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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment Report on extension(s) of marketing authorisation

Remsima

International non-proprietary name: infliximab

Procedure No. EMEA/H/C/002576/X/0062

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.



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List of abbreviations

| | |
|------------------|---|
| 6-MP | 6-Mercaptopurine |
| ACP | Assay (screening) cut point |
| ACR | American College of Rheumatology |
| ACR20 | 20% improvement according to the ACR criteria |
| ACR50 | 50% improvement according to the ACR criteria |
| ACR70 | 70% improvement according to the ACR criteria |
| ADA | Anti-drug antibodies |
| ADCC | Antibody-dependent cellular cytotoxicity |
| ADR | Adverse drug reaction |
| AE | Adverse event |
| AESI | Adverse events of special interest |
| AI | Auto-injector |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| ANCOVA | Analysis of covariance |
| Anti-CCP | Anti-cyclic citrullinated peptide |
| AR | Analytical recovery |
| ARR | Administration-related reaction |
| AS | Ankylosing spondylitis |
| ASAS | Assessment of spondyloarthritis international society score |
| ASAS20 | At least 20% improvement of Assessment of spondyloarthritis international society score |
| AST | Aspartate aminotransferase |
| AUC | Area under the concentration-time curve |
| AUC0-672hr | Area under the serum concentration-time curve from time zero to 672 hours |
| AUC0-inf | Area under the concentration-time curve from time zero to infinity |
| AUC0-last | Area under the concentration-time curve from time zero to the last quantifiable concentration |
| AUC0-t | Area under the serum concentration-time curve from time zero to the last quantifiable concentration |
| AUC22-30wk | Area under the curve from week 22 - 30 |
| AUCextrap | Area under the concentration-time curve extrapolated from time zero to infinity |
| AUCss | Area under the concentration-time curve at steady state |
| AUCss8W | Area under the concentration-time curve normalized to an 8-week interval, calculated over actual dosing interval |
| AUC _r | Area under the serum concentration time curves at steady state over the actual dosing interval calculated using the linear trapezoidal rule |
| AUCextrap % | Area under the concentration-time curve extrapolated from time zero to infinity as a percentage of total AUC |
| AZA | Azathioprine |
| BA | Bioavailability |
| BASDAI | Bath ankylosing spondylitis disease activity index |
| BDAS28 | Apparent zero-order rate constant for production of the response |

| | |
|-------------|---|
| BE | Bioequivalence |
| BLQ | Below the lower limit of quantification |
| BMI | Body mass index |
| BP | Blood pressure |
| BSA | Bovine serum albumin |
| BSV | Between-subject variability |
| C0 | Concentration at time zero |
| C1q | Complement component 1q |
| Cal | Calibrator |
| CCP | Confirmatory cut point |
| CD | Crohn's disease |
| CD | Compact Disc |
| CDAI | Clinical disease activity index or Crohn's disease activity index |
| CDC | Complement-dependent cytotoxicity |
| CE-SDS | Capillary Electrophoresis Sodium Dodecyl Sulfate |
| CFU | Colony Forming Unit |
| CHF | Congestive heart failure |
| CHMP | Committee for Medicinal Products for Human Use |
| CI | Confidence interval |
| CL | Total body clearance |
| CL/F | Total body clearance after SC dosing |
| CL/F | Apparent clearance after SC dosing |
| CL/Fss | Total body clearance at steady state for SC cohort |
| CLss | Total body clearance at steady state for IV cohort |
| Cmax | Maximum serum or plasma concentration |
| Cmax, ss | Maximum serum concentration at steady state |
| CMC | Chemistry, manufacturing and control |
| Cmin | Minimum serum concentration |
| Cmin,ss | Minimum serum concentration at steady state |
| CPK | Creatine phosphokinase |
| CPP | Critical Process Parameter |
| CPV | Cut point value |
| CQA | Critical quality attribute |
| CrI:CD (SD) | Charles River:Caesarean-derived Sprague Dawley rat |
| CRO | Contract research organisation |
| CRP | C-reactive protein |
| CS | Clinically significant |
| CSR | Clinical study report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CT-P13 | Remicade® biosimilar (CELLTRION) |
| CT-P13 IV | Infliximab (CELLTRION) for intravenous infusion |
| CT-P13 SC | Infliximab (CELLTRION) for subcutaneous injection |
| Ctrough | Trough serum concentration |
| Ctrough,ss | Trough serum concentration at steady state |
| CV | Coefficient of Variation |
| CV% | Percent coefficient of variation |

| | |
|--------------------|---|
| CWRES | Conditional weighted residuals |
| CYP450 | Cytochrome P450 |
| DAS28 | Disease Activity Score using 28 joint counts |
| DBP | Diastolic blood pressure |
| DFT % | Percent difference from theoretical value |
| DLP | Data lock point |
| DMARD | Disease-modifying antirheumatic drug |
| DNA | Deoxyribonucleic acid |
| DNAUC _T | Oral dose-normalized AUC over the dosing interval |
| DNC _{max} | Dose normalised peak exposure |
| DP | Drug product |
| DS | Drug substance |
| DSMB | Data Safety Monitoring Board |
| EC50 | Effective concentration yielding a 50% response |
| ECG | Electrocardiogram |
| ECL | Electrochemiluminescence |
| eCRF | Electronic Case Report Form |
| ELISA | Enzyme-Linked-Immuno-Sorbent-Assay |
| EMA | European Medicines Agency |
| EOS | End-of-study |
| ESR | Erythrocyte sedimentation rate |
| EU | European Union |
| EULAR | European League Against Rheumatism |
| F | Female |
| F/T | Freeze-thaw |
| FA | Folic acid |
| Fab | Fragment antigen binding |
| FC | Fecal calprotectin |
| Fc | Crystallisable fragment |
| FcRn | Neonatal Fc receptor |
| FcγRIIIa | Fc-gamma receptor IIIa |
| FDA | Food and Drug Administration |
| FM | Frozen matrix |
| GCP | Good Clinical Practice |
| GGT | Gamma-glutamyl transferase |
| GLP | Good Laboratory Practice |
| GMP | Good Manufacturing Practices |
| HAQ | Health assessment questionnaire |
| HBV | Hepatitis B virus |
| HC | Heavy Chain |
| hcDNA | Host cell DNA |
| HCP | Host Cell Protein |
| HCP | Health care professional |
| HFS | Human factor study |
| HIV | Human immunodeficiency virus |
| HMW | High molecular weight |

| | |
|--------|--|
| HPC | High positive control |
| HQC | High quality control |
| hr | Hour(s) |
| HRP | Horseradish peroxidase |
| HSTCL | Hepatosplenic T-cell lymphoma |
| HV | Healthy volunteers |
| IBD | Inflammatory bowel disease |
| IC50 | Drug concentration that produces 50% of maximum inhibition |
| ICH | International Conference on Harmonisation |
| IFN | Interferon |
| IFU | Instructions for Use |
| IGF-1 | Insulin-like growth factor 1 |
| IgG | Immunoglobulin G |
| IgG1 | Immunoglobulin G, subtype 1 |
| IGRA | Interferon- γ release assay |
| Imax | Maximum fractional ability of the drug to affect BDAS28 |
| INN | International non-proprietary name |
| IPC | In Process Control |
| IRR | Infusion-related reaction |
| ISR | Injection site reaction |
| ITT | Intent-to-treat |
| IU | International unit |
| IV | Intravenous |
| JP | Japanese Pharmacopeia |
| KD | Dissociation constant |
| Kel | Elimination rate constant |
| kg | Kilogram(s) |
| Kout | First-order rate constant for loss of the response |
| LC | Light Chain |
| LIF | Laser-induced fluorescence |
| LLoQ | Lower limit of quantification |
| LoQ | List of questions |
| LPC | Low positive control |
| LQC | Low quality control |
| LS | Least squares |
| M | Male |
| MAA | Marketing Authorisation Application |
| mAb | Monoclonal antibody |
| MAR | Missing at random |
| Max | Maximum |
| MBS | Matrix blank spike control |
| MCB | Master Cell Bank |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MFDS | Korea Ministry of Food and Drug Safety |
| mg | Milligram(s) |
| MI | Multiple imputation |

| | |
|-------|---|
| Min | Minimum |
| mL | Millilitre(s) |
| MO | Major objection |
| MPC | Medium positive control |
| MQC | Medium quality control |
| MRD | Minimum required dilution |
| MRT | Mean Residence Time |
| MSD | Meso Scale Discovery |
| MTX | Methotrexate |
| MuLV: | Murine Leukemia Virus |
| MVM | Minute Virus of Mice |
| N/A | Not applicable |
| NAb | Neutralising antibody |
| NC | Negative control |
| NCF | Normalisation correction factor |
| NCS | Not clinically significant |
| NYHA | New York Heart Association |
| NZW | New Zealand White rabbit |
| OC | Other concern |
| OD | Optical density |
| OECD | Organization for Economic Co-operation and Development |
| PBS | Phosphate buffered saline |
| PC | Positive control |
| pcVPC | Prediction-corrected visual predictive check |
| PD | Pharmacodynamics |
| PFS | Pre-filled syringe |
| PFS-S | Pre-filled syringe with automatic needle guard |
| PI | Principal Investigator |
| PK | Pharmacokinetics |
| PLA | Parallel line analysis |
| PMS | Post-marketing surveillance |
| PMT | Photomultiplier tube |
| PNC | Pooled negative control |
| PP | Per-protocol population |
| PPD | Pharmaceutical Product Development |
| PR | Pulse rate |
| Ps | Plaque psoriasis |
| PsA | Psoriatic arthritis |
| PT | Preferred term |
| PY | Patient-years |
| Q | Intercompartmental clearance |
| Q2W | Every 2 weeks |
| Q8W | Every 8 weeks |
| QC | Quality control |
| qPCR | Quantitative Polymerase Chain Reaction |
| QTcF | QT interval corrected for heart rate using Fridericia's formula |

| | |
|-----------------|--|
| RA | Rheumatoid arthritis |
| Remsima IV | Infliximab (CELLTRION) for intravenous infusion |
| Remsima SC | Infliximab (CELLTRION) for subcutaneous injection |
| RF | Rheumatoid factor |
| RLU | Relative light unit |
| Rmin | Maximum efficacy |
| RP-HPLC | Reverse Phased High Performance Liquid Chromatography |
| rProtein | A Recombinant Protein A |
| RR | Respiratory rate |
| RSD | Relative standard deviation |
| RSE | Relative standard error |
| RT | Room temperature |
| S/N | Signal-to-noise |
| SA | Scientific advice |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SBP | Systolic blood pressure |
| SC | Subcutaneous |
| SD | Standard deviation |
| SDAI | Simplified Disease Activity Index |
| SDS | Sodium Dodecyl Sulfate |
| SE | Standard error |
| SEC-HPLC | Size exclusion-high-performance liquid chromatography |
| SES-CD | Simplified endoscopic activity score for Crohn's disease |
| SF-36 | Medical outcomes study short form health survey |
| SI | Système International d'Unités |
| SIBDQ | Short Inflammatory Bowel Disease Questionnaire |
| SmPC | Summary of Product Characteristics |
| SNR | Signal-to-noise ratio |
| SOC | System Organ Class |
| SOI | Start of infusion |
| SOP | Standard operating procedure |
| SP | Individual human serum sample |
| SPF | Individual human serum samples spiked with the positive control |
| SPR | Surface Plasmon Resonance |
| sTNF α | Soluble tumour necrosis factor alpha |
| ST-TNF α | Sulfo-tag-labelled TNF α |
| SWFI | Sterile water for injection |
| T $_{1/2}$ | Terminal elimination half life |
| TB | Tuberculosis |
| TEAE | Treatment-emergent adverse event |
| TESAE | Treatment-emergent serious adverse event |
| TE % | Percent total error |
| TK | Toxicokinetic |
| TM | Thawed matrix |
| Tmax | Time to reach Cmax |

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|---------------------|---|
| T _{max,ss} | Steady state time to reach C _{max} |
| TMB | 3,3',5,5'-tetramethylbenzidine |
| TNF | Tumour necrosis factor |
| TNF α | Tumour necrosis factor alpha |
| TSE | Transmissible Spongiform Encephalopathy |
| U | Unit |
| UA | Urinalysis |
| UC | Ulcerative colitis |
| UF/DF | Ultrafiltration/Diafiltration |
| uFMEA | Use Failure Mode Effects Analysis |
| UK | United Kingdom |
| ULN | Upper limit of normal |
| ULOQ | Upper limit of quantification |
| US(A) | United States (of America) |
| USP | United States Pharmacopeia |
| UV | Ultraviolet |
| UV-Vis | Ultraviolet-visible |
| W | Week |
| V ₁ | Central volume of distribution |
| V ₃ | Peripheral volume of distribution |
| VAS | Visual analogue scale |
| WCB | Working Cell Bank |
| V _d | Volume of distribution |
| WHO | World Health Organization |
| wk | Week |
| VPC | Visual predictive check |
| V _{ss} | Volume of distribution at steady state |
| V _z | Volume of distribution during the terminal phase |
| V _z /F | Apparent volume of distribution during terminal phase |
| λ_z | Elimination rate constant |
| μg | Microgram(s) |

1. Background information on the procedure

1.1. Submission of the dossier

Celltrion Healthcare Hungary Kft. submitted on 10 November 2018 an extension of the marketing authorisation.

The MAH applied for the addition of a new strength of 120 mg, an addition of a new pharmaceutical form (solution for injection) and an addition of a new route of administration (subcutaneous use).

The RMP (version 9.1) is updated in accordance.

Furthermore, the PI is brought in line with the latest QRD template version 10.1.

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point(s) (c) (d) (e) - Extensions of marketing authorisations.

Article 10(4) of Directive 2001/83/EC, as amended – relating to applications for a biosimilar medicinal product.

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH received Scientific Advice from the CHMP on 14 January 2016, 14 April 2016, 2 September 2016, 1 December 2016, 30 November 2017 and 12 April 2018. The Scientific Advice pertained to pre-clinical, clinical and quality aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Outi Mäki-Ikola Co-Rapporteur: Kristina Dunder

CHMP Peer reviewer(s): N/A

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| The application was received by the EMA on | 10 November 2018 |
| The procedure started on | 29 November 2018 |
| The Rapporteur's first Assessment Report was circulated to all CHMP members on | 18 February 2019 |

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| The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on | 18 February 2019 |
| The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on | 26 February 2019 |
| The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on | 14 March 2019 |
| The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on | 28 March 2019 |
| The MAH submitted the responses to the CHMP consolidated List of Questions on | 23 May 2019 |
| The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on | 25 June 2019 |
| The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on | 26 February 2019 |
| The CHMP agreed on a list of outstanding issues in writing to be sent to the MAH on | 25 July 2019 |
| The MAH submitted the responses to the CHMP List of Outstanding Issues on | 19 August 2019 |
| The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on | 4 September 2019 |
| The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Remsima on | 19 September 2019 |

2. Scientific discussion

2.1. Problem statement

This is a line extension application to introduce a subcutaneous formulation of Remsima (infliximab).

Infliximab is a chimeric human-murine monoclonal antibody that binds with high affinity to both soluble and transmembrane forms of TNF α . Infliximab prevents TNF α receptor activation by binding to TNF α , thereby neutralizing the biological activity of TNF α .

Whereas initial TNF α expression in response to infection or injury is beneficial, sustained or excessive expression has been identified in several chronic inflammatory autoimmune disorders such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriasis (Ps), psoriatic arthritis (PsA), Crohn's disease (CD) and ulcerative colitis (UC).

The efficacy of infliximab IV is well established. Most of the serious adverse effects of infliximab are based on its pharmacodynamics effects. Anti-TNF-antibodies impair the host defence. This leads to an increased risk of infections, including serious and opportunistic infections, and malignancies, notably skin tumours and lymphomas. The impaired immunoregulation also leads to an increase of autoimmune reactions. Infliximab is also highly immunogenic and the development of anti-drug antibodies (ADA) is

known to reduce its efficacy as well as to induce acute and delayed hypersensitivity reactions. The main cause for immunogenicity is the chimeric (mouse-human) structure of infliximab.

Infliximab was first authorised in the EU on 13 August 1999 under the name of Remicade. Remsima was initially developed for intravenous (IV) infusion (hereafter referred to as Remsima IV) and was approved in the EU in September 2013 (EMA/H/C/002576) as a biosimilar product to Remicade.

The reference product Remicade does not have an authorised SC formulation. .

In summary, compared to the approved IV Remsima, this extension principally proposes two major changes;

- 1) a new SC version of Remsima with different pharmacokinetics and
- 2) flat dosing (after iv loading dosed according to mg/kg).

An important aim of this assessment is to evaluate whether it can be concluded that these changes do not translate into a loss of benefit or increased risk in such extent that B/R is changed for the SC Remsima compared to approved IV Remsima.

A thorough assessment of PK and PK/PD-data, including a cautious analysis of the pattern of exposure and its relation to efficacy and safety parameters is pivotal for the overall assessment and in particular for the analysis of the potential consequences of flat dosing (which is of special interests for individuals that belong to the extremes with regards to body weight). Smooch

2.2. About the product

The active substance of Remsima is infliximab, an immunosuppressant (L04AB02).

Remsima SC is formulated at 120 mg/mL and presented as a solution for injection in a pre-filled syringe. Each syringe is designed to deliver a single dose of 120 mg infliximab in 1 mL solution. Remsima SC drug product is presented in a pre-filled syringe (PFS), a pre-filled syringe with an automatic needle guard (PFS-S) and a pre-filled pen (also referred to as auto-injector AI) assembled with PFS.

Remsima IV is approved in adult patients for treatment of rheumatoid arthritis (RA), Crohn's disease (CD), ulcerative colitis (UC), ankylosing spondylitis (AS), psoriatic arthritis (PsA), and psoriasis (Ps). Treatment is initiated with infusions at weeks 0, 2 and 6, followed by maintenance infusions every 8 weeks (Q8W) in RA and other indications or every 6-8 weeks in AS. In RA administration every 4 weeks, may be considered in case of inadequate response or loss of response. The dose of Remsima IV depends on the therapeutic indication: 3 mg/kg (up to a maximum maintenance dose of 7.5 mg/kg every 8 weeks in case of inadequate response or loss of response) in RA and 5 mg/kg in CD, UC, AS, PsA and Ps.

Remsima IV is also approved for children and adolescents aged 6 to 17 years in treatment of severe, active CD and UC.

