Observational Plan

Non-interventional Study (NIS) to provide Information about

Infliximab-Pen

for Subcutaneous Infliximab Application

Multicentre, cross-sectional, non-interventional study with Infliximab-Pen to evaluate its usability and acceptance in adult patients

Study Code/Number:	CT-P13 SC PEN 1.0
Observational Plan Version Number:	Final 3
Observational Plan Date:	28 January 2021
Pharmalog Project Number:	20549
Responsible Pharmaceutical Company:	Celltrion Healthcare Deutschland GmbH [redacted] Medical Officer Rathausplatz 12 61348 Bad Homburg vor der Höhe Germany
Clinical Research Organisation (CRO):	PHARMALOG Institut für klinische Forschung GmbH Oskar-Messter-Straße 29 85737 Ismaning Germany

SIGNATURES

This observational plan was carefully reviewed by the signatories. The information in this document is in accordance with the ethical principles and legal requirements of non-interventional studies.
By signing this form I confirm having read this observational plan carefully and that it encloses all necessary information for conduct of this non-interventional study.

This observational plan was released by:

RESPONSIBLE PERSON AT THE RESPONSIBLE PHARMACEUTICAL COMPANY

Celltrion Healthcare Deutschland GmbH

Rathausplatz 12

61348 Bad Homburg vor der Höhe

(Germany)

	Date	*Signature*
[redacted] Medical Officer		[redacted]

SIGNATURES

This observational plan was carefully reviewed by the signatories. The information in this document is in accordance with the ethical principles and legal requirements of non-interventional studies.
By signing this form I confirm having read this observational plan carefully and that it encloses all necessary information for conduct of this non-interventional study.

RESPONSIBLE PERSONS AT THE CRO

PHARMALOG Institut für klinische Forschung GmbH
Ismaning (Germany)

	Date	*Signature*
[redacted] Statistician, Author of the biometric part of the observational plan		[redacted]
[redacted] Project Manager, Author of the observational plan		[redacted]

SIGNATURES

I have read the attached observational plan of the non-interventional study CT-P13 SC PEN 1.0 with Infliximab-Pen and agree to comply with all described provisions.
I assure that this document or enclosed confidential information will only be used for conduct this observation.

RESPONSIBLE PHYSICIAN AT THE CENTRE

Date *Signature*

Name of responsible physician at the centre

(in capital letters)

RESPONSIBILITIES AND CONTACT DETAILS

Participating Physicians / Centres	A list of all physicians / centres participating in this non-interventional study (including contact details) is filed in the Trial Master File.
Responsible Pharmaceutical Company	**Celltrion Healthcare Deutschland GmbH** Rathausplatz 12 61348 Bad Homburg vor der Höhe (Germany)
• Project Manager	[redacted] (address see above) Phone: [redacted] Email: [redacted]
• CRO Observational Plan, CRF-Development and Data Management, Project Management, Biometric Analysis, Final Report	**Pharmalog Institut für klinische Forschung GmbH** Oskar-Messter-Straße 29 85737 Ismaning (Germany) Phone: +49 (0) 89 544637-0 Fax: +49 (0) 89 544637-50 Email: pharmalog@pharmalog.com
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SUMMARY OF CHANGES

Version Final 3 compared to Final 2

- In July 2020 the EMA granted extension of indications for Remsima®-Pen. Thus, in accordance with the current Summary of Product Characteristics for the Remsima®-Pen the study indication was extended to ankylosing spondylitis (AS) and psoriatic arthritis (PsA) in order to reflect the use of Remsima®-Pen in a broader spectrum of patients: Synopsis, Sections 3, 4, 5.3, 6, 7, 9.3 and 13.4.
- Study duration was extended from 12 to 18 months: Sections 5.2 and 7.
- The pharmaceutical company (Celltrion Healthcare Deutschland GmbH) moved to a new location. Thus, the address was updated: Cover Page, Signature Page und Section “Responsibilities and Contact Details”.
- Due to current market share evaluations, the sample size was reduced accordingly for a similar precision from 500 to 1,000 patients to 286 to 500 patients. Sample size estimation was adapted accordingly: Synopsis, Sections 5.2 and 13.6.
- Literature reference no. 8 was replaced by the full publication of the registration study in rheumatoid arthritis: Section 17.

