP reported in at least 0.5% patients - Safety Set

MedDRA (V17.1) System Organ Class Preferred Term	SS N=1111 n (%) [#]
Any System Organ Class	254 (22.9) [336]
Skin and subcutaneous tissue disorders	**68 (6.1) [70]**
Alopecia	5 (0.5) [5]
Dermatitis allergic	7 (0.6) [7]
Psoriasis	12 (1.1) [12]
Rash	11 (1.0) [11]
Rash generalized	5 (0.5) [5]
Musculoskeletal and connective tissue disorders	**43 (3.9) [43]**
Arthralgia	5 (0.5) [5]
Rheumatoid arthritis	22 (2.0) [22]
General disorders and administration site conditions	**29 (2.6) [31]**
Fatigue	5 (0.5) [5]
Gastrointestinal disorders	**21 (1.9) [27]**
Nausea	6 (0.5) [6]
Nervous system disorders	**21 (1.9) [26]**
Dizziness	7 (0.6) [7]
Immune system disorders	**6 (0.5) [7]**
Hypersensitivity	5 (0.5) [6]

#=number of individual TEAE occurrences; CZP=certolizumab pegol; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients in group; n=number of patients reporting at least 1 TEAE within system organ class/preferred term; SS=Safety Set; TEAE=Treatment-Emergent Adverse Event
Data source: Table 5.2.5

As summarized in Table 10–28, the majority of discontinuations were in the SOCs due to Skin and subcutaneous tissue disorders (68 patients [6.1%]), Musculoskeletal and connective tissue disorders (43 patients [3.9%]), and General disorders and administration site conditions (29 patients [2.6%]). The most commonly reported TEAE leading to permanent discontinuation PTs were RA (2.0%), psoriasis (1.1%), and rash (1.0%).

10.6.8 Pregnancies

One incidence of pregnancy was reported during the study. Patient [redacted] ([redacted] years old, [redacted] [German]) reported a pregnancy that ended in [redacted], reported as 2 SAEs. The patient started CZP on [redacted] and was receiving CZP 200mg every 2 weeks.

The patient's last menstrual period was on [redacted]; [redacted]. The event of pregnancy was reported on [redacted] and patient discontinued CZP as a result of the pregnancy (withdrawn from study on [redacted]). [redacted] The events of pregnancy and [redacted] were both considered possibly related to CZP by the treating physician. The patient recovered.

11 DISCUSSION

11.1 Key results

11.1.1 Efficacy results

The percentage of remitters using nonmissing observations, MMRM imputation, and NRI was 120/240 patients (50%), 168/851 patients (19.7%), and 120/851 patients (14.1%), respectively. The higher R of all patients with nonmissing observations are likely to be biased due to the higher probability that more responders complete the study and are therefore to be interpreted with care. It is known that the CI values are affected by number of patients, which means that an increase in patient number results in narrower CIs. Therefore, results for imputed data (N=851) had narrower CIs when compared to the observed data (N=240). Based on the sample size estimate (Section 9.7.1), analysis of data from1068 patients was estimated to be sufficient to derive accurate CI values, to allow conclusions regarding clinical remission in the study. Despite not having achieved the estimated sample size, the CI values for the study were narrow, indicating the reliability of the results, and are still considered sufficient to draw conclusions for clinical remission.

The imputation analysis implemented to account for missing data, represents a more conservative and less biased approach to demonstrate the beneficial effect of CZP in this patient population.

The results on clinical remission over time were consistent with those at Week 104, indicating the long-term therapeutic effect of CZP in patients with RA. The percentage of patients in clinical remission, using NRI, increased steadily up to Week 36 (176/851 patients [20.7%]) and then decreased towards Week104. Patients who withdrew and therefore had missing data at later visits were considered nonresponders in the NRI analysis.

The secondary objective for the study was explored by analyzing mean change from Baseline at Week 104 in PAAP (nonmissing observations: -22.7; MMRM imputation: -16.43), HAQ-DI (nonmissing observations: -0.40; MMRM imputation: -0.26), and CDAI (nonmissing observations: -17.91; MMRM imputation: -14.57). The mean change observed for all the 3 variables over time demonstrates that the CZP treatment had a positive effect on the patient's arthritis pain, physical functioning, and disease activity after 2 years of therapy (Table 10–8, Table 10–9, and Table 10–10).

The benefit of CZP treatment was observed early (ie, up to Week 12), and the treatment continued to be beneficial until Week 104.