The following indication is sought for Remsima SC:

Rheumatoid arthritis:

Remsima, in combination with methotrexate, is indicated for the reduction of signs and symptoms as well as the improvement in physical function in:

- adult patients with active disease when the response to disease-modifying antirheumatic drugs (DMARDs), including methotrexate, has been inadequate.
- adult patients with severe, active and progressive disease not previously treated with methotrexate or other DMARDs.

In these patient populations, a reduction in the rate of the progression of joint damage, as measured by X-ray, has been demonstrated (see section 5.1).

During the assessment, the MAH withdrew the initially claimed indications of ankylosing spondylitis (AS), psoriasis (Ps) and psoriatic arthritis (PsA), and decided to pursue the rheumatoid arthritis (RA) indication only for CT-P13 SC with this extension application. This was mainly due to the unavailability of Study CT-P13 1.6 Part 2 data at the time of evaluation. This data was considered important by the CHMP to support extrapolation for the proposed dosage, efficacy and safety to the AS, Ps and PsA indications due to the differences in the use of concomitant immunosuppressants and dosing.

2.3. Type of Application and aspects on development

This is a line extension application to introduce a subcutaneous formulation of Remsima IV, which is a biosimilar of EU approved Remicade. The clinical development programme for CT-P13 SC includes two phase I -studies in healthy volunteers; CT-P13 1.5 and CT-P13 1.9, a phase I study in IBD; CT-P13 1.6 and a phase I/III study; CT-P13 3.5 in RA. A total of 688 subjects; 253 healthy controls and 435 patients, have been treated in the 4 controlled, comparative, clinical studies during the development of CT-P13 SC. Multiple central Scientific Advices (January 2016, September 2016, December 2017, April 2018) have been given. Issues that were discussed included selection of comparator for the comparability analysis, endpoints, non-inferiority margin and the overall extent and nature of data required to support the application. The use of Remsima IV as a comparator was agreed on. It was commented that if non-inferior efficacy could be demonstrated in the RA setting and PK data from an IBD population would show similar exposure and C_{trough} levels between SC and IV formulations, full extrapolation to other indications could be possible given that SC dosing and regimen schedules for both the rheumatology and the IBD indications were identified.

It was commented that the safety data base should be sufficiently large to provide for a meaningful comparison of safety and immunogenicity; one year of comparative assessment of immunogenicity was considered critical to assess the benefit/risk of the proposed SC formulation given the high level of ADA with Remsima IV and the known much higher immunogenicity of the SC route. It was clarified that an indirect comparison to historical IV immunogenicity data could be acceptable.

Overall, the MAH appears to have followed the advice given by CHMP with regards to key aspects of the development programme.

The MAH states that the clinical development programme of CT-P13 SC has specifically considered the EU guidelines for clinical trials and biotechnology products. No important deviations from relevant CHMP guidance with implications for the overall interpretation of data have been noted.

2.4. Quality aspects

2.4.1. Introduction

Remsima (infliximab) is currently authorised as a 100 mg powder for concentrate for solution for infusion, also referred to as Remsima IV.

The scope of this line extension application is the introduction of a 120 mg solution for subcutaneous injection in pre-filled syringe (PFS) or pre-filled pen (PFP) (1 mL sterile solution each, packs of 1, 2 and 4 each, with alcohol pads).

A Type II variation (EMA/H/C/002576/II/0060/G) was approved in January 2019 to introduce a modified active substance (also referred to as DS) manufacturing process (Process II). The manufacturing process II for the CT-P13 SC DS is identical to CT-P13 IV until the final ultrafiltration/diafiltration (UF/DF) step

to deliver new SC formulation. Therefore, only those manufacturing steps directly influenced by the introduction of the SC presentation were discussed in detail during the procedure. An adequate exercise was performed to demonstrate comparable quality of infliximab formulated for SC and IV presentations. Appropriate formulation studies have been performed to support the use of the proposed excipients (acetic acid, sodium acetate trihydrate, sorbitol, polysorbate 80 (PS80) and water for injections) of the liquid presentations.

2.4.2. Active Substance

General Information

Infliximab is a recombinant chimeric human-murine monoclonal antibody (IgG1) and the active substance of Remsima that is a biosimilar for Remicade. Infliximab binds to both soluble and transmembrane forms of tumour necrosis-factor-alpha (TNFα) and prevents TNFα receptor activation thereby neutralizing the biological activity of TNFα. Infliximab bears the Fc portion of complement-activating IgG1 and binds to Fc receptors with different patterns of expression on immune cells including monocytes, macrophages, granulocytes, natural killer cells, B cells and platelets. CT-P13 SC active substance is a colourless to pale brown, and clear to opalescent solution which should be free of foreign particles.

Manufacture, process controls and characterisation

The approved DS CT-P13 IV manufacturing process and the CT-P13 SC Process are similar. Briefly, the manufacturing process is a conventional cell culture process initiated by single vial of WCB which is expanded in shake flasks and seed bioreactors until final fermentation in fed batch production bioreactor. The cell culture fluid is harvested using continuous centrifugation, depth filtration and membrane filtration. The upstream process is controlled with critical parameters and in-process controls. The purification steps involve Protein A affinity chromatography followed by a low pH treatment for viral inactivation. Subsequent cation- and anion exchange chromatography steps remove process- and product-related impurities. The purification process for DS was validated for adequate removal of process-related impurities host cell protein (HCP), DNA and leaching Protein A. Further viral safety is assured by nano-filtration step. The viral filtration pool is concentrated using Tangential Flow Filtration (TFF). Finally, the concentrated CT-P13 SC product pool is diafiltered and formulated to CT-P13 SC in sodium acetate, sorbitol, and polysorbate 80 buffer at 108–132 g/L. After sterile filtration the DS is stored in polycarbonate bottles.

The CT-P13 SC active substance manufacturing process is described with sufficient amount of details, with information on input and output variables.

A change in the active substance control strategy has been implemented. Process variables and process controls for each step, including terminology, are clearly described in the dossier.

Control of critical steps and intermediates

The critical process parameters (CPPs) and critical in-process tests (CIPTs) with their acceptance criteria are the same as those approved for IV Process II. The only exception is the process parameters and in-process tests associated with the concentration and diafiltration step which are specific for the SC Process II. Briefly, the quality target product profile (QTPP) was determined for CT-P13 SC finished product (also referred to as DP) in accordance with ICH Q8 (R2). In order to ensure production of a DS that meets the quality requirements at release, critical quality attributes (CQA), CPPs and CIPTs were determined. The acceptance criteria for the in-process tests were established through process development and process characterisation studies and safety considerations. The acceptance criteria have been verified using accumulated commercial scale production data and non-clinical, clinical and process validation batches.

Process validation

CT-P13 DS commercial scale Process II validation was carried out at the active substance manufacturing site and approved as part of variation II/0060/G. The only change to support CT-P13 SC was change to UF/DF step

The final UF/DF and fill step of CT-P13 SC batches were validated separately from the CT-P13 IV process with no critical or major deviations. The results comply with the pre-defined acceptance criteria and acceptable ranges of CPP, non-CPP, CIPT, IPT and DS release specifications. The validation of the UF/DF and final fill steps was acceptably performed.

Shipping validation to support the active substance transportation from DS manufacturing site to DP manufacturing site was performed using the active shipping container which is used in commercial production.

Overall the data submitted from the validation runs are sufficiently detailed and suggest consistent performance of the manufacturing process.

Manufacturing process development

CT-P13 SC formulation has been developed by modifying the final formulation of intravenous (CT-P13 IV) presentation. The DS manufacturing process of CT-P13 IV and the CT-P13 SC is essentially identical with the exception of the UF/DF step.

Changes to CT-P13 DS manufacturing Process I to introduce Process II were approved as part of variation II/0060/G.

Comparability studies

Thorough comparability studies have been performed. The comparability exercise for the two CT-P13 SC processes demonstrated no significant differences in any of the biological activity assays evaluated. It is deemed unlikely that the minor differences for the attributes described above will impact clinical safety and efficacy of Remsima.

Characterisation

Several batches of CT-P13 SC (Process II) DS and several batches of DP have been characterised using an extended array of analytical and functional assays to confirm comparable primary, secondary, higher order structures and biological functionality. CT-P13 SC has been sufficiently characterised.

Low levels of deamidation was detected in all samples at similar Asn sites, similarly low levels of Met oxidation were also found in all samples. Peptide mapping confirmed the C-terminal lysine variability in CT-P13 SC (Process II).

The applicant has employed a range of state-of-the-art techniques to elucidate the higher order structure of CT-P13 SC, The results (antibody typical) are provided in the dossier.

A small difference in low molecular weight (LMW) species between CT-P13 SC (Process II) active substance (not detected) and finished product was observed when analysing purity with SEC-HPLC, which may be attributable to the variability of the method when measuring such low levels. The same trend was noted in SEC-Multi Angle Light Scattering (MALS).

There is no difference in impurities between IV and SC formulation for Process I as the process steps are same for the whole downstream process.

The clearance of Process II related impurities (IGF-1, insulin, HCP, protein-A and DNA) has been characterised in spiking studies and shown to remain at appropriately low levels.

Because of the similarity between the IV and SC process it is anticipated that product-related impurities would be the same as those identified for CT-P13 IV would be similar. Therefore, only the impurities possibly influenced by the new SC formulation were assessed within this line extension application (i.e. oxidation and HMW species).

Specification, analytical procedures, reference standards, batch analysis, and container closure

Acceptance criteria for specifications are based on both Remsima and CT-P13 SC DS batches manufactured throughout at Korea (plant 1).

The release specification for CT-P13 SC is identical to the specification approved for Remsima IV Process II specification, except for the appearance and SC formulation protein concentration. The revised acceptance criteria for these attributes have been sufficiently justified and are acceptable.

With respect to the oligosaccharide profile, the specification limits were revised due to the introduction of Process II (same acceptance criteria for both IV and SC active substance). The proposed specification aligns closely with values for the combined oligosaccharides. The proposed acceptance criteria for the oligosaccharide profiles are acceptable.

Analytical procedures and reference standards

The analytical methods are considered capable to control the quality of the active substance (DS) at release and stability testing. The analytical release methods are unchanged from those currently registered for CT-P13 IV active substance, with the exception of the method for protein concentration which has been revised and validated for new equipment. In addition, acceptance criteria for pH and protein concentration have been adjusted suitable for SC liquid presentation. The proposed specifications are appropriately justified and acceptable.

The residual HCP method uses new Process-II-specific standard and reagents. This method has been acceptably described and validated, for assessment see variation application EMEA/H/C/002576/II/0060/G.

Verification of the compendial methods was acceptably performed using CT-P13 SC active substance. All compendial methods were verified fit for purpose.

The additional validations performed on the non-compendial methods using SC samples and SC formulation buffer are acceptable.

An in-house reference standard material has been established. The primary reference standard for CT-P13 SC was manufactured and has been extensively characterised and qualified in accordance with ICH Q6B. Re-qualification of reference standard will be performed using a pre-defined assay panel and specification to monitor stability. The primary reference standard is stored at $\leq -60^{\circ}\text{C}$. The manufacturing process used in production of working reference standard and the use of reference standards during analytical method validations is adequately described

All reference standards are well described, characterized and considered as representative of the commercial manufacturing process. The reference standards used for extended characterisation, comparability testing, stability testing and routine batch release testing of the finished product are the same as those employed for the active substance. Qualification of the hcDNA standard is appropriately described in the dossier.

A working reference standard will be established post approval and will be qualified against the primary reference standard according to a specification.

Batch analysis

Batch release data of CT-P13 SC active substance is presented for batches manufactured in Korea. The batches were tested with analytical methods for SC product. The Process I and Process II batch release data is highly comparable and meet commercial specifications. The CT-P13 SC manufacturing process is considered robust and consistent.

Container closure

No change in container closure system is proposed within the Remsima line extension.

Stability

Stability studies follow ICH Q5C and ICH Q1B guidelines. Comparative real time and accelerated stability data from process I and II alongside forced degradation data were provided.

Data remain within the approved stability specifications.

The photo-stability results show that DS is light-sensitive and should be protected from light.

On the basis of the stability data provided, the proposed shelf life for CT-P13 SC active substance stored at $-40\pm 5^{\circ}\text{C}$ (45 months) and at $5\pm 3^{\circ}\text{C}$ (3 months) is acceptable.

2.4.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The CT-P13 SC DP 120 mg/ml of infliximab solution for subcutaneous injection is filled primary container closure consisting of type I borosilicate glass syringe (1 mL) with a hypodermic stainless steel needle closed with a siliconized plunger all components comply with Ph.Eur requirements. Devices to be registered with the CT-P13 SC finished product include a pre-filled syringe with an automatic needle guard (PFS-S), and a pre-filled pen (PFP)/auto-injector (AI).

The compatibility (leachables and extractables) of the Type I borosilicate glass syringe with plunger and the product has been determined. The manufacture of PFS is appropriately described. There are no overages applied to CT-P13 SC finished product.

Pharmaceutical development

Formulation development

Adequate information is provided for the formulation development. CT-P13 was initially developed for administration by intravenous (IV) infusion following reconstitution and dilution of the lyophilised finished product. Studies of variable formulations were performed to find appropriate excipients for liquid formulation in prefilled syringe for SC administration and for sustaining the stability of active substance. The selected formulation excipients are commonly used in parenteral products. Stability studies support the chosen formulation. As requested for all new applications a summary of the risk assessment for elemental impurities in accordance with ICH Q3D is has been included in the dossier.

Manufacturing process development

The DS is ready to be filled in syringes. The DP manufacturing process consists of formulation i.e. blending of DS, from various containers and batches, bioburden filtration, sterile in-line filtration, filling of syringes, stoppering and visual inspection processes to produce "nude syringes".

Container closure system

All components comply with Ph.Eur requirements. The stability studies show that the nude PFS is able to keep the DP quality attributes within the specification limits and sterile.

The nude syringe can be further assembled with backstop and the plunger rod to prepare the PFS. The PFS-S is a device in which, in addition to the finger flange and the plunger rod, a safety guard of polycarbonate with stainless steel spring (CE-marked) is assembled to protect users from accidental needle-stick injury after injection.

The auto-injector is a single-use device that consists of the CT-P13 SC DP (nude syringe) with the addition of the front and rear assembly. CT-P13 SC in nude syringe is assembled in auto-injector. The container closure systems used for the DP packaging are appropriately described in text and with technical drawings. Each syringe is designed to deliver a single dose of 120 mg infliximab in 1 mL. The primary and secondary packaging of the DP presentations have been properly described for their quality and testing.

Each CT-P13 SC finished product is packaged in a carton to protect the CT-P13 SC finished product solution from light and from any potential physical damaged during handling, shipping and storage.

Compatibility

The compatibility of Type I borosilicate glass syringe with plunger stopper has been analysed. All components comply with Ph. Eur requirements.

The suitability of the AI pen has been studied to identify potential risks for the user. The AI components are biocompatible and free of phthalate (DEHP). AI components have passed biocompatibility testing and comply with the applicable sections of ISO 10993. The manufacturer has provided certificates for pharmacopoeial compliance of the container closure components and declaration of conformity with directive 93/42/EEC 14 June 1993.

PFS syringes with rigid needle shield and with safety guard for CT-P13 SC finished product comply with the requirements of ISO 10993 standard ("Biological Evaluation of Medical Devices" – Part 1: 2009 Evaluation and testing within a risk management process). The safety of the glass syringe and the elastomeric plunger stopper are ensured through compliance with Ph. Eur. and USP. The components of AI comply with Ph.Eur. The AI complies with ISO 11608-1 and ISO 11608-5.

The nude PFS and the medicinal product form a single, integral product which is intended exclusively for use in the given combination and which is not reusable, therefore the single product is governed by Directive 2001/83/EC. As such a CE-mark is not required for the nude pre-filled syringe.

Similarly, the nude syringe containing medicinal product and assembled in AI form a single, integral product which is intended exclusively for use in the given combination and which is not reusable, therefore the single product is governed by Directive 2001/83/EC. As such a CE-mark is not required.

Manufacture of the product and process controls

Manufacture

The manufacturing process starts with formulation (pooling) of DS batches to produce a single DP batch, mixing, bioburden reduction filtration, sterile filtration (inline filtration), filling of "nude syringes", stoppering and visual inspection.

Nude syringes are further assembled with components of PFS or PFS-S or AI.

The information given on manufacturers and batch formula is found acceptable.

All relevant sites have valid manufacturing authorisations or valid GMP certifications as appropriate. No additional issues that would trigger a GMP inspection have been identified during the assessment of the information in Module 3 of the dossier.

Process controls

The QTPP has been modified to conform to the SC presentation.

Appropriate CPPs have been set. Acceptable ranges are provided for process parameters and brief process flow diagrams are provided for the manufacturing of finished product as well as for the assembly processes of the PFS, PFS-S and the AI/pen. The processing and holding times were evaluated during process development and validated during process validation and a summary has been provided.

No reprocessing is claimed for the finished product manufacturing process.

Process validation

Process validation was performed on commercial scale batches of the finished product. In-process test results and final product quality data demonstrated that the processes are appropriately controlled and capable of producing a product that meets the pre-defined acceptance criteria and specifications. The provided data indicate that the manufacturing process is capable of consistently produce DP which meets the specifications.

Validation for assembly has been performed with consecutive batches and process validation results were provided. The pre-defined acceptance criteria were all met.

Comparability

Extensive comparability studies have been performed to support changes introduced during DP manufacturing process development.

No significant differences in quality were noticed in the above-mentioned comparability studies. In conclusion, comparability has been demonstrated.

Product specification, analytical procedures, batch analysis

Specifications

Descriptions for all analytical methods used for the solution for injection and the functionality of devices (PFS, PFS-S and AI) are included and all methods are validated in accordance with ICH guidelines.

The solution for injection specifications include tests and limits for: general properties (clarity, colour, visible particles, pH, osmolality, sub-visible particles, uniformity of dosage units and extractable volume), safety (endotoxin and sterility), identity (IEF, IEC-HPLC), purity/impurity (IEC-HPLC, CE-SDS (reduced/non-reduced), SEC-HPLC), content (protein concentration, polysorbate 80 concentration) and potency (In vitro Bioactivity).

Analytical procedures and reference standards

The SC finished product is tested by a combination of compendial and non-compendial analytical methods. Many of the non-compendial analytical methods used for release testing and stability testing of finished product are also used for release testing and stability testing of the active substance. These methods and validation results are fully described in the dossier and discussed and cover both the active substance and finished product.