1 LIST OF ABBREVIATIONS

AMG	“Arzneimittelgesetz” (German Medicinal Act)
ADR	Adverse Drug Reaction
AS	Ankylosing spondylitis
AWB	“Anwendungsbeobachtung” (German NIS)
bDMARDs	Biological Disease Modifying Anti Rheumatic Drugs
CRO	Contract Research Organisation
CRP	C-Reactive Protein
csDMARDs	Conventional Synthetic Disease Modifying Anti Rheumatic Drugs
DAS28-CRP	Disease Activity Score Using C-Reactive Protein
DMP	Data Management Plan
DVP	Data Validation Plan
e.g.	Exempli Gratia (for example)
eCRF	Electronic Case Report Form
ESR	Erythrocytes Sedimentation Rate
GCP	Good Clinical Practice

IFX	Infliximab
IV	Intravenous
JAK	Janus Kinase
MD	Doctor of Medicine
MSc	Master of Science
N	Number
NIS	Non-Interventional Study
NRS	Numerical Rating Scale
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
PsA	Psoriatic arthritis
RA	Rheumatoid Arthritis
SC	Subcutaneous
SDV	Source Data Verification
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
TNF	Tumor Necrosis Factor
tsDMARDs	Targeted Synthetic Disease Modifying Anti-Rheumatic Drugs
V	Visit

2 SYNOPSIS

Study Code	CT-P13 SC PEN 1.0
Title of the Observational Study	Non-interventional Study (NIS) to provide Information about Infliximab-Pen for Subcutaneous Infliximab Application (product: Remsima® 120 mg)
Type of Observation	Observational Study (AWB) in accordance with §4 (23) sentence 3 and §67 (6) German Medicinal Act (AMG)
Study Design	Multicentre, prospective, non-interventional, cross-sectional
Indication	Rheumatoid arthritis (RA), ankylosing spondylitis (AS) or psoriatic arthritis (PsA)
Study Objective	Usability of Infliximab-Pen as application device for treatment of rheumatoid arthritis (RA), ankylosing spondylitis (AS) or psoriatic arthritis (PsA) with Remsima® 120 mg
Study Treatment	Remsima® 120 mg
Physicians / Centres	40 physicians (rheumatologists)
Number of Patients	At least 286 patients and up to 500 patients are planned to be included
Countries	Germany
Duration of Observation	1 Day / 1 Visit – Cross-sectional observational study
Documentation Criteria	Following documentation criteria should be fulfilled: ▪ Signed informed consent (data protection) ▪ Male and female outpatient aged ≥18 years with the further need of treatment of rheumatoid arthritis (RA), ankylosing spondylitis (AS) or psoriatic arthritis (PsA) ▪ Experience with Remsima®-Pen for at least 3 self-injections at first or later re-visit of patient after hand-over of the Remsima®-Pen at the physician site Patients with the following conditions are excluded from the documentation in this NIS: ▪ Patient <18 years (children and adolescents) ▪ Patient who exhibit contraindications according to SPC (Summary of Product Characteristics) for Remsima® 120 mg or hypersensitivity to any of the ingredients of Remsima® 120 mg is known and therefore treatment with Remsima® 120 mg is not indicated
"Study Visits"/ Time points of Documentation	Documentation of usability ("Visit 1": Day 1) "Visit 1" = routine visit at a physician of a patient to obtain the next prescription for Remsima® 120 mg or for other routine reasons ▪ Informed consent (data protection) of the patient ▪ Baseline characteristics: age, gender, weeks of experience with the Remsima®-Pen, previous experience with application systems (yes, no). For further details refer to section 9.3. ▪ Disease (RA, AS or PsA) characteristics including previous