Using MMRM imputation for the FAS, the percentage of patients in clinical remission or with LDA according to DAS28, respectively, increased from zero at Baseline to 177/851 patients (20.8%) and 153/851 patients (18.0%) respectively, at Week 12. At Week 104, 168/851 patients (19.7%) and 118/851 patients (13.9%) of the patients were in remission and LDA category,

respectively. A higher percentage of DAS28 clinical remitters was observed compared to ACR/EULAR clinical remitters; this is most likely due to the more stricter criteria for the ACR/EULAR remission than for DAS28.

Though the absolute values were different, the decreases in the disease activity across the weeks were consistent for all the variables of the study.

In both TNF inhibitor pretreated and TNF inhibitor naïve patients, changes in DAS28 over time followed a similar trend as for the overall population. Both categories of patient had similar mean DAS28 values at Baseline. However, using both the nonmissing observations and MMRM imputation, patients who were TNF inhibitor naïve had lower mean values (and greater mean decrease) of DAS28 at all timepoints when compared to TNF inhibitor pretreated patients.

Data for patients who had received MTX and other DMARDS were generally consistent with those for patients who had received prior TNF inhibitor treatment. Patients who had received other biologics prior to the start of CZP had generally slightly higher mean DAS28 values throughout the study and mean changes from Baseline were lower.

In both TNF inhibitor pretreated and TNF inhibitor naïve patients, DAS28 categories followed a similar trend as for the overall population. Using nonmissing observations, the percentage of patients in remission or with LDA increased throughout the study. Using MMRM imputation, results were similar although, as expected, the absolute values were lower (37.9% and 26.6%, respectively, at Week 104). Data for patients who had received MTX and other DMARDS were between those of TNF inhibitor naïve and pretreated patients. However, the proportion of patients in remission or with LDA was lower for patients who had received other biologics prior to the start of CZP (36.8% using nonmissing observations, 15.4% using MMRM imputation, at Week 104).

At Week 104, using nonmissing observations, the percentage of patients in DAS28 remission was higher for patients with early DAS28 response (54.8%) than in patients without early DAS28 response (31.1%). Similar results were observed using MMRM and NRI imputation (although with lower percentages in both categories). All the other analyses based on early DAS28 response showed similar trends of greater mean increase when compared to patients without early response.

11.1.2 Safety results

In the study, the mean duration of treatment for the SS was 449.2 days (ranging from 14 to 1821 days), with a total exposure of 1537.8 patient-years. For the FAS, the mean duration of study treatment was 475.8 days (ranging from 14 to 1821 days), with a total exposure of 1239.9 patient-years.

In the SS, 745 patients (67.1%) reported at least 1 TEAE, 212 patients (19.1%) reported serious TEAEs, and 253 patients (22.8%) reported TEAEs leading to the discontinuation of CZP. There were 485 patients (43.7%) with drug-related TEAEs, 135 patients (12.2%) with severe TEAEs, 9 deaths (0.8%), and 440 patients (39.6%) with TEAEs requiring dose change. Rheumatoid arthritis was reported as a TEAE by 45 patients (4.1%) overall, and in 17 of the 485 patients who reported drug-related TEAEs (Table 10–21), which can be concluded as a reflection of lack of efficacy rather than an AE.

The most commonly reported TEAE PTs were nasopharyngitis (10.0%), RA (4.1%), bronchitis (3.7%), and fatigue, nausea, and rash (each 2.8%).

Out of the 9 fatal TEAEs (0.8%) during the study, majority were due to Infections and infestations (3 patients [0.3%]) and Neoplasms benign, malignant and unspecified (including cysts and polyps) (2 patients [0.2%]). Of these, 2 patients had fatal TEAEs that were considered at least possibly related to CZP.

The EAIR for deaths was 0.59 (0.27, 1.11) per 100 patient-years. This is in line with the identified incidence rate of deaths in a pooling of RA studies, with cut-off 31 Dec 2014; ie, 0.53 (0.41-0.67) deaths per 100 patient-years for the ALL CZP in all studies' group. However, caution must be applied when comparing real-life data with data from clinical studies, due to differences that might exist like the study population or length of follow up of the patients.

In the SS, 485 patients (43.7%) reported at least 1 drug-related TEAE, 85 patients (7.7%) reported drug-related serious TEAEs, 205 patients (18.5%) reported discontinuations due to drug-related TEAEs, 83 patients (7.5%) reported severe drug-related TEAEs, 3 patients (0.3%) had drug-related TEAEs with fatal outcome, and 327 patients (29.4%) reported drug-related TEAEs requiring dose change.

The most commonly reported drug-related TEAE PTs were nasopharyngitis (4.8%), fatigue (2.4%), bronchitis (2.2%), and rash (2.2%).

Of the TEAEs identified as "of interest," the most commonly reported PTs were pneumonia (10 patients [0.9%]), sepsis (4 patients [0.4%]), urinary tract infection (3 patients [0.3%]), and cardiac failure chronic (3 patients [0.3%]).