The proposed control strategy and test methods are considered adequate to control the quality of the DP at release and stability testing.

Batch analysis

Batch analyses data of the SC finished product manufactured throughout development to full commercial scale are given. Batch release data is provided for DP batches manufactured. Subsets of batches have been used in non-clinical, clinical, stability and comparability studies. The release data of all batches remain within the specifications.

Stability of the product

The proposed shelf-life for CT-P13 SC finished product is 30 months when stored at the recommended storage condition of $+5 \pm 3$ °C. Additionally, storage for 14 days up to 25 °C is proposed.

Stability studies for infliximab solution in PFS, PFS-S and PFS assembled with auto-injector have been conducted in line with ICH Q5C guideline. The stability studies are presented to support shelf-life, comparability of nude syringe batches manufactured at different manufacturers as well as comparability of Process I and Process II material.

Stability data is provided for multiple batches at long term (5 ± 3 °C), accelerated (25 ± 2 °C) and stressed (40 ± 2 °C) conditions.

The applicant proposes a shelf-life of 30 months at 5 ± 3 °C, this is considered acceptable as the comparability is demonstrated for the DP manufactured at different sites, and for the Process I and –II material. Additionally, on the basis of the data provided, storage for 14 days up to 25 °C is considered acceptable.

Post-approval stability protocol and stability commitment:

The MAH commits to continue the ongoing stability studies at long-term ($+5$ °C), accelerated ($+25$ °C) and stressed ($+40$ °C) conditions of the CT-P13 SC finished product (nude syringe) and the CT-P13 SC AI until completion.

The functionality of the CT-P13 SC PFS and CT-P13 SC AI will be assessed during storage. Any out-of-specification results will be reported to the regulatory authorities.

Adventitious agents

The virus safety studies for the Process II were approved through the Type II group variation application EMEA/H/C/002576/II/0060/G.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

No major objection was identified during the procedure. The applicant adequately addressed the Other Concerns raised by CHMP.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

In conclusion, based on the review of the data provided, this extension application is considered approvable from a quality point of view.

2.4.6. Recommendation(s) for future quality development

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommended a point for investigation.

2.5. Non-clinical aspects

2.5.1. Introduction

This is an application to register the subcutaneous (SC) formulation of Remsima (Remsima SC) containing the active substance infliximab which is already approved as a similar biological medicinal product to Remicade for intravenous infusion, including a limited nonclinical data package.

Remsima SC contains the same active ingredient formulated for subcutaneous administration. The manufacturing process of Remsima SC DS is identical to that of Remsima IV except for the UF/DF step of downstream process.

2.5.2. Pharmacology

Comparable primary *in vitro* PD bioactivity (TNF α neutralisation activity) and binding affinities to TNF α , Fc γ RIIIa (V type), FcRn and C1q of Remsima IV and Remsima SC were demonstrated and summarised in Table 1.

Table 1 - The *in vitro* activity ranges of Remsima SC and Remsima IV

| Study | Activity range | | | |
|---|----------------|---------------|---------------|------------------------|
| | Remsima IV DS | Remsima SC DS | Remsima SC DP | Remsima SC clinical DP |
| TNFα neutralisation | 97-108 % | 89-91% | 88-107% | 98-102% |
| TNF α binding affinity | 106.9-121.6% | 101.8-115.8% | 96.5%-110.3% | 115.4-115.8% |
| FcγRIIIa (V type) | 81-88% | 88-101% | 98-107% | 103-111% |
| FcRn binding | 96-98% | 98-100% | 96-100% | 97 % |
| C1q binding affinity | 99-104% | 93-102% | 98-102% | 108-109% |

Thus, the formulation is not expected to influence the therapeutic activity of infliximab when administered subcutaneously.

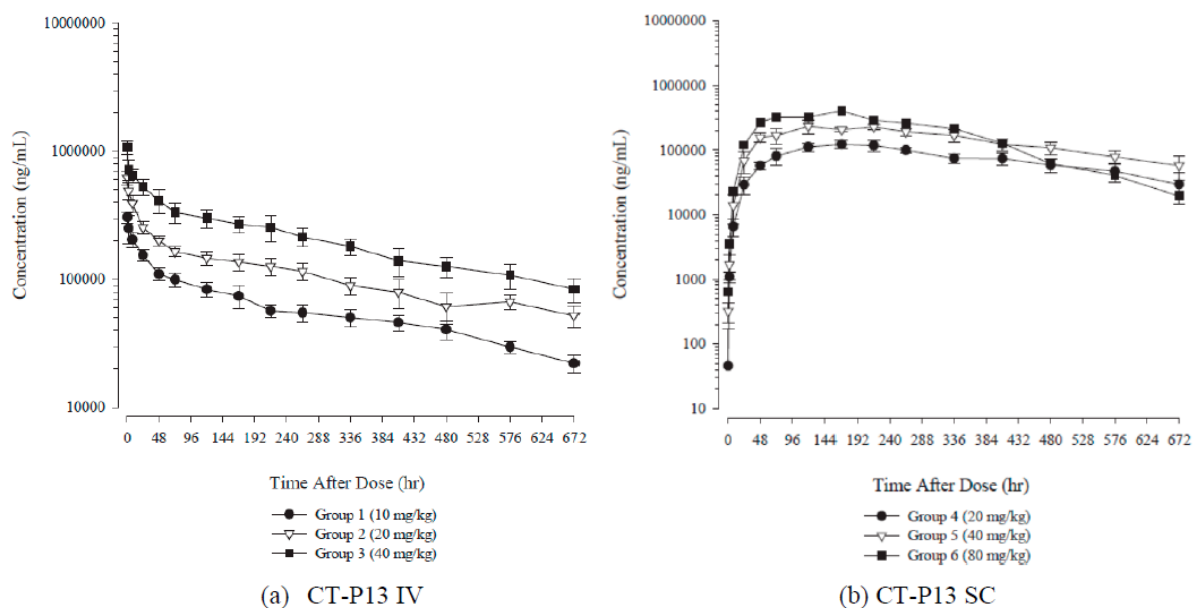
No secondary pharmacodynamics, safety pharmacology and pharmacodynamics drug interaction studies were conducted and are not required.

2.5.3. Pharmacokinetics

A rat PK study was conducted to compare the bioavailability and pharmacokinetic profiles of Remsima SC to Remsima IV in rats after a single drug dose. The limited nonclinical pharmacokinetics data package is considered adequate based on that both IV and SC formulations use the same upstream process and the products only differ in part of the downstream process from the UF/DF step.

The increases in Remsima mean C_{max} and $AUC_{0-672hr}$ values were in general dose-proportional when Remsima was administered intravenously or subcutaneously (Figure 1). Remsima SC bioavailability ranged from 58.4 to 68.3% at 20 and 40 mg/kg/day SC dose levels compared to the 10, 20 and 40 mg/kg/day IV dose levels.

Figure 1 - Mean (\pm SD) concentrations (ng/mL) of Remsima in male rat serum following IV and SC administration



Note: Animals with anti-drug antibody positive results at 672 hours post-dose are not presented here.

The SC delivery of Remsima triggered higher and dose-dependent anti-drug antibody (ADA) response in comparison to the Remsima IV. Most ADA positive samples in Remsima SC group were observed in animals receiving 40 mg/kg/dose (7/10) and 80 mg/kg/dose (9/10). Animals with ADA positive results in the Remsima-SC groups at 672 hours post-dose were removed from the PK parameter calculations. Due to the ADA response in the Remsima SC group at the higher doses, the comparability of Remsima IV and Remsima SC remains inconclusive. Moreover, the pharmacokinetics of Remsima SC in comparison to the Remsima IV may not be representative to the human pharmacokinetic responses, when the immune responses in animals are not predictive to the responses in humans.

The analytical procedures are considered fit-for-purpose.

No metabolism or excretion studies have been conducted and are not required. Remsima SC (infliximab) metabolism and excretion will likely be the same as for normal immunoglobulin clearance pathways. No studies assessing PK drug interactions have been performed and are not required.

2.5.4. Toxicology

A limited toxicology data package was submitted to support the line extension application. No single or repeated dose toxicity studies, genotoxicity or carcinogenicity studies were conducted for Remsima SC and are not required. Infliximab binds only to TNF α from humans and chimpanzees and does not cross react with TNF α from other species.

A local tolerance study with Remsima SC was conducted in rabbits to evaluate the injection site tolerance for a single SC injection of Remsima at 120 mg/mL concentration. The administration of Remsima SC to rabbits was well tolerated at the concentration of 120 mg/mL, the concentration intended for use in humans. No abnormal signs were observed except for minimal to mild leukocyte infiltration in Remsima SC group at 2 out of 5 rabbits analysed at day 1 post-injection. Infiltration was temporary and not seen at 7 days after injection. No irritation responses were evident at the injection site.

Table 2 - Summary of local tolerance of Remsima SC in rabbits

| Study Type | Method | Results | | |
|---|--|-------------|--|--|
| Local tolerance study of CT-P13 SC 110B in New Zealand White rabbits Study B15613 (GLP) | 120 mg/mL CT-P13 SC or saline once subcutaneously in 10 animals respectively | Evaluation | CT-P13 SC (Treatment group) | Saline (Negative control) |
| | | Macroscopic | Haemorrhage in a few animals - incidental, unrelated | Haemorrhage in a few animals - incidental, unrelated |
| | | Microscopic | 1st necropsy (Day 1): Minimal and mild leukocyte infiltrations in 2 animals 2nd necropsy (Day 7): no abnormal signs | No abnormal findings |

No specific studies investigating antigenicity were conducted with Remsima SC. Immunogenicity of infliximab was assessed as part of the single dose PK study following Remsima IV or SC administration to rats.

The proposed excipients (sodium acetate, sorbitol, and polysorbate 80) represent pharmaceutical excipients with an established safety profile.

2.5.5. Ecotoxicity/environmental risk assessment

No environmental risk assessment was performed in line with the CHMP Guideline on the environmental risk assessment of medicinal products for human use (EMA/CHMP/SWP/4447/00) which states that proteins are exempted from the need for an assessment of impact on the environment because they are unlikely to result in significant risk to the environment. CT-P13 is a monoclonal antibody and is a protein; therefore, an environmental risk assessment is not required for this medicinal product.

2.5.6. Discussion on non-clinical aspects

The submitted non-clinical studies included the comparative *in vitro* primary PD bioactivity and binding affinities to TNF α , Fc γ RIIIa, FcRn and C1q, a single dose pharmacokinetic study in rats of Remsima IV and Remsima SC formulation, and a local tolerance study in rabbits with Remsima SC formulation.

No concerns were identified, and the limited non-clinical data is considered sufficient to support the line extension application.

2.5.7. Conclusion on the non-clinical aspects

From a nonclinical point of view, the available non-clinical package supports the line extension of Remsima SC.

2.6. Clinical aspects

2.6.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH (please refer to *Design and conduct of clinical studies* in the efficacy discussion of clinical efficacy).

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

The clinical development programme of Remsima (aka CT-P13) SC included two single-dose studies in healthy volunteers (study CT-P13 1.5 and study CT-P13 1.9), one study in patients with rheumatoid arthritis (RA; study CT-P13 3.5) and one study in patients with Crohn's disease (CD) and ulcerative colitis (UC; study CT-P13 1.6). The studies are summarised in Table 3; studies in target populations are also briefly described below.

- **Study CT-P13 3.5** is a randomised, parallel-group, Phase I/III study to evaluate efficacy, PK, PD and safety between Remsima SC and Remsima IV in patients with active RA. The study was conducted in 2 parts. **Part 1** was planned to determine the optimal dose of Remsima SC based on PK endpoints, whereas **Part 2** was designed to demonstrate non-inferiority of Remsima SC vs. Remsima IV in efficacy based on DAS28 (CRP).

Results up to Week 54 of Part 1 and Week 30 of Part 2 were available at submission while the 64-week data from Part 2 was submitted during the evaluation.

- **Study CT-P13 1.6** is an open-label, randomised, parallel-group, Phase I study to evaluate PK, efficacy and safety between Remsima SC and IV in patients with active CD and active UC. The study was conducted in 2 parts. **Part 1** was conducted in CD patients and was designed to determine the optimal dose of Remsima SC for treating IBD, based on PK endpoints. **Part 2** was conducted in CD and UC patients to demonstrate non-inferiority of PK based on C_{trough} at Week 22 of Remsima SC compared to Remsima IV.

Only results up to Week 54 of Part 1 were available during the evaluation. The 30-week data from Part 2 was not available at the time of this assessment.

Table 3 - Overview of Clinical Study Programme for Remsima (aka CT-P13) SC

| Protocol No. | Population | Design | Objective(s) | Study Treatments |
|-------------------|--|--|--|--|
| CT-P13 1.5 | HV Enrolled: 38 CT-P13 SC 120 mg: 6 CT-P13 SC 180 mg: 7 CT-P13 SC 240 mg: 7 CT-P13 IV 3 mg/kg: 10 CT-P13 IV 5 mg/kg: 8 | Open-label, dose-escalating, single-dose, Phase I study to evaluate safety and PK of CT-P13 SC administration | Primary Objective: <ul style="list-style-type: none"> To evaluate the safety of CT-P13 SC administration and CT-P13 IV administration Secondary Objective: <ul style="list-style-type: none"> To evaluate PK and immunogenicity over 12 weeks of CT-P13 SC and CT-P13 IV in healthy subject | Test product: CT-P13 SC 120 mg, 180 mg and 240 mg by SC injection via PFS administered as a single dose on Day 0 Reference product: CT-P13 IV 3 mg/kg or 5 mg/kg by 2-hour IV infusion administered as a single dose on Day 0 |
| CT-P13 1.9 | HV Randomised: 218 CT-P13 SC 120 mg AI: 109 CT-P13 SC 120 mg PFS: 109 | Open-label, randomised, single-dose, two-arm, parallel-group, Phase I study to compare PK and safety of CT-P13 SC via AI and PFS | Primary Objective: <ul style="list-style-type: none"> To demonstrate comparable PK in terms of the AUC_{0-inf}, AUC_{0-last}, and C_{max} of CT-P13 SC administered by AI versus PFS Secondary Objective: <ul style="list-style-type: none"> To evaluate additional PK variables, safety and immunogenicity over 12 weeks of a single dose of CT-P13 SC using AI versus PFS | Test product: CT-P13 SC 120 mg by SC injection via AI administered as single dose on Day 0. Reference product: CT-P13 SC 120 mg by SC injection via PFS administered as single dose on Day 0. |

| | | | | |
|--------------------------------------|---|---|--|---|
| <p>CT-P13 3.5¹</p> | <p>RA</p> <p>Part 1</p> <p>Randomised: 48</p> <p>CT-P13 IV 3 mg/kg: 13</p> <p>CT-P13 SC 90 mg: 11</p> <p>CT-P13 SC 120 mg: 12</p> <p>CT-P13 SC 180 mg: 12</p> <p>Part 2</p> <p>Randomised: 348</p> <p>CT-P13 IV 3 mg/kg: 179</p> <p>CT-P13 SC 120 mg: 169</p> | <p>Randomised, parallel-group, Phase I/III study to evaluate efficacy, PK and safety of CT-P13 SC and CT-P13 IV¹</p> | <p>[Part 1]</p> <p>Primary Objective:</p> <ul style="list-style-type: none"> To find the optimal dose of CT-P13 SC over the first 30 weeks as determined by AUC_T at steady state between Week 22 and Week 30 <p>Secondary Objective:</p> <ul style="list-style-type: none"> To evaluate efficacy, PK, PD and safety of CT-P13 SC in comparison with CT-P13 IV up to Week 54 <p>[Part 2]</p> <p>Primary Objective:</p> <ul style="list-style-type: none"> To demonstrate that CT-P13 SC is non-inferior to CT-P13 IV at Week 22, in terms of efficacy as determined by clinical response according to change from baseline in disease activity measured by DAS28 (CRP) <p>Secondary Objective:</p> <ul style="list-style-type: none"> To evaluate efficacy, PK, PD, and overall safety of CT-P13 SC in comparison with CT-P13 IV (over the first 30 weeks) To evaluate efficacy, PK, PD and overall safety of CT-P13 SC up to Week 54 To evaluate usability of CT-P13 SC via AI from Week 46 to Week 54 (Bulgaria, Poland and Russia only) To evaluate usability of CT-P13 SC via PFS from Week 56 to Week 64 (Bulgaria, Poland and Russia only) <p>Tertiary Objective:</p> <ul style="list-style-type: none"> To evaluate genotypes as biomarkers (optional) | <p>[Part 1]</p> <p><Dose-loading phase> - Week 0 to 6</p> <p>Two doses of CT-P13 IV 3 mg/kg at Weeks 0 and 2 for all patients</p> <p><Maintenance phase> - Week 6 to 54</p> <ul style="list-style-type: none"> Cohort 1: CT-P13 IV 3 mg/kg at Week 6 and then every 8 weeks up to Week 54 Cohort 2: CT-P13 SC 90 mg via PFS at Week 6 and then every 2 weeks up to Week 54 Cohort 3: CT-P13 SC 120 mg via PFS at Week 6 and then every 2 weeks up to Week 54 Cohort 4: CT-P13 SC 180 mg via PFS at Week 6 and then every 2 weeks up to Week 54 <p>[Part 2]</p> <p><Dose-loading phase> - Week 0 to 6</p> <p>Two doses of CT-P13 IV 3 mg/kg at Weeks 0 and 2 for all patients</p> <p><Maintenance phase> - Week 6 to 64</p> <ul style="list-style-type: none"> Arm 1: Further 3 doses of CT-P13 IV is administered at Week 6 and every 8 weeks thereafter up to Week 22 with placebo SC at Week 6 and every 2 weeks thereafter through Week 28. CT-P13 IV is then switched to CT-P13 SC 120 mg at Week 30. Further doses of study treatment with CT-P13 SC 120 mg every 2 weeks are given up to Week 54. Arm 2: First CT-P13 SC 120 mg via PFS at Week 6 and then every 2 weeks up to Week 54 with placebo IV at Weeks 6, 14 and 22. <p>In Bulgaria, Poland and Russia only, patients were administered CT-P13 SC via AI at Week 46 and every 2 weeks thereafter up to week 54 and then via PFS at Week 56 up to Week 64 for usability assessment.</p> |
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| | | | | |
|-------------------|--|---|--|---|
| CT-P13 1.6 | <p>IBD</p> <p>Part 1 with CD</p> <p>Randomised: 44</p> <p>CT-P13 IV 5 mg/kg: 13</p> <p>CT-P13 SC 120 mg: 11</p> <p>CT-P13 SC 180 mg: 12</p> <p>CT-P13 SC 240 mg: 8</p> <p>Part 2 with CD and UC</p> <p>Minimum 130</p> | <p>Open-label, randomised, parallel group, Phase I study to evaluate the PK, efficacy and safety of CT-P13 SC and CT-P13 IV</p> | <p>[Part 1]</p> <p>Primary Objective:</p> <ul style="list-style-type: none"> To find the optimal dose of CT-P13 SC over the first 30 weeks as determined by the AUC_τ at steady state between Week 22 and Week 30 <p>Secondary Objective:</p> <ul style="list-style-type: none"> To evaluate efficacy, PK, PD and overall safety of CT-P13 SC in comparison with CT-P13 IV up to Week 54 <p>[Part 2]</p> <p>Primary Objective:</p> <ul style="list-style-type: none"> To demonstrate that CT-P13 SC is non-inferior to CT-P13 IV in terms of PK, as determined by the C_{trough, week22} (pre-dose level at Week 22) <p>Secondary Objective:</p> <ul style="list-style-type: none"> To evaluate efficacy, PK, PD, and overall safety of CT-P13 SC in comparison with CT-P13 IV (over the first 30 weeks) To evaluate efficacy, PK, PD and overall safety of CT-P13 SC up to Week 54 <p>Tertiary Objective:</p> <ul style="list-style-type: none"> To evaluate genotypes (optional) and amino acids as biomarkers To evaluate patient overall satisfaction of CT-P13 IV and CT-P13 SC | <p>[Part 1]</p> <p><Dose-loading phase> - Week 0 to 6</p> <p>Two doses of CT-P13 IV 5 mg/kg at Weeks 0 and 2 for all patients</p> <p><Maintenance phase> - Week 6 to 54</p> <ul style="list-style-type: none"> Cohort 1: CT-P13 IV 5 mg/kg at Week 6 and then, every 8 weeks up to Week 54 Cohort 2: CT-P13 SC 120 mg via PFS at Week 6 and then, every 2 weeks up to Week 54 Cohort 3: CT-P13 SC 180 mg via PFS at Week 6 and then, every 2 weeks up to Week 54 Cohort 4: CT-P13 SC 240 mg via PFS at Week 6 and then, every 2 weeks up to Week 54 <p>[Part 2]</p> <p><Dose-loading phase> - Week 0 to 6</p> <p>Two doses of CT-P13 IV (5 mg/kg) at Weeks 0 and 2 for all patients</p> <p><Maintenance phase> - Week 6 to 54</p> <ul style="list-style-type: none"> Arm 1: Further 3 doses of CT-P13 IV was administered at Week 6 and every 8 weeks thereafter up to Week 22 (Weeks 14 and 22). CT-P13 IV is then switched to CT-P13 SC at Week 30. Further doses of study treatment with CT-P13 SC every 2 weeks are given up to Week 54. Arm 2: First CT-P13 SC via PFS at Week 6 and then CT-P13 SC via PFS every 2 weeks up to Week 54 <p>The dosage of CT-P13 SC was determined based on the patient's body weight (Arm 1: body weight at week 30, Arm 2: body weight at week 6, CT-P13 SC 120 mg for patients < 80 kg; 240 mg for patients ≥ 80 kg).</p> |
|-------------------|--|---|--|---|