	pharmacological therapy. For further details refer to section 9.3. ▪ Assessment of satisfaction in usability of the Remsima®-Pen ▪ Assessment of satisfaction with quality and understandability of the training material of the Remsima®-Pen ▪ Assessment of personal experience with the Remsima®-Pen
Primary Endpoint	Primary endpoint ▪ Percentage of participants that are either "Very Satisfied (4)" or "Satisfied (3)" in the usability with the Remsima®-Pen.
Secondary Endpoints	Secondary Endpoints ▪ Percentage of patients that are either "Very Satisfied" (4) or “Satisfied” (3) with quality and understandabilitly of the training materials of the Remsima®-Pen. ▪ Personal experience with the Remsima®-Pen using a patient questionnaire
Statistical Analysis	Statistical analysis for primary and secondary endpoints will be carried out by default by tabular display of the number of valid observations (Nvalid), number of missing observation values (Nmissing - if necessary), arithmetic means, standard deviation, minimum, median and maximum. This applies in case of analysis of metric-scaled data, but also in case that metric method seems also reasonable to ordinal-scaled data. Otherwise, categorical data will be displayed in tables by absolute frequencies and their percentages. Primary endpoint and satisfaction with the training material will be analysed by a logistic regression using categorical factors of age, experience with the Infliximab-Pen, gender, BMI, switch constellation and reason for switch to IFX SC. If differences in one or more potential confounders are observed in this analysis, respective subgroup evaluations will be performed for all endpoints with respect to this (these) confounder(s). For subgroup analysis in rating scores, the Wilcoxon rank-sum test will be applied for the differences between groups. Underlying indications might also be investigated as confounder. For the subgroup analysis of differences in of proportions, Fisher’s exact test will be applied. Correlation analysis will be performed between satisfaction (with the Pen, with the training material - using all categories) and each of the personal experience items in order to recognize the importance of the personal experience items on the general satisfaction.
Sample Size Calculation	Sample size was justified in order to obtain a high precision on the estimation of patient that are either “very satisfied” or “satisfied” with the Remsima®-Pen. A sample size of 500 patients guarantees that the 95% confidence interval is within a range of ± 4%, if the percentage of very satisfied/satisfied patient is 75% (interval: from 71.0% to 78.6%). The confidence width, defined as range from lower to upper limit, will be at maximum, if the rate is 50%. Here the width is 8.7%. To attain a confidence width of 10% at maximum (assuming a satisfaction rate of 75%), at least 286 patients will be required.

3 BACKGROUND

The product CT-P13 (Remsima®, CELLTRION Healthcare and Inflectra®, Pfizer Inc.) is an Immunoglobulin G1 chimeric human-murine monoclonal antibody (mAb) biosimilar to reference infliximab (Remicade®, Janssen Inc.). CT-P13 IV and reference infliximab are both currently approved for use by the European Medicines Agency (EMA) for administration to patients via intravenous (IV) infusions for the treatment of rheumatoid arthritis (RA), ankylosing spondylitis, psoriatic arthritis, Crohn's disease and ulcerative colitis[1,2]. In clinical trials and observational cohorts, CT-P13 IV has shown equivalent pharmacokinetics and efficacy, and demonstrated comparable safety and immunogenicity, to reference infliximab[3–7].

CELLTRION Inc. has developed a subcutaneous (SC) formulation of CT-P13 for injection into the fatty tissue under the skin. CT-P13 SC offers patients the opportunity to self-inject the drug at home, extending the options for treatment administration and potentially reducing the burden of treatment. Initial results of ongoing clinical trials have shown comparable efficacy and safety for the IV and SC formulations of CT-P13 in patients with ulcerative colitis (phase I trial, 1-year results) and RA (phase I/III trial, 54 week results)[8,9].

The Committee for Medicinal Products for Human Use (CHMP) of the EMA has released a positive opinion for CT-P13 SC (as a 120 mg solution for SC injection use in prefilled pens or syringes) for use in people with RA in September 2019.[10] The marketing authorization was granted by the European Commission on 22nd November 2019. CT-P13 SC was approved by the EMA on 28th July 2020 for use in patients with ankylosing spondylitis, psoriatic arthritis, Crohn's disease and ulcerative colitis. It is anticipated that this post-authorization non-interventional study will provide valuable insight into the convenience and user friendliness of CT-P13SC prefilled Pen in the real-world clinical setting.

4 STUDY OBJECTIVE

The main aim of this study is to ascertain general satisfaction among participants with RA, AS or PsA with day-to-day use of the Infliximab-Pen by means of a standardised participant questionnaire. In addition, it is to be investigated whether differences exist in general participant satisfaction between participant groups having different characteristics.

Furthermore, the participants are to evaluate various aspects of using the Infliximab-Pen based on their personal experience, such as e.g. handling, user-friendliness and features of the Infliximab-Pen, as well as the effectiveness of the training on injection with the Remsima®-Pen, based on participant satisfaction with the training received with the training pen and the evaluation of the training material received.