Infections and infestations are reported as "common" in the SmPC for CZP. In this study, 2 patients reported serious TEAEs of tuberculosis and 2 patients reported pulmonary tuberculosis; latent tuberculosis was reported as a nonserious TEAE in 1 patient. No serious opportunistic infections were reported.

The EAIR for serious infections was 2.84 (2.06; 3.83). In a pooling of RA clinical studies with a cut-off of 31 Dec 2014, the incidence rate for serious infections was 4.20 in the ALL CZP in all studies group. Any comparison between these data sets must however be interpreted with caution due to potential differences in study population and duration of follow up.

During the study, 3 patients reported SAEs of cardiac failure chronic and 2 patients reported SAEs of cardiac failure.

Neurologic events were rare, and there were no reports of new onset or exacerbation of clinical symptoms and/or radiographic evidence of demyelinating disease, including multiple sclerosis. Although not identified as AEs of interest, 1 patient reported ischemic cerebral infarction, 1 patient reported cerebrovascular accident, 1 patient reported a cerebrovascular accident and transient ischemic attack, and an additional 4 patients reported a transient ischemic attack.

Bleeding disorders are reported as "uncommon" in the SmPC. In this study, 6 patients reported serious TEAEs relating to bleeding, including gastrointestinal hemorhage, diarrhea hemorrhagic, melena, hematoma, contusion, and hemoptysis. Epistaxis was nonserious but resulted in CZP withdrawal in 3 patients.

Solid organ tumor, gastrointestinal tumor, benign tumor, and cysts (includes skin papilloma) are reported as "uncommon" in the SmPC. In this study, malignant neoplasms were reported in few patients. The only neoplasm reported in more than 1 patient was basal cell carcinoma (2 patients). There were no reports of lymphoma. In addition, 1 case of metastatic breast cancer was reported as a posttreatment case 3 months after stop of CZP and therefore not in the list of malignancies reported while on CZP treatment.

One patient reported systemic lupus erythematous (nonserious). There were no reports of other immunogenic events such as sarcoidosis.

Blood and lymphatic system disorders are reported as "common" in the SmPC. In this study, serious TEAEs of anaemia (2 patients), leukopenia (1 patient), and thrombocytopenia (1 patient) were reported. There were no reports of aplastic anemia, pancytopenia, or neutropenia.

The most commonly reported TEAE leading to permanent discontinuation PTs were RA (2.0%), psoriasis (1.1%), and rash (1.0%).

Overall, the incidence of TEAEs was consistent with the known safety profile of CZP and did not reveal any new safety signal for CZP.

11.2 Limitations

The majority of discontinuations during the study were due to lack of efficacy (ES: 332 patients, SS: 332 patients, and FAS: 263 patients). In this study, a high proportion of the patients were pretreated with other biologics; 38.1% of the patients had prior anti-TNFα treatment, 13.7% had prior treatment with other biologics, 73.1% of the patients had prior MTX treatment, and 80.5% of the patients had prior treatment with other synthetic DMARDs, for the FAS (see Section 10.2.1.3). This could be considered as a factor contributing to large number of discontinuations due to lack of efficacy. In addition, the assessment of the lack of efficacy was based on the physician's judgment and not further specified in the protocol. Therefore, this could have imbalanced interpretation.

All the statistical and analytical issues were handled as detailed in Section 9.9.2.8. As mentioned in Section 11.1, the results from the nonmissing observations tend to be biased as only the data from the responders were considered for analysis. To compensate for this bias, analysis was also conducted using MMRM imputation and NRI.

11.3 Interpretation

The primary objective of the study was met. There were an increasing percentage of DAS28 clinical remitters across the weeks, for nonmissing observations, thus displaying the rapid efficacy of CZP treatment in adult RA patients over an initial 12-week period, and remaining stable over a treatment period of 104 weeks (2 years). See Section 11.1.1 for a discussion of CIs and imputation analysis in relation to the primary analysis.

Data from the secondary and other variables supported the results from the primary variable. The mean change from Baseline observed at Week 104 in PAAP, HAQ-DI, and CDAI values demonstrated that the CZP treatment had a positive effect on the patient's arthritis pain, physical functioning, and disease activity after 2 years of therapy. The benefit of CZP treatment was observed early (ie, up to Week 12) and the treatment continued to be beneficial until Week 104.