¹ The Maintenance Phase in Part 2 was double-blinded up to Week 30. While the study data were analysed by the predefined unblinded team at Week 30, all the patient and physician and predefined blinded team from CELLTRION and CRO (PPD) remained blinded until all patients had completed the study and the database had been finalised for study termination. There were 5 patients excluded in all analysis populations due to the significant GCP non-compliance of one site.

AI: Auto-injector, AUC_{0-inf}: Area under the concentration-time curve from time zero to infinity, AUC_{0-last}: Area under the concentration-time curve from time zero to the last quantifiable concentration, AUC_τ: Area under the serum concentration time curves at steady state over the actual dosing interval calculated using the linear trapezoidal rule,

CD: Crohn's disease, C_{max} : Maximum serum concentration, CRP: C-reactive protein, CSR: Clinical study report, $C_{trough, week22}$: pre-dose level at Week 22, DAS28: Disease activity score using 28 joint counts, HV: Healthy volunteer, IBD: Inflammatory bowel disease, IV: Intravenous, PD: Pharmacodynamics, PFS: Pre-filled syringe, PK: Pharmacokinetics, RA: Rheumatoid arthritis, SC: Subcutaneous, UC: Ulcerative colitis

2.6.2. Pharmacokinetics

Intravenously administered Remsima powder for concentrate for solution for infusion (hereafter Remsima IV or CT-P13 IV) is a biosimilar of Remicade powder for concentrate for solution for infusion. There are no other approved pharmaceutical forms or routes of administration for the reference product. The MAH is applying for a new formulation of Remsima, intended to be given as a subcutaneous injection (hereafter Remsima SC or CT-P13 SC).

The same formulation of Remsima SC was used throughout the clinical development programme and the same formulation will be used for the product to be marketed. It was demonstrated in study CT-P13 1.9 that PK of infliximab is similar following SC injection using the pre-filled syringe and the autoinjector device.

Approved posology for Remsima IV and proposed posology for Remsima SC

The approved maintenance dose in treatment of RA is 3 mg/kg given intravenously every 8 weeks (Q8W). The proposed maintenance dose in treatment of RA is 120 mg given subcutaneously Q2W, which was used in the clinical efficacy/safety study CT-P13 3.5 Part 2.

The other initially proposed indications (AS, Ps, PsA) were withdrawn during the assessment. The CHMP considered that without data from the full planned clinical development package, including long-term data and the full additional study in IBD-patients (including data on patients >80 kg with 240mg dosing) extrapolation to these indications would be impossible due to differences in the use of concomitant immunosuppressants and dosing in these indications.

Rationale for Remsima SC dose selection

The MAH selected the proposed posology based on population PK and PK-PD modelling. The objective was to exceed a target C_{trough} threshold of 1 µg/mL in RA and 5 µg/mL in other indications and to generate a steady state AUC over 8 weeks ($AUC_{8weeks,ss}$) that aligned as closely as possible to that achieved following 3 mg/kg IV administration to RA patients and 5 mg/kg IV administration for other indications. It is generally believed that C_{trough} is the driver for efficacy. The C_{trough} thresholds for optimal efficacy were set following a literature review by the MAH and they were agreed with by the CHMP (EMA/H/SA/3220/1/FU/1/2016/II; EMA/H/SA/3220/1/FU/2/2017/II).

Exploratory PK and efficacy/safety data were collected in small open-label studies CT-P13 3.5 Part 1 (RA patients; Remsima SC 90 mg / 120 mg / 180 mg Q2W) and CT-P13 1.6 Part 1 (CD patients; Remsima SC 120 mg / 180 mg / 240 mg Q2W). Subsequently, population PK modelling was conducted to find Remsima SC posology that would achieve the aforementioned PK endpoints for C_{trough} and AUC. The selected Remsima SC dosing regimen was then used in confirmatory studies CT-P13 3.5 Part 2 and CT-P13 1.6 Part 2.

Bioanalytics

It is acknowledged that the MAH has developed the bioanalytical methods since the approval of the CT-P13 IV product and the initial CT-P13 SC dose-finding study. The initial methods were subjected to validation according to EMA guidelines and the performance of the bioanalytical methods were appropriately bridged between CT-P13 IV and CT-P13 SC products. Later, the methods for determining the CT-P13 concentration and anti-CT-P13 antibodies (both ADAs and Nab) in human serum were

modified and optimized. Cross validation studies indicated that performance of the original methods used in the initial dose-finding study (CT-P13 SC 1.5) and the actual clinical studies (CT-P13 1.9, CT-P13 3.5 and CT-P13 1.6) have acceptable comparability. The methods used in studies CT-P13 1.9, CT-P13 3.5 and CT-P13 1.6 were validated according to the current EMA guidelines.

The performance of the two methods (Gyrolab xP and MSD ECL) for measuring human serum levels of the active substance of CT-P13 was appropriately shown.

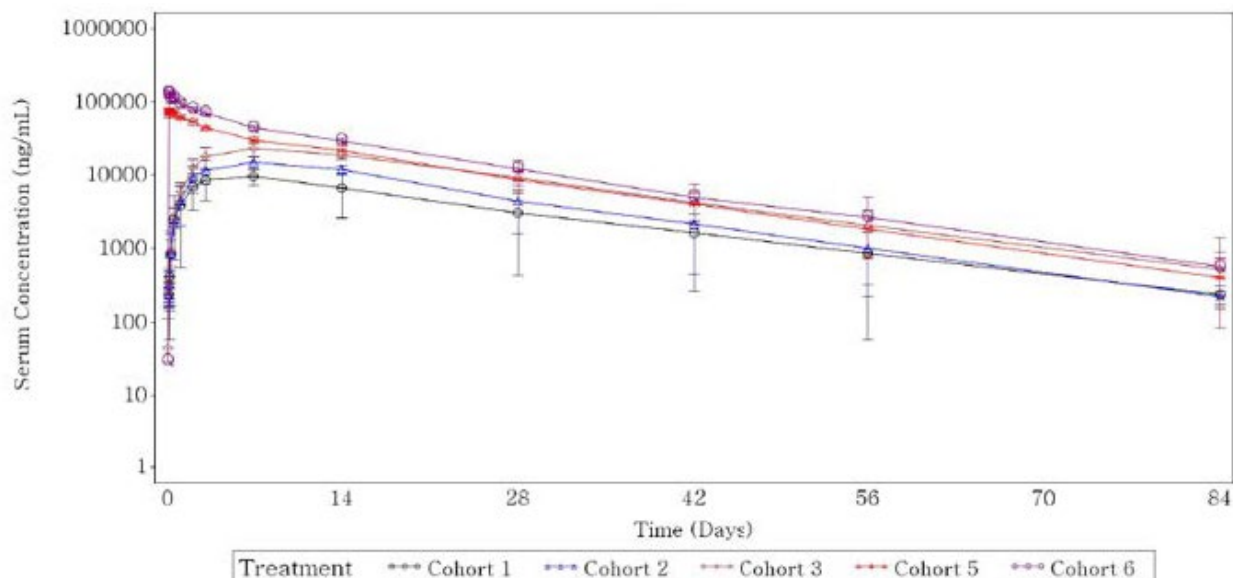
During the clinical studies, the assessment of antibodies against CT-P13 followed a standard hierarchical approach to identify binding antibodies (ADAs) with screening and confirmation/titration by drug inhibition, using a validated enzyme-linked immunosorbent (ELISA) bridging immunoassay. In addition, serum samples were tested for neutralizing anti-CT-P13 antibodies (NABs) using a MSD ECL based method. It appears that both methods have limitations regarding the drug tolerance levels and the performance of the assay at levels close to the assay cut point. Methodological uncertainties also remain related to the sensitivity and drug tolerance of the Nab assay, particularly to analyzing the lipemic samples from RA patients.

However, even if some of the NABs went undetected due to higher drug concentrations and low sensitivity to detect low titres of Nabs, it can be concluded that the formation of NABs was not greater with the SC formulation.

Pharmacokinetics following a single dose

Pharmacokinetics of Remsima SC (120 mg, 180 mg and 240 mg) compared with Remsima IV (3 mg/kg and 5 mg/kg) after a single dose were explored in healthy subjects (N = 6 to 10 in each cohort) in a study CT-P13 1.5. Median T_{max} was at approximately 170 h (range 72 to 314 h) in each SC cohort. The mean terminal elimination half-life ($T_{1/2}$) was between 271 h and 329 h in the five cohorts and it was similar in SC cohorts and in IV cohorts (Figure 2). The mean bioavailability was 60.56% (90% CI 51.93% - 70.63%) for overall Remsima SC cohorts to overall IV cohorts.

Figure 2 - Mean (\pm SD) Serum Concentrations of Infliximab by Cohort (Study CT-P13 1.5)



Cohort 1: 120 mg SC; Cohort 2: 180 mg SC; Cohort 3: 240 mg SC; Cohort 5: 3 mg/kg IV; Cohort 6: 5 mg/kg IV

Pharmacokinetics at steady state

In study CT-P13 3.5 Part 1 patients with RA were initially treated in the loading phase with Remsima IV 3 mg/kg at baseline (Week 0) and Week 2. A total of 48 patients were randomised at Week 6 to Remsima 3 mg/kg IV Q8W, 90 mg SC Q2W, 120 mg SC Q2W and 180 mg SC Q2W. Primary PK analyses were conducted using steady state PK data collected from Week 22 to Week 30.

The mean pre-dose levels maintained consistent levels from Week 14 onwards indicating that steady state was achieved at the PK monitoring period from Week 22 to Week 30 (Figure 3 and Table 4). The steady state AUC normalized to 8-week interval from Week 22 to Week 30 (AUC_{ss8W}) of SC cohorts was approximately 1.5-fold to 3.4-fold greater than that of IV cohort. The mean C_{trough} levels were several times higher than the target C_{trough} ($>1 \mu\text{g/mL}$) in each SC cohort. The mean AUC, C_{trough} and C_{max} were approximately dose proportional across the SC cohorts, taking into account high within-group variability and parallel-group study design.

Figure 3 - Mean (\pm SD) Serum Concentration of Infliximab versus Time by Cohort: Weeks 22 to 30 (Study CT-P13 3.5 Part 1)

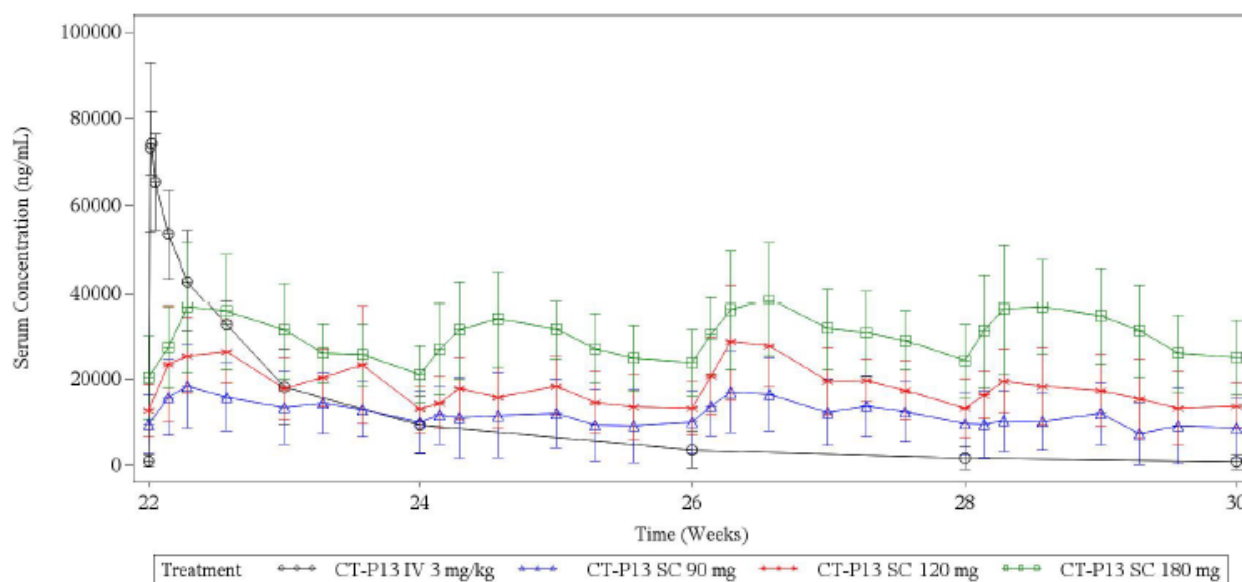


Table 4 - Pre-dose infliximab Levels (C_{trough}) (Study CT-P13 3.5 Part 1)

| | | Remsima IV 3 mg/kg | Remsima SC 90 mg | Remsima SC 120 mg | Remsima SC 180 mg |
|---------------------------------------|-----------|-----------------------------------|---------------------------------|----------------------------------|----------------------------------|
| Pre-dose concentration (µg/mL) | | | | | |
| Week 2 | n | 13 | 11 | 12 | 12 |
| | Mean ± SD | 16.78 ± 2.44 | 14.64 ± 6.79 | 15.14 ± 3.34 | 18.98 ± 4.24 |
| Week 6 | n | 13 | 11 | 12 | 12 |
| | Mean ± SD | 10.04 ± 3.76 | 8.41 ± 5.59 | 9.26 ± 4.88 | 11.25 ± 7.90 |
| Week 14 | n | 13 | 10 | 11 | 12 |
| | Mean ± SD | 1.37 ± 1.40 | 9.13 ± 6.05 | 13.47 ± 5.78 | 21.25 ± 8.29 |
| Week 22 | n | 13 | 10 | 11 | 12 |
| | Mean ± SD | 0.96 ± 1.39 | 9.46 ± 6.71 | 12.68 ± 6.09 | 20.20 ± 9.60 |
| Week 30 | n | 13 | 9 | 10 | 12 |
| | Mean ± SD | 0.80 ± 1.63 | 8.62 ± 6.83 | 13.64 ± 5.27 | 24.89 ± 8.58 |
| Week 38 | n | 13 | 9 | 10 | 10 |
| | Mean ± SD | 0.63 ± 1.39 | 8.40 ± 6.84 | 12.21 ± 6.42 | 21.54 ± 10.07 |
| Week 46 | n | 12 | 9 | 11 | 10 |
| | Mean ± SD | 0.63 ± 1.20 | 8.01 ± 6.75 | 10.76 ± 6.99 | 22.48 ± 8.85 |
| Week 54 | n | 12 | 9 | 10 | 9 |
| | Mean ± SD | 0.59 ± 1.06 | 8.62 ± 7.24 | 11.32 ± 6.32 | 15.66 ± 7.67 |

Table 5 - Infliximab AUC over 8 weeks at Steady State (AUC_{ss8W}; Study CT-P13 3.5 Part 1)

| Parameter | Visit | Summary | CT-P13 IV 3 mg/kg | CT-P13 SC 90 mg | CT-P13 SC 120 mg | CT-P13 SC 180 mg |
|---|----------------|----------------|------------------------------|----------------------------|-----------------------------|-----------------------------|
| AUC_{ss8W} (h*ug/mL) | Week 22 | n | 13 | 9 | 10 | 12 |
| | | Mean | 11860 | 18110 | 26420 | 40050 |
| | | CV% | 45.0 | 50.4 | 29.8 | 29.3 |

Note: AUC_{ss8W}: area under the concentration-time curve at steady state between Week 22 and Week 30; AUC_τ: area under the serum concentration-time curve over the dosing interval at steady state (between Week 22 and Week 30); CV%: coefficient of variation; NA: Not applicable.