5 STUDY DESIGN, PATIENT POPULATION AND SELECTION CRITERIA

5.1 Justification of choice of study design

The investigation is conducted as a non-interventional study (NIS) in accordance with §4 (23) sentence 3 and §67 (6) Medicines Act (AMG) in a multicentre, prospective cross-sectional study design to generate further data about usability in patients who are treated with the Remsima®-Pen for Infliximab application (product: Remsima® 120 mg). This NIS enables the assessment of usability information in patients' routine application of the application device.

5.2 Number of patient and centres

This NIS shall be conducted in about 40 centres in Germany in "at least 286 patients and up to 500 patients (within a recruitment period of 18 months) who are using the Remsima®-Pen for at least 2 weeks. A total of 10-15 patients per centre are aspired. Documentation criteria are defined in section 5.3. Treatment of participants with the Remsima®-Pen takes place in accordance with the prescribing information and standard medical practice.

5.3 Documentation criteria

The following documentation criteria should be fulfilled:

- Signed informed consent (data protection)
- Male and female outpatient aged ≥18 years with the further need of treatment of rheumatoid arthritis (RA), ankylosing spondylitis (AS) or psoriatic arthritis (PsA)
- Experience with the Remsima®-Pen for at least 3 self-injections at first or later re-visit of patient after hand-over of the Remsima®-Pen at the physician site

Patients with the following conditions are excluded from the documentation in this NIS:

- Patient <18 years (children and adolescents)
- Patient who exhibit contraindications according to SPC (Summary of Product Characteristics) for Remsima® 120 mg or hypersensitivity to any of the ingredients of Remsima® 120 mg is known and therefore treatment with Remsima® 120 mg is not indicated

6 APPLICATION OF DEVICE AND MEDICATION

In this NIS, the use of an Infliximab-Pen for Infliximab application (product: Remsima® 120 mg) shall be assessed in the treatment of rheumatoid arthritis (RA), ankylosing spondylitis (AS) or psoriatic arthritis (PsA) in adults.

Remsima® 120 mg was prescribed to the patients according to the physician's decision in daily medical routine. The application form was switched from intravenous application at the physician site to subcutaneous application by using the Remsima®-Pen, so that application can be done on daily basis by the patients themselves at home.

The application of the Remsima®-Pen was explained during the first use at the site by the physician and also respective learning material was handed-out to the patient. This cross-

sectional study should assess the usability of this device including the detailed experience and also the quality and understandability of the training material.

Patients should be documented in this study, if the Remsima®-Pen was applied at least 3 times at home by the patient, and the patient returns to the first regular or later re-visits after hand-over of the Remsima®-Pen at the physician site.

7 STUDY SCHEDULE

The recruitment of the patients for the NIS shall start in approx. June 2020 and last for a period of about 18 months. As this is a cross-sectional study only one visit at the physician takes place.

The assessments during this observational study (Visit 1) are as follows:

Evaluation / measure	**Visit 1 (Day 1)**
• Documentation criteria fulfilled	X
• Patient information and informed consent	X
• Demographic data: age (≥18 years), gender • Start date of use of the Remsima®-Pen • Previous experience with application systems (yes, no) • Smoking status (smoker, ex-smoker, non-smoker) • Body height and weight, body mass index (BMI) - calculated by eCRF • Date of disease diagnosis (RA, AS or PsA) • Previous treatment for RA, AS or PsA: drug(s) used and stopped immediately before switch to IFX SC (name, classification and duration of treatment, i.e. start and stop date) according to following categories (multiple answers possible): o IFX IV o Other TNF-alpha inhibitors (adalimumab, golimumab, etanercept, certolizumab-pegol) o JAK inhibitors (tofacitinib, baricitinib, upadacitinib) o Others • IFX switch constellation (IFX IV to SC switch patient [IFX maintenance patient], IFX start patient [IFX naïve patient]) • Reason for switch to IFX SC: loss of efficacy, side effects, patient's preference (patient's wish), physician's preference (physician's recommendation), other (including specification), unknown	X
• Assessment of satisfaction with in usability of the Remsima®-Pen (for details refer to section 9.3)	X

Evaluation / measure	Visit 1 (Day 1)
• Assessment of satisfaction with quality and understandability of the training material of the Remsima®-Pen (for details refer to section 9.3)	X
• Personal experience with the Remsima®-Pen (for details refer to section 9.3)	X