Overall, the incidence of TEAEs was consistent with the known safety data of CZP and did not raise any new concern regarding the safety profile of CZP. The rates of fatalities, serious TEAEs, TEAEs, and discontinuations due to TEAEs were as expected. For events that are listed as important identified risks or potential risks in the current Risk Management Plan for CZP, data were consistent with the current SmPC. This includes serious infections (including opportunistic infections and tuberculosis), malignancies (including lymphoma), congestive heart failure, demyelinating-like disorders, hypersensitivity reactions, and blood and lymphatic system disorders.

11.4 Generalizability

The efficacy and safety results from this study are in general agreement with data from other studies with CZP (alone or in combination with MTX) in patients with RA (Smolen et al, 2009; Fleischmann et al, 2009; Keystone et al, 2009). Treatment response and improvement of patient-related outcomes was greater in TNF inhibitor naïve patients than in TNF inhibitor pretreated patients. Patients responding early to CZP therapy have a greater long-term improvement in disease activity, function, and patient-related outcomes.

The results confirm that long-term (up to 2 years) CZP administration is safe and effective to patients with RA in standard clinical practice when administered in accordance with the SmPC.

12 OTHER INFORMATION

Not applicable.

13 CONCLUSION

The study provides results of 2 years treatment with CZP in adult patients with RA in daily practice in Germany and describe the benefits and risks associated with the treatment.

- After 2 years of treatment with CZP (at Week 104), there was a substantial increase observed in the percentage of DAS28 remitters using nonmissing observations, NRI, and MMRM imputation. The percentage of DAS28 remitters was higher using nonmissing observations.
- The mean change from Baseline at Week 104 values for all 3 secondary variables (PAAP, HAQ-DI, and CDAI) indicated decreased pain and disease activity, and an improvement in physical functioning of the patient. The results support the efficacy of CZP treatment on patients' arthritis pain, physical functioning and disease activity.
- Overall, the incidence of TEAEs in this large scale NIS was consistent with the known safety profile of CZP and did not reveal any new safety signal for CZP.

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APPENDICES

The following are provided:

- Narratives of deaths, serious adverse events and other significant adverse events
- Tables and figures
- Data listings

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

The following are available on request:

Number	Document reference number	Date	Title
1	NA	02 May 2012	Protocol amendment 3
2	NA	19 Aug 2009	Sample Case Report form
3	NA	29 Jun 2009	Model Patient Data Consent form
4	NA	[get this date from the final doc in MIKADO]	List of Independent Ethics Committees
5	NA	[get this date from the final doc in MIKADO]	List of investigators
6	NA	09 Mar 2015	Statistical Analysis Plan, amendment 1
7	NA	02 Mar 2016	Signature page for the coordinating physician

ANNEX 2. ADDITIONAL INFORMATION

Not applicable.

SPONSOR SIGNATURE

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

RA0027 - Study Report Body - <study_title>

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Approval Date (dd-mon-yyyy (HH:mm))
[redacted]	Clinical Approval	14-Mar-2016 14:46 GMT+01

LIST OF INVESTIGATORS

The Clinical Study Report accounts for 163 sites who recruited at least 1 patient in the study in Germany.

The report lists 164 treating physicians who were captured in the database.

In total 170 principal treating physicians participated in the study and are listed below.

In 7 of the sites (sites: 008, 037, 041, 098, 118, 146, 166), 2 principals treating physicians have been involved.

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[redacted]	005	[redacted] Innere Medizin [redacted] Hildesheim 311[redacted] GERMANY
[redacted] (replaced by [redacted])	037	[redacted] [redacted] Essen 453[redacted] GERMANY
[redacted] (replaced [redacted])	118	Klaus-Miehlke-Klinik Wiesbaden Leibnizstrasse 23 Wiesbaden 65191 GERMANY

Principal investigator	Site number	Hospital/institution address
[redacted]	082	[redacted] Rendsburg 247[redacted] GERMANY
[redacted]	069	[redacted] Salzwedel 294[redacted] GERMANY
[redacted]	024	Rheumazentrum Ratingen [redacted] Ratingen 408[redacted] GERMANY
[redacted]	081	Rheumapraxis [redacted] Planegg 821[redacted] GERMANY
[redacted]	002	Rheumatologische Schwerpunktpraxis [redacted] Erlangen 910[redacted] GERMANY
[redacted]	117	[redacted] Schramberg-Sulgen 787[redacted] GERMANY

Principal investigator	Site number	Hospital/institution address
[redacted]	178	Endokrinologikum Muenchen Promenadeplatz 12 Muenchen 80333 GERMANY
[redacted]	123	Wilhelms-Universitaet Muenster Albert-Schweitzer-Strasse 33 Muenster 48149 GERMANY
[redacted]	074	Praxis [redacted] [redacted] Wiesbaden 651[redacted] GERMANY
[redacted]	025	[redacted] [redacted] Berlin 130[redacted] GERMANY