The dosing regimen Remsima SC 120 mg SC Q2W was selected for RA indication and used in the pivotal efficacy/safety study CT-P13 3.5 Part 2. Sparse PK data were collected in study CT-P13 3.5 Part 2. Data indicate that the target C_{trough} (>1 µg/mL) is achieved in majority of patients following maintenance dosing regimen Remsima SC 120 mg SC Q2W.

Table 6 - Descriptive Statistics of Observed Serum Infliximab C_{trough} (Study CT-P13 3.5 Part 2)

| | | Remsima IV 3 mg/kg Q8W | Remsima SC 120 mg Q2W |
|--|----------------|-----------------------------------|----------------------------------|
| Steady state pre-dose concentration (µg/mL) | | | |
| Week 30 | n | 156 | 153 |
| | Mean | 1.030 | 12.293 |
| | SD | 1.854 | 9.7208 |
| | CV(%) | 179.9 | 79.1 |
| | Geometric Mean | 0.323.6 | 5.373 |
| | Minimum | 0.1 | 0.1 |
| | Median | 0.1 | 11.70 |
| | Maximum | 13.2 | 62.3 |

Steady state PK data following administration of Remsima SC 240 mg Q2W is available from 6 patients with CD from study CT-P13 1.6 Part 1. A total of 45 patients with CD were initially treated in the loading phase with Remsima IV 5 mg/kg at baseline (Week 0) and Week 2. A total of 44 patients were randomised at Week 6 to Remsima 5 mg/kg IV Q8W, 120 mg SC Q2W, 180 mg SC Q2W and 240 mg Q2W. Primary PK analyses were conducted using steady state PK data collected from Week 22 to Week 30.

Mean (\pm SD) serum concentrations of infliximab versus time by cohort are presented in Figure 4. The mean pre-dose concentration in each SC cohort was substantially greater (above 15 mg/mL) than that of IV cohort (\sim 1.1 to 1.9 µg/mL) throughout the study period (Table 7). The steady state AUC normalized to 8-week interval from Week 22 to Week 30 (AUC_{ss8W}) of SC cohorts was approximately 1.3-fold to 2.0-fold greater than that of IV cohort (Table 8). Mean C_{max} at steady state was approximately 3- to 4-fold higher in Remsima IV 5 mg/kg Q8W cohort than in Remsima SC Q2W cohorts.

Figure 4 - Mean (\pm SD) Serum Concentration of Infliximab versus Time by Cohort (Study CT-P13 1.6 Part 1; Weeks 22 to 30)

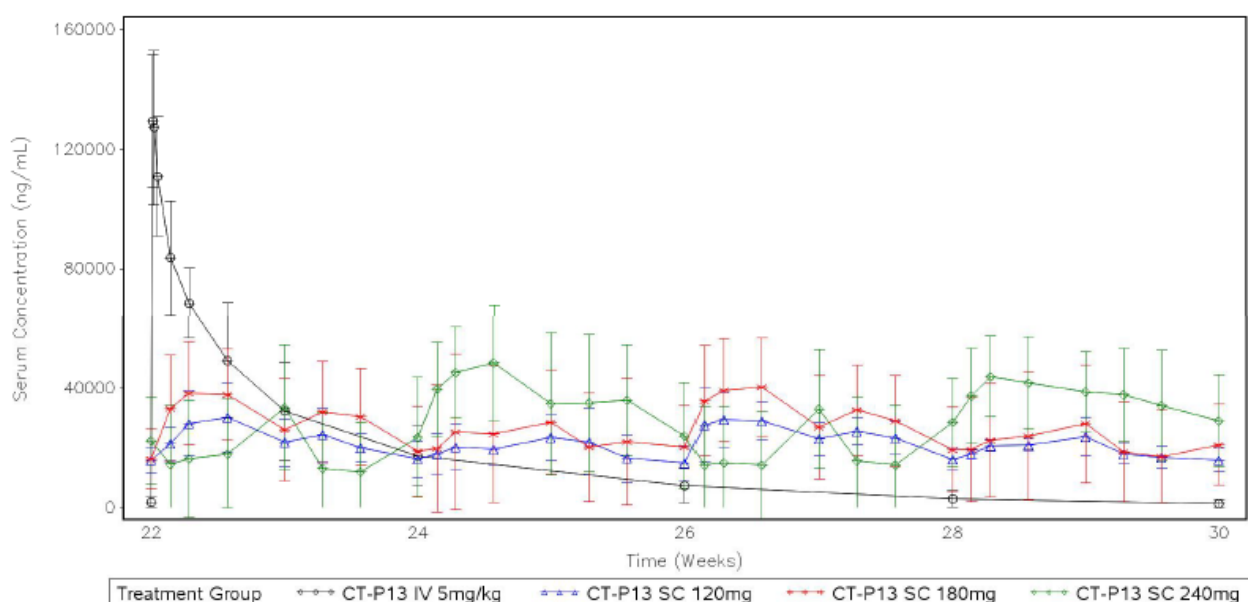


Table 7 - Pre-dose Infliximab Levels (C_{trough}) (Study CT-P13 1.6 Part 1)

| | | Remsima IV 5 mg/kg | Remsima SC 120 mg | Remsima SC 180 mg | Remsima SC 240 mg |
|---------------------------------------|-----------|-----------------------------------|----------------------------------|----------------------------------|----------------------------------|
| Pre-dose concentration (µg/mL) | | | | | |
| Week 2 | n | 12 | 11 | 12 | 6 |
| | Mean ± SD | 24.67 ± 8.29 | 21.95 ± 4.80 | 22.53 ± 9.50 | 15.66 ± 10.23 |
| Week 6 | n | 12 | 11 | 12 | 6 |
| | Mean ± SD | 11.49 ± 10.06 | 12.73 ± 6.97 | 13.04 ± 14.19 | 6.60 ± 6.40 |
| Week 14 | n | 12 | 10 | 12 | 6 |
| | Mean ± SD | 2.98 ± 3.60 | 14.09 ± 6.27 | 17.51 ± 12.46 | 22.88 ± 19.46 |
| Week 22 | n | 11 | 9 | 11 | 6 |
| | Mean ± SD | 1.71 ± 1.74 | 15.67 ± 4.32 | 16.23 ± 10.08 | 22.33 ± 14.61 |
| Week 30 | n | 10 | 9 | 10 | 5 |
| | Mean ± SD | 1.22 ± 1.45 | 15.83 ± 3.84 | 20.97 ± 13.54 | 29.00 ± 15.51 |
| Week 38 | n | 10 | 9 | 9 | 5 |
| | Mean ± SD | 1.12 ± 1.61 | 16.98 ± 4.75 | 22.45 ± 13.28 | 27.20 ± 14.74 |
| Week 46 | n | 9 | 9 | 7 | 5 |
| | Mean ± SD | 1.90 ± 2.51 | 12.95 ± 6.25 | 22.40 ± 15.72 | 26.04 ± 14.44 |
| Week 54 | n | 8 | 9 | 7 | 5 |
| | Mean ± SD | 1.55 ± 1.92 | 15.40 ± 7.44 | 20.89 ± 10.42 | 26.00 ± 18.53 |

Table 8 - Infliximab AUC over 8 Weeks at Steady State (AUC_{ss8W}; Study CT-P13 1.6 Part 1)

| Parameter | visit | Summary | CT-P13 IV 5 mg/kg | CT-P13 SC 120 mg | CT-P13 SC 180 mg | CT-P13 SC 240 mg |
|----------------------------------|---------|---------|----------------------|---------------------|---------------------|---------------------|
| AUC _{ss8W} (h*ug/mL) | Week 22 | n | 11 | 10 | 11 | 6 |
| | | Mean | 20950 | 28250 | 34260 | 41140 |
| | | CV% | 41.2 | 32.8 | 67.5 | 66.1 |

Note: ¹ Data were summarized for the Full Dose Patients (All Doses Received) subset of the PK population.
AUC_{ss8W}: area under the serum concentration-time curve normalized to 8 weeks; AUC: area under the serum concentration-time curve over the dosing interval; CV%: coefficient of variation; NA: not available; NC: not calculated.

Population PK modelling

Population PK (PPK) models were developed to describe the PK of infliximab following SC or IV administration. The overall aim of the analyses was to provide supportive evidence of the appropriateness of the dosing regimen using the Remsima SC formulation by producing model-informed simulations of clinical scenarios of interest. The model was updated when new data were available; the results below are for the model that includes data for SC formulation from studies CT-P13 1.5, CT-P13 3.5 Part 1 and Part 2, and CT-P13 1.6 Part 1.

Infliximab serum concentrations less than LLOQ were treated as missing in the PPK analysis. Following completion of the base model development, conditional weighted residuals (CWRES) with absolute values greater than 6 were deemed to be outliers and removed from the analysis. The first-order conditional estimation with η - ϵ interaction (FOCE-INT) in NONMEM was employed for all model runs. Following a visual inspection of covariate plots, those covariates that demonstrated trends and had not already been included in the base model, were tested. A sensitivity check was performed to assess any potential

impact of the formulation (IV or SC) and/or disease status on the drug model parameter estimates. The association between patient covariates and PK parameters was evaluated in a stepwise manner, applying an iterative addition and deletion model selection strategy. A 2-compartment PK model with linear elimination from the central compartment was employed. Infliximab could be administered either directly into the central compartment as an IV infusion, or into a depot compartment as a subcutaneous injection with a first order absorption rate (K_A) into the central compartment. Bioavailability (F) after SC administration was estimated. An allometric scaling approach with estimated exponents was adopted on central and peripheral volume (V_1 and V_3 , respectively) and clearance and intercompartmental clearance (CL and Q , respectively). Between-subject variability was estimated for CL and V_1 . Emergence of anti-drug antibodies (ADA), neutralizing anti-drug antibodies (NAB) and concomitant use of methotrexate (MTX) were incorporated in a time-dependent manner. The residual error was described with a proportional error model.

Parameter estimates of the final PPK model are shown in Table 9. Estimated bioavailability following SC administration was 57.6%. Estimated CL for a reference subject (70 kg; ADA-; NAB-; not on MTX) was 12.6 mL/h and estimated volume of distribution approximately 4.95 L. The values are similar to values reported in scientific literature. Estimated CL was increased 1.28-fold (i.e. approximately to 16.1 mL/h) in presence of neutralising anti-drug antibodies. Presence of ADA (in absence of NAB) and concomitant use of MTX did not significantly affect clearance after the effect of NAB on CL was accounted for. Post hoc PK parameter estimates were similar in all patient groups (RA, CD, AS, and healthy subjects), indicating that clearance of infliximab was not affected by disease.

Table 9 - Model and Bootstrap Estimates (1000 bootstrap runs) for Final Remsima PK Model

| Parameter | Final Estimate | | Bootstrap results | | |
|---|----------------|---------|-------------------|------------------|---------|
| | Typical Value | RSE (%) | Median | 95% CI | RSE (%) |
| F | 0.576 | 3.7 | 0.576 | [0.537;0.616] | 3.6 |
| K_A (h^{-1}) | 0.00902 | 9.5 | 0.00898 | [0.00747;0.0113] | 10.2 |
| CL_{NAB-} (L/h) | 0.0126 | 1.4 | 0.0126 | [0.0123;0.013] | 1.4 |
| ADA+ on CL_{NAB-} (proportional) | 1.03 | 8 | 1.04 | [0.888;1.22] | 8.3 |
| NAB+ on CL_{NAB-} (proportional) | 1.28 | 3.8 | 1.29 | [1.2;1.39] | 4 |
| Q (L/h) | 0.0359 | 6.5 | 0.0356 | [0.0309;0.0401] | 6.3 |
| V_1 (L) | 2.89 | 0.7 | 2.89 | [2.85;2.93] | 0.7 |
| V_3 (L) | 2.06 | 2.2 | 2.06 | [1.97;2.15] | 2.3 |
| Allometric exponent on CL Q | 0.639 | 7.9 | 0.637 | [0.541;0.74] | 7.9 |
| Allometric exponent on V_1 V_3 | 0.606 | 6.3 | 0.608 | [0.536;0.682] | 6.2 |
| Effect of MTX on CL_{NAB-} (proportional) | 1.04 | 1.8 | 1.04 | [1;1.08] | 1.9 |
| Proportional error (CV%) | 35.3 | 1.8 | 35.3 | [34;36.5] | 1.8 |
| BSV CL (CV%) | 38.6 | 6 | 38.6 | [36.2;41.1] | 6 |
| BSV V_1 (CV%) | 23.7 | 9.8 | 23.6 | [21.4;26.1] | 10 |

Abbreviations: RSE = Relative Standard Error; n/a = not applicable; F = Bioavailability SC administration; K_A = Absorption rate constant from the SC depot compartment; CL_{NAB-} = Central CL with negative neutralizing antibody titer and no MTX co-administration; ADA+ = Proportional effect of positive anti-drug antibody titer on CL_{NAB-} ; NAB+ = Proportional effect of positive neutralizing antibody titer on CL_{NAB-} ; MTX = Proportional effect of methotrexate on CL_{NAB-} ; Q = Intercompartmental CL ; V_1 = Central volume of distribution; V_3 = Peripheral volume of distribution; BSV = Between-subject variability; CV = coefficient of variation.

Note: CV % of proportional error is calculate as $100 * \text{THETA}$, error is estimated as a THETA in run030; CV % of exponential ETAs is calculated as $100 * \sqrt{\exp(\text{OMEGA})-1}$ as it is estimated using FOCEI method in NONMEM

Effect of weight on predicted exposure

The population PK model indicated that clearance and volume of distribution of infliximab increase with increasing body weight. When a fixed dose dosing regimen (e.g. 120 mg SC Q2W, as proposed in treatment of RA) is used, subjects with high body weight will have decreased exposure to infliximab compared with subjects with low body weight.

Simulations investigating the impact of body weight (50 to 150 kg at 10 kg intervals) following administration of maintenance regimens 120 mg Q2W and 3 mg/kg Q8W were conducted using the PPK model. The predicted C_{trough} was approximately 7-fold to 17-fold higher following SC regimen compared with IV regimen (Figure 5). The steady state AUC over 8 weeks in the entire simulated population was comparable for the SC and IV dosing regimens (geometric mean ratio 0.97; 90% CI 0.96-0.98) but, as expected, subjects with low body weight had higher predicted AUC and subjects with high body weight had lower predicted AUC following 120 mg SC Q2W regimen (

Figure 6). As expected, the C_{max} was consistently lower following 120 mg SC Q2W dose regimen than following 3 mg/kg IV Q8W dose regimen, due to lower single dose, incomplete bioavailability, and delayed absorption.

Figure 5 - Summary Forest Plots of C_{trough} GMRs (90% CIs) for the Simulated 120 mg SC Q2W Maintenance Dosing Regimen vs 3 mg/kg IV Q8W Regimen by Weight Bands

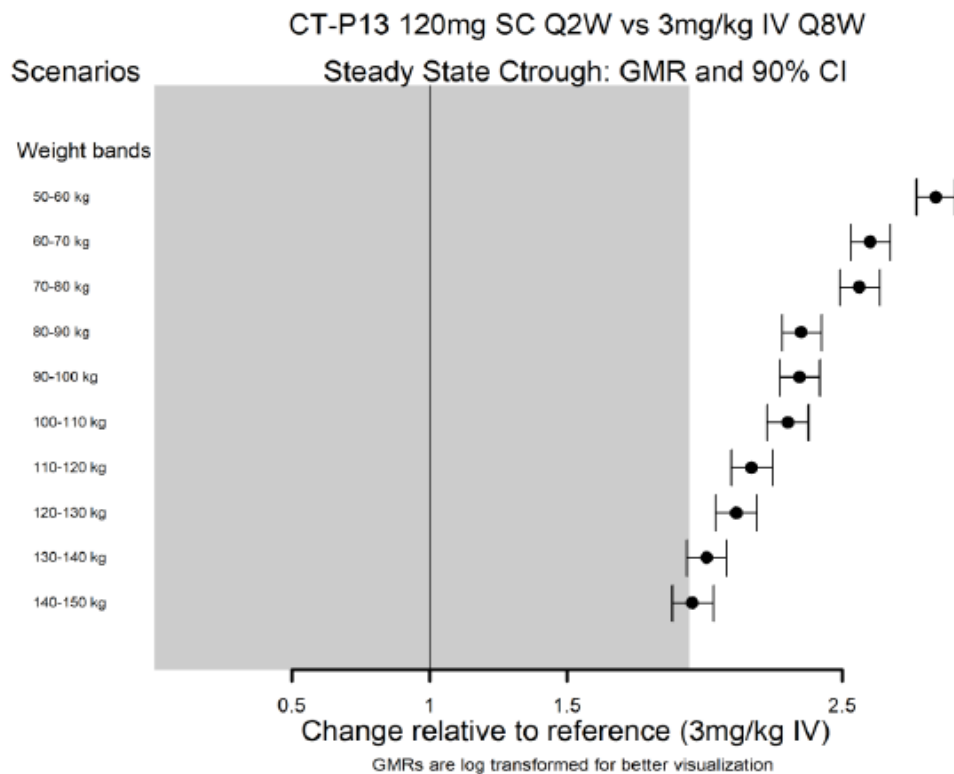
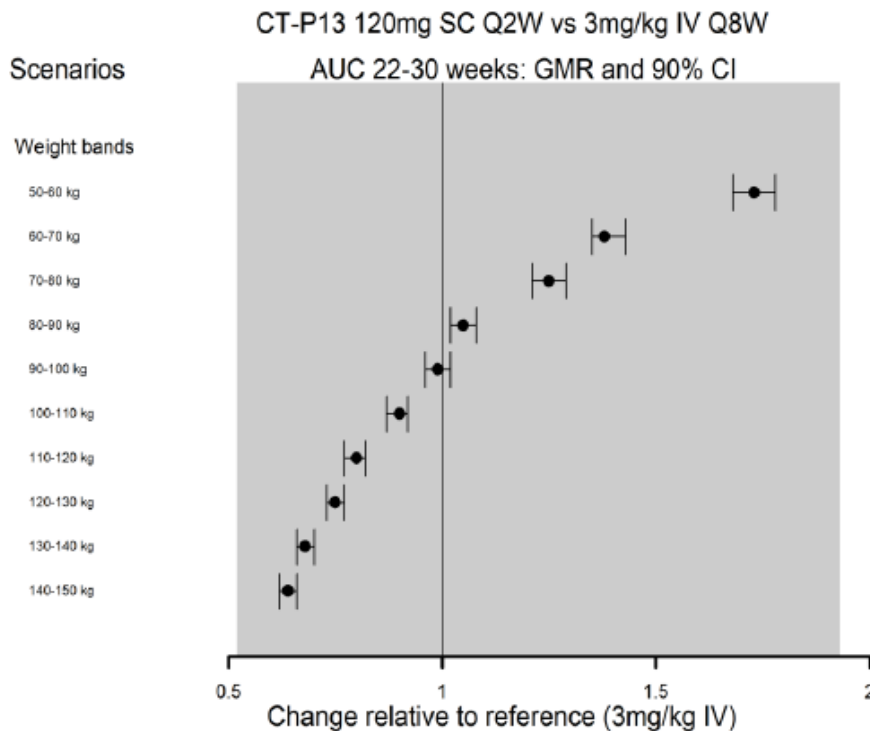


Figure 6 - Summary Forest Plots of AUC_{22-30wk} GMRs (90% CIs) for the Simulated 120 mg SC Q2W Maintenance Dosing Regimen vs 3 mg/kg IV Q8W Regimen by Weight Bands



Special populations

Clinical studies to investigate pharmacokinetics of Remsima SC in subjects with impaired renal or hepatic function, in elderly subjects and in paediatric population have not been carried out

The product information contains the appropriate warnings for these populations: no dose adjustment is required for elderly patients and no dose recommendations can be made for those with renal or hepatic impairment. Remsima is only recommended for use in adults.