8 PATIENT INFORMATION AND INFORMED CONSENT, DATA PROTECTION

8.1 Patient information and informed consent

Prior inclusion in this NIS every patient will be informed by the treating physician about study targets as well as about the type and extent of the documentation. Without the written informed consent for documentation of his/ her data for this NIS as well as for the inspection of his/ her patient file for data reconciliation (monitoring) the patient will not be included in this NIS. This includes also the willingness to answer the patient questionnaires. The patient will receive the patient information and his/ her signed informed consent form, the second copy of the informed consent form is designated to remain at the physician.

8.2 Data protection

The data protection of the patient will be ensured. Patient data collected within the scope of the NIS will be documented in a pseudonymised manner in the eCRF, i.e. only with the patient number and without disclosing name, initials, date of birth or address of the patient.

In case of publication of the study results personal data may only be used in anonymous form. Only authorized representatives of the responsible pharmaceutical company bound to secrecy will have access to personal data as far as this is required for check of proper conduct of the NIS.

9 DOCUMENTATION AND EVALUATIONS

9.1 Source data

For evaluation of the study objectives following source data will be used in this non-interventional study:

- Patient file
- Patient Questionnaire assessing the personal experience the Remsima®-Pen (local language: Information recorded by the patient in the questionnaire will be transcribed into the eCRF).

9.2 Data collection

- Every participating physician receives a folder including observational plan, SPC for

Remsima® 120 mg, printout of the template of the electronic documentation form, patient information and informed consent forms, patient questionnaires

- Every included patient will be assigned to a unique patient identifying number (digits 1 to 2 = unique center number; digits 3 to 5 = patient number within the center) which will remain unchanged for the entire study.
- The electronic documentation forms (eCRF) have to be filled completely and in a timely manner (within 10 days after collection of the respective patient data).
- The patient questionnaire has to be filled personally by the patient in the investigator's office but not by an employee of the study centre.
- The answers of the patient on the questionnaire have to be transferred in the eCRF. The original of the completed questionnaire remains with the physician at the site.

9.3 Evaluations and documentation at routine visit (Visit 1)

The evaluation will be done at "Visit 1", which is a routine visit of the patient at a physician for clinical assessment and to obtain the next prescription for Remsima® 120 mg or for other routine reasons. The following usability assessments of the Remsima®-Pen will be performed:

- Informed consent (data protection) of the patient
- Information and obtaining written informed consent of the patient
- Demographic data: age, gender
- Previous experience with application systems (yes, no)
- Start date of the use of the Remsima®-Pen
- Smoking status (smoker, ex-smoker, non-smoker)
- Body height and weight, body mass index (BMI) - calculated by eCRF
- Date of disease diagnosis (RA, AS, or PsA)
- Pharmacologic treatment for RA, AS, PsA: drug(s) used and stopped immediately before switch to IFX SC (name, classification and duration of treatment, i.e. start and stop date) according to following categories (multiple answers possible):
  - IFX IV
  - Other TNF-alpha inhibitors (adalimumab, golimumab, etanercept, certolizumab-pegol)
  - JAK inhibitors (tofacitinib, baricitinib, upadacitinib)
  - Others
- IFX switch constellation (IFX IV to SC switch patient [IFX maintenance patient], IFX start patient [IFX naïve patient])
- Reason for switch to IFX SC: loss of efficacy, side effects, patient's preference (patient's wish), physician's preference (physician's recommendation), other (including specification), unknown
- Satisfaction with usability of the Remsima®-Pen (0 = very dissatisfied, 1 = dissatisfied, 2 = neither dissatisfied nor satisfied, 3 = satisfied, 4 = very satisfied)
- Satisfaction with quality and understandability of the training material of the Remsima®-Pen (0 = very dissatisfied, 1 = dissatisfied, 2 = neither dissatisfied nor satisfied, 3 = satisfied, 4 = very satisfied)

- Personal experience with the Remsima®-Pen, i.e. regarding

  1. Intuitive / self-explaining to use
  2. Attractiveness of design
  3. Size of the pen
  4. Weight of the pen
  5. Easiness to grip
  6. Easiness to operate the self-injection with the pen
  7. Satisfaction with the time required for the injection (time between 1st and 2nd click)
  8. Second click well audible after successful injection
  9. Complete emptiness of the pen after successful injection clearly visible in the viewing window
  10. Complete retraction of the injection needle in the pen after successful injection

  will be assessed each for importance of the feature on a scale from 1 to 7 (1 = not important at all; 7 = extremely important) and for satisfaction with the feature on a scale from 0 to 4 (0 = very dissatisfied; 4 = very satisfied).