Interactions

Drug-drug interaction studies have not been conducted for Remsima SC.

2.6.3. Pharmacodynamics

Mechanism of action

Infliximab is a known active substance. It is a chimeric human murine immunoglobulin G₁ (IgG₁) monoclonal antibody that binds with high affinity to both soluble and transmembrane forms of TNF- α . Remsima IV was developed and approved as an infliximab biosimilar. The current application concerns the SC formulation of Remsima. Remsima SC contains the same active ingredient infliximab as Remsima IV. No new clinical studies have been conducted to investigate the mechanism of action and primary and secondary pharmacology of infliximab.

Primary and Secondary pharmacology

According to the MAH, the primary, possibly sole, mechanism of action of infliximab therapy in all indications, namely RA, AS, PsA, Ps, CD, and UC, involves binding to and neutralisation of TNF α . The

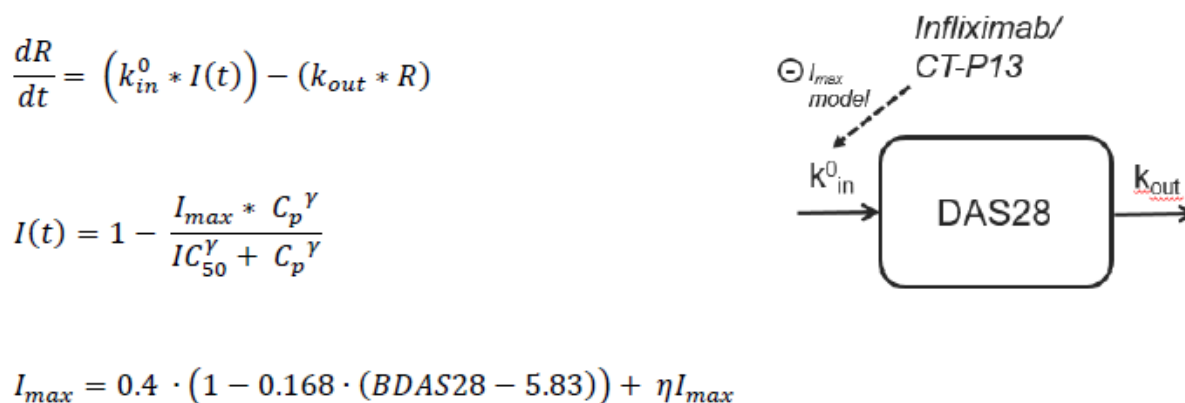
binding of soluble TNF α and inhibition of TNF α induced cytokine release from macrophages, T-cells and endothelial cells appears to be particularly important in mediating a therapeutic effect in RA, AS, PsA, and Ps; in inflammatory bowel disease (IBD), binding to transmembrane TNF α appears to be of high importance in mediating therapeutic effect through, it is generally thought, the stimulation of apoptosis by reverse signalling and induction of regulatory macrophages. Complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity are generally considered to be of no clinical relevance in any of the indications, including CD and UC.

A population PK-PD model for efficacy in RA was developed using the DAS28(CRP) score observed in clinical studies as the PD endpoint. Individual patient simulated plasma concentrations were obtained from the individual patient post-hoc PK parameter estimates from the final population PK model.

Exploratory analyses of the observed data indicated that maximum response was observed approximately between Week 14 and Week 22 after the first dose. Furthermore, the baseline DAS28 score appeared to be related to the maximum response so that patients with a higher baseline DAS28 score appeared to demonstrate a higher on-treatment DAS28 score in the presence of infliximab, in comparison with patients with lower baseline scores.

PK-PD model diagram is shown in Figure 7. Effect of infliximab was parameterized as an inhibitory I_{max} model to affect the zero-order rate constant of DAS28 score "production" (k_{in}). A covariate relationship between I_{max} and baseline DAS28 score (BDAS28) was incorporated into the structural model from the outset. Between-subject variability (BSV) was included on BDAS28 and I_{max} , implemented in the additive form. The unexplained residual error was, likewise, implemented in the additive form.

Figure 7 - Final RA PK-PD Model Equations and Model Diagram



k_{out} : First-order rate constant for loss of the response; k_{in}^0 (=BDAS28): Apparent zero-order rate constant for production of the response; I_{max} : Maximum fractional ability of the drug to affect BDAS28; IC_{50} : Is the drug concentration that produces 50% of maximum inhibition; BDAS28 on I_{max} : Is the effect of baseline DAS28 on I_{max} .
Note: 5.83 represents the median of the baseline DAS28 score

No statistically significant covariates were identified. Effect of concomitant medications could not be estimated because all but one patient used MTX and none of them used azathioprine or 6-mercaptopurine. The parameter estimates are summarized in

Table **10**. Model parameters were estimated with good precision, except for IC_{50} that had relative standard error of 83.7%. The results of the bootstrap analysis demonstrated minimal bias in the model parameters in comparison with the final model parameters estimates. Visual predictive check plots indicated that the model could sufficiently describe the observed changes in DAS28 score (Figure 8).

Table 10 - Model and Bootstrap Estimates for the Final RA PK-PD Model

| Parameter | Final parameter estimate | | Bootstrap results | | |
|--------------------------|--------------------------|---------|-------------------------|-----------------------|----------------------|
| | Typical value | RSE (%) | Estimate ^(a) | 95% CI ^(c) | % RSE ^(b) |
| k_{out} (h^{-1}) | 0.00147 | 11.5 | 0.00148 | [0.0012;0.00183] | 11 |
| BDAS28 | 5.82 | 0.5 | 5.82 | [5.76;5.88] | 0.5 |
| I_{max} | 0.4 | 3.4 | 0.401 | [0.378;0.426] | 3.1 |
| IC_{50} ($\mu g/mL$) | 0.0922 | 83.7 | 0.0913 | [0.00446;0.261] | 79 |
| BDAS28 on I_{max} | -0.168 | 14 | -0.169 | [-0.218;-0.124] | 14.1 |
| Additive residual error | 0.595 | 4 | 0.595 | [0.551;0.641] | 4 |
| BSV in BDAS28 (CV%) | 8.15 | 19 | 8.12 | [6.49;9.52] | 18.9 |
| BSV in I_{max} (CV%) | 41.7 | 6.1 | 41.6 | [39.3;44] | 5.8 |

Abbreviations: BSV = between-subject variability, CI = confidence interval; IC_{50} = drug concentration that produced 50% of maximum inhibition, I_{max} = maximum fractional ability of the drug to affect DAS28 response, BDAS28 = baseline DAS28 score, K_{out} = first-order rate constant for loss of the response, RSE = relative standard error; CV = coefficient of variation

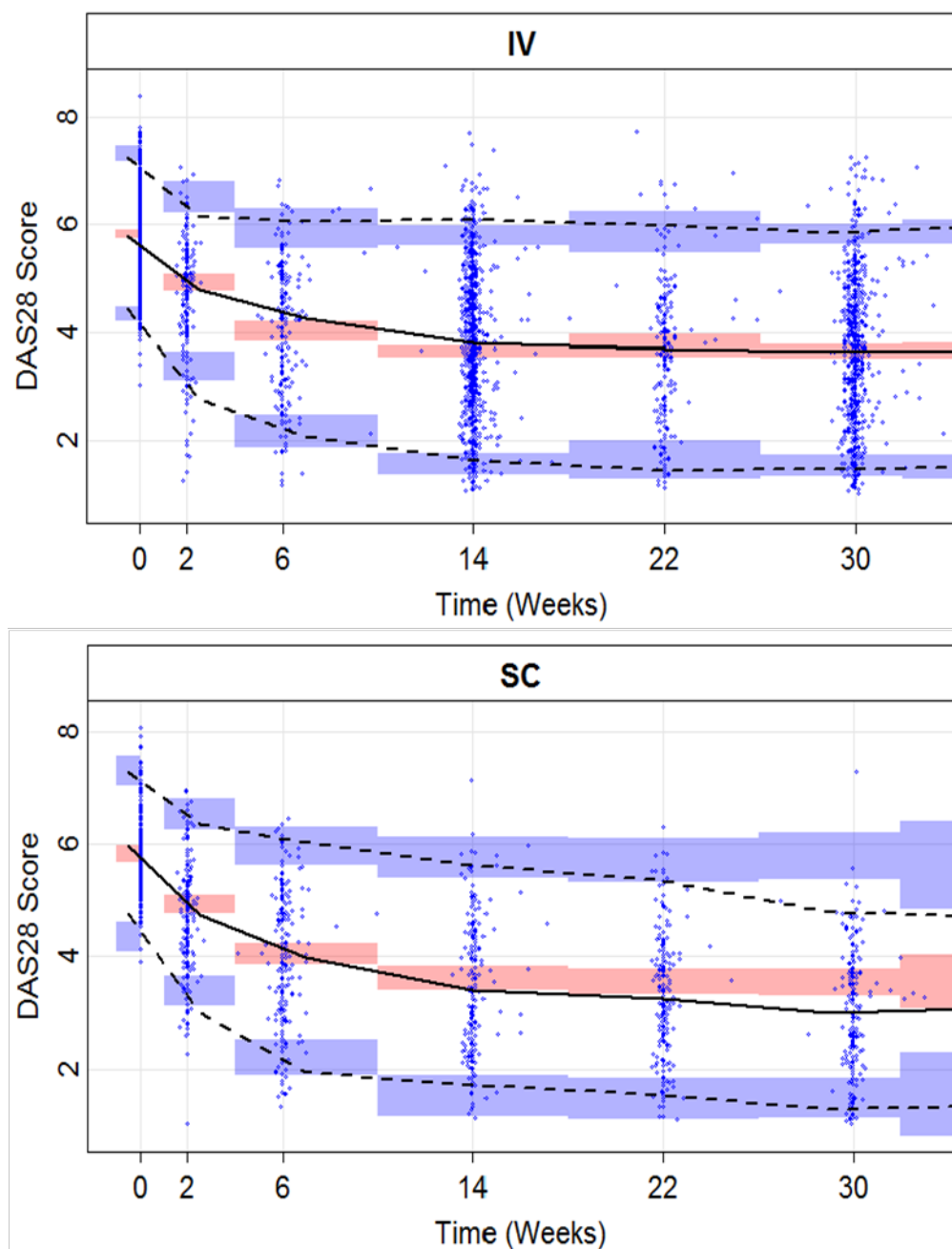
Note: Bootstrap datasets obtained by replicated with replacement from cel-pkpd-s31-35-20170921i.csv

^(a) % CV = SD / Mean Parameter Estimate

^(b) % RSE derived from bootstrap analysis according to the following equation: (standard error / mean) *100

^(c) 2.5th and 97.5th percentile confidence intervals obtained from the bootstrap analysis.

Figure 8 - Visual Predictive Check of Final RA PK-PD Model

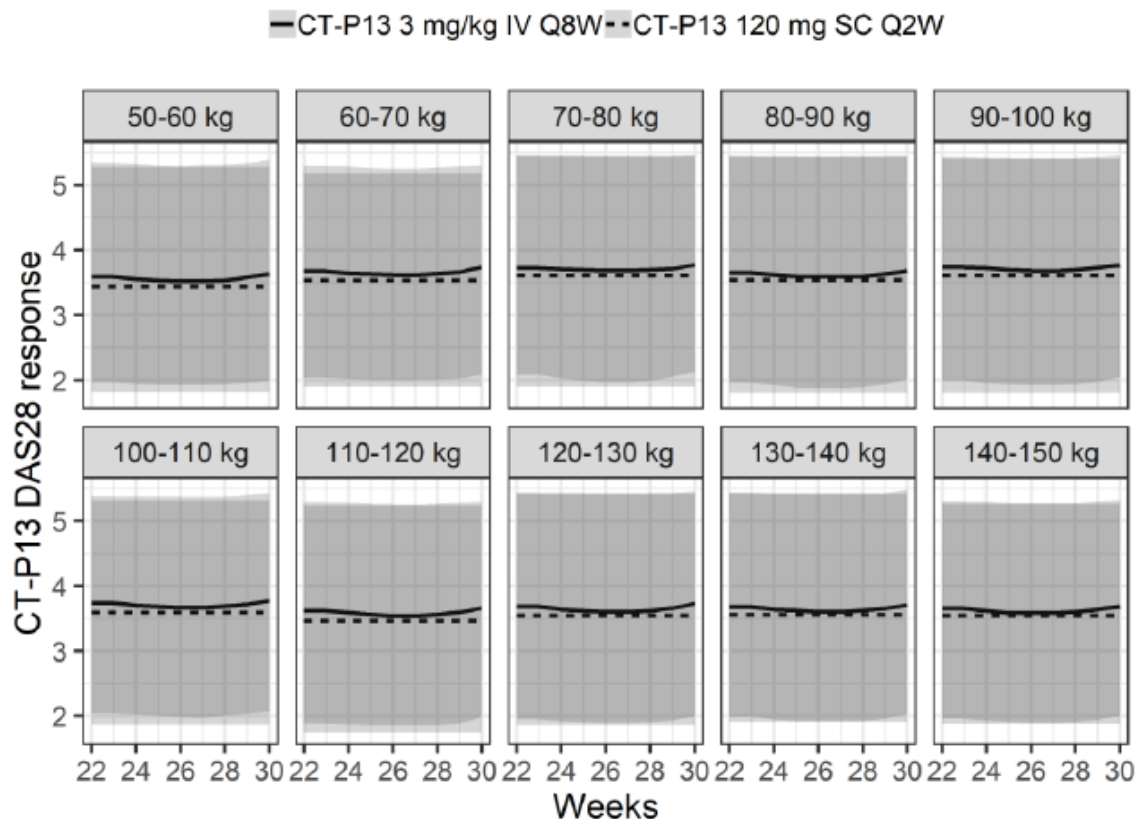


IV: intravenous; SC: subcutaneous

The PK model indicated that high body weight decreased exposure to infliximab. Therefore, simulations were performed to investigate the impact of the reduced exposure on the predicted DAS28 scores following administration of Remsima SC 120 mg Q2W and Remsima IV 3 mg/kg Q8W at steady state. The results are summarised in

Figure 9. The predicted DAS28 score was similar following SC and IV dosing regimens in all weight categories.

Figure 9 - Mean (\pm 90% PI) Simulated Steady State DAS28 vs Time Profiles for the Simulated 120 mg SC Q2W Maintenance Dosing Regimen with Overlaid 3 mg/kg IV Q8W Maintenance Reference Treatment by Weight-Bands



Notes: solid line = 3 mg/kg IV Q8W IV reference regimen; dashed line = 120 mg SC Q2W test regimen. Shaded areas represent 90% prediction intervals.

Abbreviations: PI = prediction interval

2.6.4. Discussion on clinical pharmacology

Single dose and multiple dose studies with dense PK sampling indicated that exposure to infliximab following SC injection increased approximately linearly with increasing dose over dose range 90 mg to 240 mg. The number of subjects in these parallel-group studies was small (approximately 10 subjects in each dose cohort). Due to limited observed data it is believed that the most reliable estimates of steady state C_{max} and AUC_T are obtained with simulations using the population PK model.

Observed steady state PK data from study CT-P13 3.5 Part 2 indicated that median C_{trough} level in Remsima SC 120 mg Q2W cohort (N=154) was 11.65 $\mu\text{g/mL}$, i.e. approximately 11-fold higher than the target C_{trough} ($>1 \mu\text{g/mL}$). The proportion of patients that achieved the target C_{trough} in Remsima SC cohort was 81.8% (126/154). PPK model predicted mean AUC over 8 weeks at steady state (AUC_{ss8W}) was approximately 1.5 times higher with Remsima SC 120 mg Q2W than for Remsima 3 mg/kg IV Q8W. The observed mean AUC_{ss8W} for Remsima SC 120 mg Q2W was approximately 2.2 times higher than the mean AUC_{ss8W} for Remsima 3 mg/kg IV Q8W in a small number of RA patients (N=11 and N=13, respectively) in study CT-P13 3.5 Part 1.

It was demonstrated in a clinical comparative PK study (CT-P13 1.9) that PK of infliximab is similar following SC injection using the pre-filled syringe and the autoinjector device.

Population PK (PPK) models were developed to describe the PK of infliximab following SC or IV administration. Overall, no major deficiencies were found in the most recent model. Some clarifications were requested, e.g. on data handling and alternative model structure and satisfactory responses to all questions were provided. It seems likely that parameterisation of the effects of ADA and NAB on clearance is not optimal, and the bioanalytical methods used for measurement of ADA and NAB could be improved. Nevertheless, the model was considered sufficient for the intended use.

Simulations investigating the impact of body weight (50 to 150 kg at 10 kg intervals) following administration of maintenance regimens 120 mg SC Q2W and 3 mg/kg IV Q8W were conducted using the PPK model. Because the proposed Remsima SC dose is the same for all patients irrespective of body weight whereas Remsima IV dose is based on body weight, overexposure in terms of AUC is predicted in patients with low weight whereas patients weighing >100 kg are predicted to be slightly underexposed in terms of AUC. In the overall virtual population, the predicted steady state AUC over 8 weeks was comparable for SC and IV dosing regimens. However, obese subjects were probably overrepresented in the virtual population, and it is expected that in typical RA patients the 120 mg SC Q2W regimen leads to slightly higher overall exposure compared with the 3 mg/kg IV Q8W regimen. Because the plasma concentration time curve has less fluctuation following the 120 mg SC Q2W regimen than following the approved 3 mg/kg IV Q8W regimen, the SC curve is fully contained (several folds lower C_{max} and several folds higher C_{trough}) within the IV curve in all RA patients irrespective of body weight. Regarding efficacy, the higher C_{trough} seen following SC administration supports the demonstrated clinical non-inferiority under the assumption that the currently approved IV dose is at an anticipated near maximal efficacy. Regarding safety, the C_{max} will be lower following the proposed SC dosing regimen, and the total exposure (AUC over 8 weeks) will be higher in most patients and slightly lower in patients with high body weight. PK data cannot address local safety.

The observed C_{trough} levels from study CT-P13 3.5 Part 2 indicate that the target C_{trough} (>1 µg/mL) is achieved in majority of patients with RA following maintenance dosing regimen Remsima SC 120 mg SC Q2W.

There is insufficient information regarding the switching of patients who received the intravenous infusions of infliximab higher than 3 mg/kg every 8 weeks to the subcutaneous formulation of Remsima which is reflected in the product information.

Clinical studies to investigate pharmacokinetics of Remsima SC in subjects with impaired renal or hepatic function, in elderly subjects and in paediatric population have not been carried out, and drug-drug interaction studies have not been conducted for Remsima SC. These studies are not considered to be necessary taking into account experience with intravenously administered infliximab. Studies in paediatric population are not required for the current application because marketing authorisation for Remsima SC is only applied for adult subjects. PPK analysis indicated that race and gender do not significantly affect the PK after the effect of body weight is accounted for. Adequate information on PK in special populations and on drug-drug interactions is provided in the product information.

New clinical studies have not been conducted to investigate the mechanism of action and primary and secondary pharmacology of infliximab. Such studies are not required because infliximab is considered to be a known active substance.

Remsima SC may be given in the upper arm, thigh or abdomen. The MAH provided additional analyses demonstrating that the total exposure (AUC) is comparable following SC injection in the three sites. A trend for slightly lower C_{trough} following SC injection in the upper arm was observed, but it was clinically not meaningful.

A population PK-PD model for efficacy in RA was developed using the DAS28(CRP) score observed in clinical studies as the PD endpoint. Effect of infliximab was parameterized as an inhibitory I_{\max} model to affect the zero-order rate constant of DAS28 score "production" (k_{in}) and the effect of baseline DAS28 score on I_{\max} was implemented in the model. The model adequately described the observed data. Simulations indicated that adequate DAS28 response is expected also for obese patients with RA, even if they have decreased exposure to infliximab.

2.6.5. Conclusions on clinical pharmacology

No major deficiencies in the clinical pharmacology sections of the dossier were found. Some methodological uncertainties remain related to the sensitivity and drug tolerance of the Nab assay, particularly to analyzing the lipemic samples from RA patients.

However, even if some of the NAb went undetected due to higher drug concentrations and low sensitivity to detect low titres of Nabs, it can be concluded that the formation of NAb was not greater with the SC formulation.

As expected, exposure in terms of C_{\max} , C_{trough} and AUC is not identical following administration of Remsima SC and Remsima IV. C_{\max} levels are several folds lower and C_{trough} levels are several folds higher following the proposed SC dosing regimens, compared with the approved IV dosing regimens. Mean AUC levels over 8-week dosing are predicted to be slightly higher following the proposed SC dosing regimens, depending on the patient's body weight. The potential significance of these differences on clinical efficacy and safety is discussed in the next sections.

2.7. Clinical efficacy

Clinical efficacy has been evaluated in two randomised studies. One Phase I/III in patients with rheumatoid arthritis (RA; study CT-P13 3.5) and one Phase I study in patients with Crohn's disease (CD) (study CT-P13 1.6). The studies are summarised in Table 3.

The pivotal study regarding efficacy for this application is Part 2 of Study CT-P13 3.5 evaluating PK, efficacy and safety of Remsima SC in RA patients.

Supporting data on clinical efficacy comes from Part 1 of Study CT-P13 3.5 (dose finding study in RA patients) and Part 1 of Study CT-P13 1.6 (dose finding study in CD patients). The results from Part 2 of Study CT-P13 1.6 (in CD and UC patients) were not included in this submission.

2.7.1. Dose-response studies

In RA patients: CT-P13 3.5 Part 1

Objectives

- Primary objective: To find the optimal dose of Remsima SC over the first 30 weeks as determined by the area under the concentration-time curve (AUC_T) at steady state between Week 22 and Week 30
- Secondary objective: To evaluate efficacy, PK, pharmacodynamics (PD), and overall safety of Remsima SC in comparison with Remsima IV up to Week 54

Overall Design (including randomization)

Study CT-P13 3.5 Part 1 was an open-label, randomized, multicenter, parallel group study designed to evaluate PK, PD, efficacy and safety between Remsima SC and Remsima IV when co-administered with methotrexate (MTX) and folic acid in patients with active RA.

Patients could also be pre-medicated 30 to 60 minutes prior to the start of study drug administration; any pre-medications such as but not limited to antihistamine, hydrocortisone, paracetamol, and/or non-sedating antihistamine could be given at the investigator's discretion.

There was no masking of study treatments in Part 1 of study CT-P13 3.5 and hence, this part of the study was open-label.

There were up to 3 periods including end-of-study (EOS) visit:

- Screening: Days -21 to -1, prior to the first administration of the study drug
- Treatment period: included 1) Dose-Loading phase: from Week 0 to Week 6 and 2) Maintenance phase: from Week 6 to Week 54
- End of Study: 8 weeks after the last dose was received, either at the end of the maintenance phase or earlier if the patient withdrew from the study

During the Dose-loading phase, all enrolled patients initially received a 2-hour CT-P13 IV infusion at Weeks 0 and 2. Patients who received 2 full doses and for whom there were no safety concerns based on the investigator's discretion were randomly assigned to receive either Remsima SC or Remsima IV before treatment on Day 42, Week 6.

The Maintenance phase of the study consisted of further doses of study drug with the last dose administered no later than Week 54:

- IV 3 mg/kg cohort (Cohort 1): further 7 doses of Remsima IV were administered at Week 6 and every 8 weeks thereafter (Weeks 14, 22, 30, 38, 46, and 54).
- SC 90 mg, SC 120 mg and SC 180 mg cohorts (Cohorts 2, 3, and 4): the first Remsima SC was administered by prefilled syringe (PFS) at Week 6. Further SC injections were given every 2 weeks up to Week 54.

Remsima SC via PFS was injected at a slow, steady rate at the front of the middle thighs, or the abdomen (except for the 5 cm area right around the navel), or the outer area of the upper arms (except for self-injection). For each new injection, a different injection site was used (i.e., injection site was rotated).

After dose finding evaluation, the SC 120 mg every 2 weeks was recommended as the optimal dose by Data Safety Monitoring Board. The initially assigned dose could be adjusted to the SC 120 mg every 2 weeks after Week 30 in applicable patients from SC 90 mg (Cohort 2) and SC 180 mg (Cohort 4) cohorts.

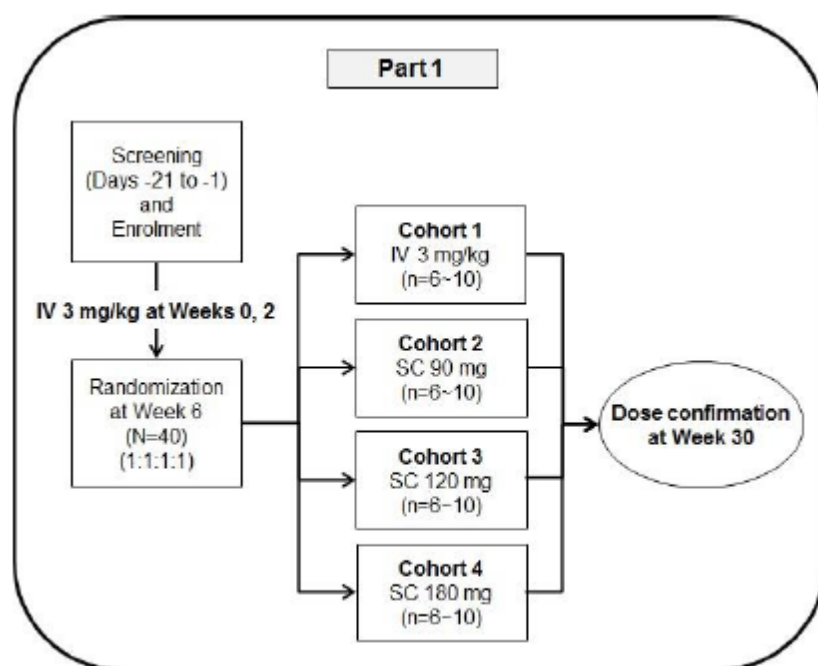
Patient assessment overview and Study schematic are presented in the figures below.

Figure 10 - Patient Assessment Overview for Study CT-P13 3.5 Part 1

| | Dose-loading | | Maintenance ¹ | | | | | | | | | | | | | | | |
|--------------------------------------|--------------|---|--------------------------|----------------|----------------|----|----|----|----|----------------|----|----------------|----|----------------|----|----|----|----|
| Week | 0 | 2 | 6 | 8 | 10 | 14 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 38 | 46 | 54 |
| Visit ² | X | X | X | X ³ | X ³ | X | X | X | X | X ³ | X | X ³ | X | X ³ | X | X | X | X |
| Evaluation | | | | | | | | | | | | | | | | | | |
| Primary Pharmacokinetic ⁴ | | | | | | | | | | | | | | | | | | |
| Efficacy | X | X | X | | | X | X | | | | | | | | X | | | X |
| Pharmacokinetic | | | | | | | | | | | | | | | | | | |
| Pharmacodynamic | X | X | X | | | X | X | | | | | | | | X | X | X | X |
| Safety Evaluation | | | | | | | | | | | | | | | | | | |

1. Additional visits only were made by patients who need extra training for CT-P13 SC injection.
2. A visit window of ± 3 days was allowed up to and including Week 30; a visit window of ± 5 days was allowed thereafter, including the End-of-Study Visit.
3. Only patients from SC 90 mg, SC 120 mg and SC 180 mg cohorts made visits for additional pharmacokinetic assessment.
4. Visit window for primary PK assessment was allowed according to [Section 9.5.1.1](#).

Figure 11 - Overall Study Design of Study CT-P13 3.5 Part 1



Abbreviations: IV, intravenous; SC, subcutaneous.

Number of Patients Analysed and definitions of Study Populations

The different populations were on a high level defined as follows:

- The ITT population consisted of all enrolled patients
- The all-randomized population consisted of all randomly assigned patients at Week 6, regardless of whether or not any study drug dosing was completed

- The PK population consisted of the all-randomized population who received at least one full dose of study drug at Week 6 or thereafter and who had at least one PK concentration result after Week 6 treatment
- The PD population consisted of the all-randomized population who received at least one full dose of study drug at Week 6 or thereafter and who had at least one PD result after Week 6 treatment
- The efficacy population consisted of the all-randomized population who received at least one full dose of study drug at Week 6 or thereafter and who had at least one efficacy evaluation result after Week 6 treatment
- The safety population consisted of all patients who received at least 1 dose (full or partial) of study drug (Remsima SC or Remsima IV) at Week 6 or thereafter

The following table summarizes the number of patients in each population.

Table 11 - The Number of Patients in Each Population in Study CT-P13 3.5 Part 1

| | IV 3 mg/kg | SC 90 mg | SC 120 mg | SC 180 mg | Total |
|----------------------------|------------|----------|-----------|-----------|-------|
| Intent-to-treat population | | | | | 50 |
| All-randomized population | 13 | 11 | 12 | 12 | 48 |
| Pharmacokinetic population | 13 | 11 | 12 | 12 | 48 |
| Pharmacodynamic population | 13 | 11 | 12 | 12 | 48 |
| Efficacy population | 13 | 11 | 12 | 12 | 48 |
| Safety population | 13 | 11 | 12 | 12 | 48 |

Note. The randomized treatment at Week 6 were used for all-randomized population. The actual treatment were used for PK, PD, Efficacy and Safety Population.

Main criteria for inclusion

- Male or female patients aged 18 to 75 years old with a Diagnosis of RA according to the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for at least 6 months prior to the first administration of the study drug (Day 0).
- Patients had to have active disease as defined by the presence of 6 or more swollen joints (of 28 assessed), 6 or more tender joints (of 28 assessed), and a serum CRP concentration >0.6 mg/dL at screening
- Patients had to have completed at least 3 months of treatment of oral or parenteral dosing with MTX between 12.5 to 25 mg/week and be on stable dosing with MTX for at least 4 weeks prior to the first administration of the study drug
- Patients also had to have adequate renal and hepatic function at screening as well as haematology laboratory test results at screening within pre-specified limits and use contraception.

Endpoints

- **Primary endpoint** was the AUC_T(SC) and AUC_T(IV) at steady state between Week 22 and Week 30, calculated using the linear trapezoidal rule. There were also a number of secondary PK-endpoints.
- **Secondary efficacy endpoints** were assessed up to Week 54: Individual components of the DAS28, DAS28(CRP) and DAS28(ESR), Individual components of the ACR, ACR20/50/70

response, Hybrid ACR response, EULAR response criteria, Simplified disease activity index (SDAI) and clinical disease activity index (CDAI) and Health assessment questionnaire (HAQ).

- **Secondary PD endpoints** were assessed up to Week 54: Rheumatoid factor (RF), Anti-cyclic citrullinated peptide (anti-CCP), CRP and ESR.
- **Secondary safety endpoints** included assessment of immunogenicity and AEs of special interest (AESIs): Delayed hypersensitivity, localised injection site reactions (ISRs), Infections, Malignancies and Infusion-related reactions (IRRs) (for IV infusion)/systemic injection reaction (SIR) (for SC injection)/hypersensitivity/anaphylactic reactions (administration-related reaction [ARR]). The last group of AESIs (referred to as ARR throughout the CSR) were all AEs related to IRRs (for IV infusion)/systemic injection reaction (SIR) (for SC injection)/hypersensitivity/anaphylactic reactions that occurred within 24 hours after study drug administration, including but not limited to: dyspnea, wheezing, bronchospasm, stridor, reduced peak expiratory flow, hypoxemia, laryngeal irritation, throat irritation, hypotonia (collapse), syncope, incontinence, dizziness, vascular headache, generalized urticaria, rash, itch, flushing, swollen lips, swollen tongue, swollen uvula, angioedema, crampy abdominal pain, nausea, vomiting, hypotension, hypertension, tachycardia, bradycardia, palpitation, arthralgia, myalgia, pyrexia (fever).

Sample size, randomisation and statistical methods

No formal sample size estimation was performed because no confirmatory analysis was planned in the study. Approximately 24 to 40 patients (6 to 10 patients per cohort) were considered to be sufficient to investigate the primary pharmacokinetic objective.

Patients who had received two full doses of CT-P13 IV at Weeks 0 and 2 without any safety concern were randomly assigned at Week 6 in a 1:1:1:1 ratio into four study cohorts. Randomisation was stratified by country, Week 2 serum CRP concentration (≤ 0.6 mg/dL vs > 0.6 mg/dL), and Week 6 body weight (≤ 70 kg vs > 70 kg). In addition, all patients in SC cohorts (Cohorts 2, 3 and 4) were randomly assigned by IWRS at Week 14 in a 1:1 ratio to either Group A or B to collect blood samples in the PK monitoring visit period; Group A (Cohorts 2A, 3A and 4A): frequent PK sampling at Weeks 22 and 26, Group B (Cohorts 2B, 3B and 4B): frequent PK sampling at Weeks 24 and 28.

Pharmacokinetic Analyses: All PK analyses were performed on the PK population. PK parameters were computed by non-compartmental methods.

Efficacy Analyses: All efficacy analyses were performed on the efficacy population. The efficacy parameters were summarized using descriptive statistics.

PD Analyses: All PD analyses were performed on the PD population. Actual values and changes from baseline in RF, anti-CCP, CRP, and ESR, along with descriptive statistics, were presented by cohorts.

Safety Analyses: All safety data analyses were conducted for the safety population. Analyses were performed on the observed cases with the safety data listed and summarized by cohort as appropriate.

Conduct of the study

There was a total of 17 amendments (including 4 global amendments with major amendments and 13 minor amendments) during the course of the study. The global amendments included:

- Deletion of primary PK objective for Part 2 as per the CHMP's comment that mean change from baseline in DAS28 (CRP) at Week 22 was an adequate and sensitive endpoint, and therefore DAS28 (CRP) would only be considered as primary endpoint for **Part 2**
- Update of the study design for **Part 2** including double-blind and double-dummy design.