In addition, only for patients who had used a pen for injection of another TNF-alpha inhibitor in the past:

- Satisfaction in usability with the Remsima®-Pen compared to the pen used in the past will be assessed on a scale from 0 to 4 (0 = much more dissatisfied; 4 = much more satisfied).

10 ADVERSE EVENTS

No adverse events will be documented during the NIS since this is a cross-sectional study with just one visit per patient and focus on evaluation of satisfaction with the Remsima®-Pen using a standardised questionnaire.

Nevertheless, adverse reactions due to the use of the Remsima®-Pen occurring during the course of this NIS are to be addressed by the physician to the Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel, Paul-Ehrlich-Institut, Paul-Ehrlich-Str. 51 - 59, 63225 Langen, Tel: +49 6103 77 0; Fax: +49 6103 77 1234; Homepage: www.pei.de

11 MONITORING

If deemed necessary, on-site monitoring will be performed. In general, remote monitoring might be sufficient to guarantee an adequate quality level in this NIS.

12 DATA MANAGEMENT

All procedures within the scope of the data management will be specified in a study specific Data Management Plan (DMP) prior to start of the study. All possible inconsistencies leading to queries for the study centres in the eCRF will be tabulated in the Data Validation Plan (DVP). All data management procedures are based on the SOPs of the contracted CRO.

All data of this non-interventional study will be documented and saved in the eCRF. The electronical data acquisition system MARVIN® of XClinical meets all relevant required provisions

of the FDA, especially 21 CFR Part 11. The data will be exclusively entered by authorised persons (the physician him- / herself or authorised study staff) with access authorisation to the eCRF. The physician is responsible for correctness and completeness of the data documented in the eCRF and he / she or an authorised person has to confirm and release the data by an electronic signature.

Plausibility checks are implemented in the eCRF and data will be checked automatically by the system once the physician saves the data (auto-edit checks). The plausibility checks are performed according to the rules laid down in the DVP. Queries have to be answered by the study centre directly in the eCRF. All changes in the eCRF will be recorded in an audit trail.

13 STATISTICAL METHODS

13.1 Tabular display – default statistics

This study is a multicentre single-arm observational study in accordance with §67 (6) AMG.

The statistical evaluation will be carried out by default by tabular display of the number of valid observations (Nvalid), number of missing observation values (Nmissing - if necessary), arithmetic means, standard deviation, minimum, median and maximum. This applies in case of analysis of metric-scaled data, but also in case that metric method seems also reasonable to ordinal-scaled data. Otherwise, categorical data will be displayed in tables by absolute frequencies and their percentages.

13.2 Primary endpoint

The primary endpoint is defined as percentage of participants that are either "very satisfied (score = 4)" or "satisfied (score = 3)" with the Remsima®-Pen. Evaluation will be performed using default statistics including two-sided 95% Wilson confidence intervals in order to show different level of confidence for estimates.

13.3 Secondary endpoints

The analysis of the secondary endpoints includes the following variables:

- The percentage of patients that are either "very satisfied (score = 4)" or “satisfied (score = 3)” with quality and understandability of the training materials of the Remsima®-Pen. Evaluation will be performed using default statistics including 95% Wilson confidence intervals in order to show the precision of estimation.
- Personal experience with the Remsima®-Pen using a patient questionnaire. Here 11 different questions will be assessed (refer to section 9.3) and evaluated using default statistics.

13.4 Analyses of subgroups, regression analyses and correlations

Regression analysis

Primary endpoint and satisfaction with the training material will be analysed by a logistic regression using following factors:

- Age: younger (≤median age) versus older (>median age) patients
- Experience with the Remsima®-Pen (≤8 weeks, >8-16 weeks, >16 weeks)
- Gender
- BMI (≤ 30 kg/m², > 30 kg/m²)
- Switch constellation (IFX maintenance patient, IFX naïve patient)
- Reason for switch to IFX SC: based on available answers, meaningful disjunct categories will be created.

Underlying indications might also be investigated as confounder if the number of patients per indication will allow such an analysis.

Subgroup analysis

If relevant differences in one or more potential confounders are observed in this analysis, respective subgroup evaluations will be performed for all endpoints based on this (these) confounder(s).

For subgroup analysis in rating scores, the Wilcoxon rank-sum test will be applied for the differences between groups.

For the subgroup analysis of differences in of proportions, the Fisher's exact test will be applied.

Correlation analysis will be performed between satisfaction (with the Pen, with the training material - using all categories) and each of the personal experience items in order to recognize the importance of the personal experience items on the general satisfaction.

13.5 Handling of missing values

Missing values will not be replaced.

13.6 Sample size calculation

Sample size was justified in order to obtain a high precision on the estimation of patient that are either "very satisfied" or "satisfied" with the Remsima®-Pen.

A sample size of 500 patients guarantees that the 95% confidence interval is within a range of ± 4%, if the percentage of very satisfied/satisfied patient is 75% (interval: from 71.0% to 78.6%). The confidence width, defined as range from lower to upper limit, will be at maximum, if the rate is 50%. Here the width is 8.7%.

To attain a confidence width of 10% at maximum (assuming a satisfaction rate of 75%), at least 286 patients will be required.

Sample size is calculated by program PASS 11 and the result is displayed below.

Confidence Intervals for One Proportion - New
Numeric Results for Two-Sided Confidence Intervals for One Proportion
Confidence Interval Formula: Score (Wilson)

Confidence Level	Sample Size (N)	Target Width	Actual Width	Proportion (P)	Lower Limit	Upper Limit	Width if P = 0.5
0,950	500		0,076	0,750	0,710	0,786	0,087

14 ETHICAL ASPECTS

According to the recommendations of the German Competent Authorities[11] for planning, conduct and analysis of observational studies as well as to the VFA-recommendations[12] for improvement of the quality and transparency of non-interventional studies, prior to the study start a professional advice will be obtained from the ethics committee constituted according to federal state law.

15 LEGAL AND REGULATORY ASPECTS

This NIS is an observational study in accordance with §67 (6) AMG and the corresponding recommendations of the Bundesinstitut für Arzneimittel und Medizinprodukte and the Paul-Ehrlich-Institut for the planning, conduct and analysis of observational studies dated 7 July 2010 (as far as still applicable) [11] as well as with the VFA-recommendations for improvement of the quality and transparency of non-interventional studies version 2014 [12].

- Prior to study start an ethics committee constituted according to federal state law will be consulted for advice.
- A written patient information concerning data protection and inspection of the patient file as well as an informed consent form will be submitted to the patient for signature. The written informed consent is mandatory for inclusion of the patient in this NIS.
- Prior to study the start the NIS will be notified in accordance with §67 (6) AMG to: competent authority, “Kassenärztliche Bundesvereinigung”, “Spitzenverband Bund der Krankenkassen” and “Verband der Privaten Krankenkassen e.V”. Location, time, aim and observational plan of the NIS as well as the participating physicians including their lifetime doctor identifying number will be reported. Furthermore, type and amount of reimbursement will be indicated as well as a copy of the contract concluded with the participating physicians will be transferred.
- Prior to the start the study will also be published in the BfArM NIS database.

16 ARCHIVING, REPORT AND PUBLICATION

Collected data as well as documents are property of the responsible pharmaceutical company. Every participating physician is obliged to archive all documents of an observational study for at least 10 years for later access and evaluations.

Within one year after the end of the observation period a final report will be prepared about conduct and results of the observational study including a biometric analysis and evaluation from a medical point of view.

The responsible pharmaceutical company will publish the final report on the web page of the competent authority, as requested by law.

17 LIST OF REFERENCES

[1] Remsima 100 mg powder for concentrate for solution for infusion - Summary of Product Characteristics (SmPC) - (eMC) [Internet]. [cited 2019 May 13]. Available from: https://www.medicines.org.uk/emc/product/3709#ORIGINAL

[2] Inflectra 100 mg powder for concentrate for solution for infusion - Summary of Product Characteristics (SmPC) - (eMC) [Internet]. [cited 2019 May 13]. Available from: https://www.medicines.org.uk/emc/product/3710/smpc

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