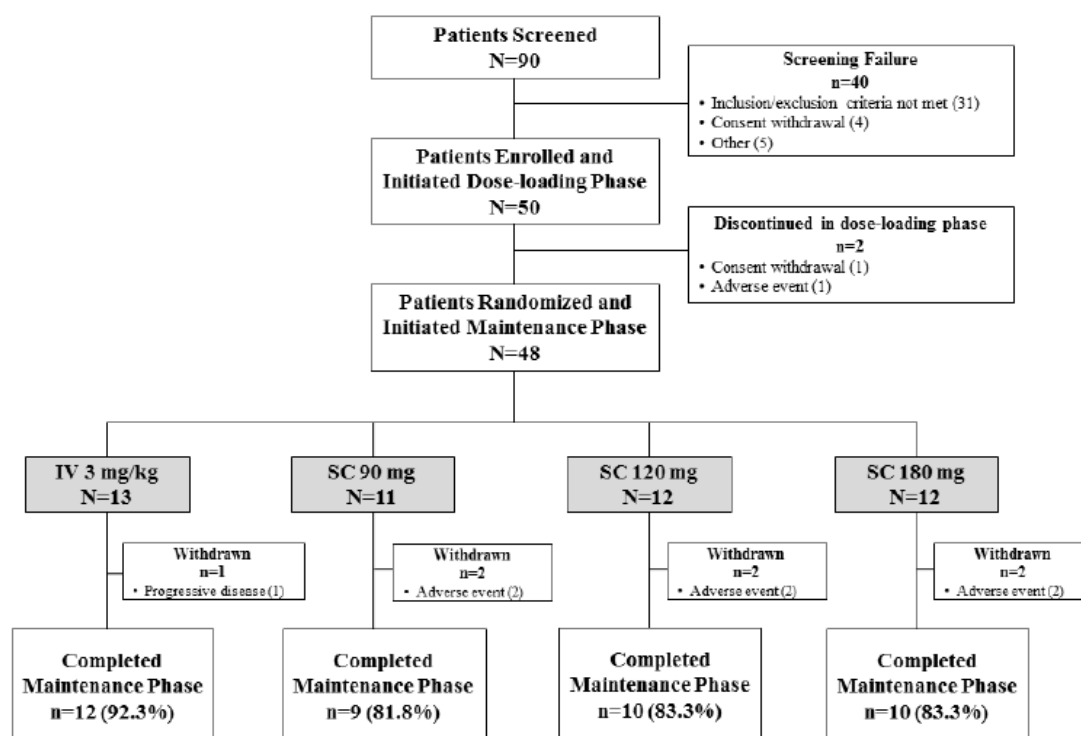
- Addition of breaking the blind for **Part 2** as per the updated design (double-blind).
- Update of the statistical analysis plan as per the updated design.
- Revision of the posology for **Part 2** from 'every 4 weeks' to 'every 2 weeks' as per the result of interim PK-PD modeling analysis.
- Modification of the time point of EOS visit from '8 weeks from the last dose was received' to '2 weeks from the last dose was received' considering administration of CT-P13 SC.
- Changed vocabularies in the description about the selection of study population for **Part 2**.
- 'infusion-related reactions' were revised to 'administration-related reactions' since the study included SC injections.

Some amendments related only to Part 2 of the study CT P13 3.5; this is highlighted in **bold** above.

Patient disposition / participant flow

Patient disposition is summarized for the all-randomized population in the figure below.

Figure 12 - Patient Disposition in of Study CT-P13 3.5 Part 1: All-Randomized Population



Abbreviation: IV, intravenous; SC, subcutaneous

Demographic Characteristics

The randomized subjects were mostly Caucasian (95.8%) and female (79.2%). Overall mean (SD) age and body weight at screening were 49.2 (11.9) years and 70.2 (14.9) kg. The total mean (SD) score for the RA classification criteria was 9.2 (1.24) and the mean (SD) dose of MTX taken was 18.80 (4.754) mg/week. All patients took MTX during the study; all but one patient took MTX as per study design and requirements (this patient did not meet inclusion criteria regarding MTX). Baseline characteristics were balanced among the 4 cohorts.

PK results

Please refer to the section "Pharmacokinetics" for the summary and assessment of PK results. The MAH states that Remsima 120 mg by SC injection every 2 weeks was determined as the optimal dose in RA patients.

Clinical efficacy and safety results

Mean (SD) for Actual Values and Change from Baseline of DAS28(CRP) and proportion of patients achieving Clinical Response According to the ACR Criteria are presented in the following tables. Please refer to section "Clinical safety" for the safety results.

Table 12 - Baseline Value and Mean Change from Baseline of DAS28 (CRP) in Study CT-P13
3.5 Part 1: Efficacy Population

| Visit Statistics | CT-P13 IV 3 mg/kg (N=13) | | CT-P13 SC 90 mg (N=11) | | CT-P13 SC 120 mg (N=12) | | CT-P13 SC 180 mg (N=12) | |
|---------------------|--------------------------------|----------------------|------------------------------|----------------------|-------------------------------|----------------------|-------------------------------|----------------------|
| | Actual Result | Change from Baseline | Actual Result | Change from Baseline | Actual Result | Change from Baseline | Actual Result | Change from Baseline |
| Baseline | | | | | | | | |
| n | 13 | - | 11 | - | 12 | - | 12 | - |
| Mean (SD) | 5.4 (0.78) | - | 6.3 (0.82) | - | 5.7 (0.91) | - | 5.5 (0.82) | - |
| Week 6 ¹ | | | | | | | | |
| n | 13 | 13 | 11 | 11 | 12 | 12 | 11 | 11 |
| Mean (SD) | 3.9 (1.48) | -1.5 (0.93) | 4.6 (1.07) | -1.7 (0.71) | 3.9 (1.19) | -1.8 (0.84) | 3.4 (1.18) | -2.0 (0.96) |
| Week 22 | | | | | | | | |
| n | 13 | 13 | 10 | 10 | 11 | 11 | 12 | 12 |
| Mean (SD) | 3.9 (1.62) | -1.5 (1.32) | 3.7 (1.04) | -2.5 (0.85) | 3.3 (1.41) | -2.4 (1.24) | 2.8 (1.33) | -2.7 (0.88) |
| Week 30 | | | | | | | | |
| n | 13 | 13 | 10 | 10 | 10 | 10 | 12 | 12 |
| Mean (SD) | 3.3 (1.25) | -2.1 (0.85) | 3.0 (1.14) | -3.2 (1.24) | 3.1 (1.01) | -2.6 (0.97) | 2.7 (0.97) | -2.8 (0.56) |
| Week 54 | | | | | | | | |
| n | 12 | 12 | 8 | 8 | 10 | 10 | 10 | 10 |
| Mean (SD) | 3.5 (1.19) | -2.0 (1.08) | 3.0 (1.02) | -3.1 (0.74) | 3.2 (0.97) | -2.5 (1.40) | 2.9 (0.99) | -2.5 (0.93) |

¹ Results at Week 6 were obtained following 2 IV infusions in the Dose-Loading Phase.

CRP: C-reactive protein, DAS28: Disease activity score in 28 joints, IV: Intravenous, SC: Subcutaneous, SD: Standard deviation

Table 13 - Proportions of Patients Achieving Clinical Response According to the ACR Criteria in Study CT-P13 3.5 Part 1: Efficacy Population

| Parameter | IV 3 mg/kg (N=13) | SC 90 mg (N=11) | SC 120 mg (N=12) | SC 180 mg (N=12) |
|-----------|------------------------|--------------------|---------------------|---------------------|
| Visit | Number (%) of patients | | | |
| ACR20 | | | | |
| Week 2 | 4 (30.8) | 3 (27.3) | 4 (33.3) | 6 (50.0) |
| Week 6 | 8 (61.5) | 8 (72.7) | 7 (58.3) | 7 (58.3) |
| Week 14 | 10 (76.9) | 8 (72.7) | 8 (66.7) | 11 (91.7) |
| Week 22 | 8 (61.5) | 8 (72.7) | 9 (75.0) | 11 (91.7) |
| Week 30 | 11 (84.6) | 10 (90.9) | 10 (83.3) | 12 (100.0) |
| Week 54 | 9 (69.2) | 9 (81.8) | 8 (66.7) | 10 (83.3) |
| ACR50 | | | | |
| Week 2 | 2 (15.4) | 2 (18.2) | 0 | 2 (16.7) |
| Week 6 | 5 (38.5) | 1 (9.1) | 0 | 4 (33.3) |
| Week 14 | 6 (46.2) | 4 (36.4) | 3 (25.0) | 7 (58.3) |
| Week 22 | 5 (38.5) | 5 (45.5) | 6 (50.0) | 8 (66.7) |
| Week 30 | 10 (76.9) | 6 (54.5) | 4 (33.3) | 10 (83.3) |
| Week 54 | 6 (46.2) | 7 (63.6) | 5 (41.7) | 9 (75.0) |
| ACR70 | | | | |
| Week 2 | 1 (7.7) | 1 (9.1) | 0 | 1 (8.3) |
| Week 6 | 4 (30.8) | 0 | 0 | 1 (8.3) |
| Week 14 | 4 (30.8) | 1 (9.1) | 1 (8.3) | 5 (41.7) |
| Week 22 | 4 (30.8) | 2 (18.2) | 2 (16.7) | 7 (58.3) |
| Week 30 | 4 (30.8) | 4 (36.4) | 2 (16.7) | 5 (41.7) |
| Week 54 | 4 (30.8) | 3 (27.3) | 2 (16.7) | 6 (50.0) |

Abbreviations: ACR, American College of Rheumatology; ACR20, ACR 20% improvement criteria; ACR50, ACR 50% improvement criteria; ACR70, ACR 70% improvement criteria; IV, intravenous; SC, subcutaneous.

In CD patients: CT-P13 1.6 Part 1

Objectives

- Primary objective: To find the optimal dose of Remsima SC over the first 30 weeks as determined by the area under the concentration-time curve (AUC_T) at steady state between Week 22 and Week 30
- Secondary objectives: To evaluate efficacy, PK, pharmacodynamics (PD), and overall safety of Remsima SC in comparison with Remsima IV up to Week 54

Overall Design (including randomization)

Study CT-P13 1.6 Part 1 was an open-label, randomized, multicenter, parallel-group, Phase I study designed to evaluate PK, efficacy, PD, and safety between Remsima SC and Remsima IV in patients with active Crohn's disease (CD).

Patients could be pre-medicated 30 to 60 minutes prior to the start of study drug administration; antihistamine, hydrocortisone, paracetamol, and/or non-sedating antihistamine could be given at the investigator's discretion.

There were up to 3 periods including End-of-Study (EOS) visit in Part 1:

- Screening: Days -21 to -1, prior to the first administration of the study drug
- Treatment Period included 1) Dose-Loading phase: from Week 0 to Week 6, and 2) Maintenance phase: from Week 6 to Week 54
- End-of-Study: EOS; 8 weeks after the last dose was received

During the Dose-loading phase, all enrolled patients initially received a 2-hour Remsima IV infusion at Weeks 0 and 2. Patients who received 2 full doses and for whom there were no safety concerns based on the investigator's discretion were randomly assigned to receive either Remsima SC or Remsima IV before treatment on Day 42, Week 6.

The Maintenance phase of the study consisted of further doses of study drug with the last dose administered no later than Week 54:

- Intravenous 5 mg/kg cohort (Cohort 1): further 7 doses of Remsima IV were administered at Week 6 and every 8 weeks thereafter (Weeks 14, 22, 30, 38, 46, and 54)
- Subcutaneous 120 mg, 180 mg, and 240 mg (Cohorts 2, 3, and 4): first Remsima SC was administered by prefilled syringe (PFS) at Week 6. Further SC injections were given every 2 weeks up to Week 54.

After dose finding evaluation, the SC 120 mg every other week in patients less than 80kg in weight, and 240 mg every other week in patients at or above 80kg were recommended as the optimal dose by Data Safety Monitoring Board. The initially assigned dose could be adjusted after Week 30 in applicable patients from SC 120 mg (Cohort 2), SC 180 mg (Cohort 3), and SC 240 mg (Cohort 4). Further SC injections with the optimal dose were given up to Week 54.

Dose escalation up to 10 mg/kg was allowed for patients from Cohort 1 since Week 30 if the patient initially responded but then lost response at each visit.

Patient assessment overview and Study schematic are presented in the figures below.

Figure 13 Patient Assessment Overview in Study CT-P13 1.6 Part 1

| | Dose-loading | | | | | | Maintenance ¹ | | | | | | | | | | | |
|--------------------------------------|--------------|---|---|----------------|----------------|----|--------------------------|----|----|----------------|----|----------------|----|----------------|----|----|----|----|
| Week | 0 | 2 | 6 | 8 | 10 | 14 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 38 | 46 | 54 |
| Visit ² | X | X | X | X ³ | X ³ | X | X | X | X | X ³ | X | X ³ | X | X ³ | X | X | X | X |
| Evaluation | | | | | | | | | | | | | | | | | | |
| Primary Pharmacokinetic ⁴ | | | | | | | | | | | | | | | | | | |
| Efficacy | X | X | X | | | X | X | | | | | | | | X | | | X |
| Pharmacokinetic | | | | | | | | | | | | | | | | | | |
| Pharmacodynamic | X | X | X | | | X | X | | | | | | | | X | | | X |
| Safety Evaluation | | | | | | | | | | | | | | | | | | |

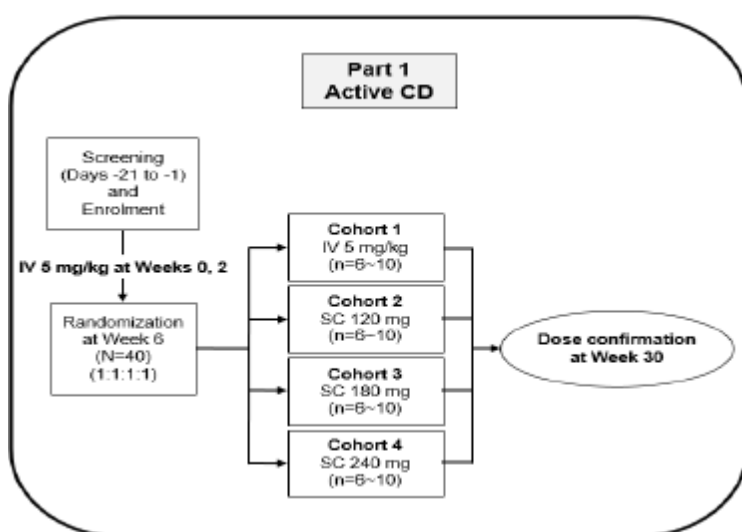
1. Additional visits were only made by patients who needed extra training for CT-P13 SC injection.

2. A visit window of ± 3 days was allowed up to and including Week 30; a visit window of ± 5 days was allowed thereafter, including the End-of-Study visit.

3. Only patients from Cohorts 2, 3, and 4 made visits for additional pharmacokinetic assessment.

4. Visit window for primary pharmacokinetic assessment was allowed according to [Table 9-4](#).

Figure 14 - Overall Study Design of Study Schematic CT-P13 1.6 Part 1



Number of Patients Analysed and definitions of Study Populations

For a high level definition of the six study populations, please refer to the description of study CT-P13 3.5, Part 1 above.

The following table summarizes the number of patients in each population.

Table 14 - The Number of Patients in Each Population in Study CT-P13 1.6 Part 1

| | IV 5 mg/kg | SC 120 mg | SC 180 mg | SC 240 mg | Total |
|----------------------------|------------|-----------|-----------|-----------|-------|
| Intent-to-treat population | | | | | 45 |
| All-randomized population | 13 | 11 | 12 | 8 | 44 |
| Pharmacokinetic population | 12 | 11 | 12 | 6 | 41 |
| Pharmacodynamic population | 12 | 11 | 12 | 8 | 43 |
| Efficacy population | 12 | 11 | 12 | 7 | 42 |
| Safety population | 13 | 11 | 12 | 8 | 44 |

Abbreviations: IV, intravenous; SC, subcutaneous.

Note: The randomized treatment at Week 6 was used for the all-randomized population. Actual treatment was used for the PK, PD, efficacy, and safety populations.

Main Criteria for Inclusion

- Male or female aged 18 to 75 years old, inclusive, with active CD of at least 3 months' disease duration prior to the first administration of the study drug (Day 0). A patient who had CD with a Crohn's Disease Activity Index (CDAI) score between 220 and 450 points was considered for enrolment in the study.
- The patient had been treated for active CD but had not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or was intolerant to or had medical contraindications for such therapies. The patient had to have stable doses of the following CD treatments or currently was not receiving for specified time frames: azathioprine (AZA) or 6-mercaptopurine (6-MP), methotrexate (MTX), steroids and 5-aminosalicylates (5-ASA).

- Patients had to have adequate renal and hepatic function at screening as well as haematology laboratory test results at screening within pre-specified limits and use contraception.

Endpoints

- **Primary endpoint** was the AUC_T (SC) and AUC_T (IV) at steady state between Week 22 and Week 30, calculated using the linear trapezoidal rule. There were also a number of secondary PK-endpoints.
- **Secondary efficacy endpoints** were assessed up to Week 54: CDAI-70 response, (defined as a decrease in CDAI score of 70 points or more from the baseline value); CDAI-100 response (defined as a decrease in CDAI score of 100 points or more from the baseline value); Clinical remission (defined as an absolute CDAI score of less than 150 points); Endoscopic response (defined as a decrease in 50% or more of Simplified Endoscopic Activity Score for Crohn's Disease [SES-CD] score); Endoscopic remission (defined as an absolute SES-CD score of 2 points or less); Short Inflammatory Bowel Disease Questionnaire (SIBDQ).
- **Secondary PD endpoints** assessed up to Week 54: Faecal calprotectin and CRP.
- **Secondary safety endpoints** included immunogenicity tests, hypersensitivity monitoring, and AEs of special interest included Infusion-related reactions (IRRs)/hypersensitivity/anaphylactic reactions (administration-related reaction [ARRs]), injection site reactions (ISRs), infections (including TB) and malignancy. For ARR throughout the CSR, please refer to the description of study CT-P13 3.5, Part 1 above.

Sample size, randomisation and statistical methods

No formal sample size estimation was performed because no confirmatory analyses were planned in the study. Approximately 24 to 40 patients (6 to 10 patients per cohort) were considered to be sufficient to investigate the primary objective (pharmacokinetics).

Approximately 40 (at least 24) male or female patients with active CD were to be randomly assigned at Week 6 in a 1:1:1:1 ratio into 4 study cohorts. The randomization was stratified by region (European or non-European), current use of treatment with AZA or 6-MP or MTX (used or not used), clinical response at Week 6 (responder or non-responder by CDAI-70 for CD), and body weight at Week 6 (≤ 70 kg or > 70 kg).

Pharmacokinetic parameters were computed by non-compartmental methods using appropriate validated software. All PK analyses were performed on the PK population. The primary PK endpoint was also analysed in patients who received all doses (full) of study drug up to Week 30 (prior to Week 30) in the PK population.

The secondary efficacy parameters were summarized using descriptive statistics. All efficacy data analyses were conducted for the efficacy population. The PD endpoint analyses were conducted for the PD population.

All safety data analyses were conducted for the safety population. Analyses were performed on observed cases. All safety data were listed and summarized by cohort as appropriate.

Results Part 1 CT-P13 1.6

Conduct of the study

The original protocol (Version 1.0), dated 18 May 2016, was amended during the course of the study.

The global amendments included:

- Posology of CT-P13 SC in **Part 2** was specified as SC 120 mg via PFS every 2 weeks

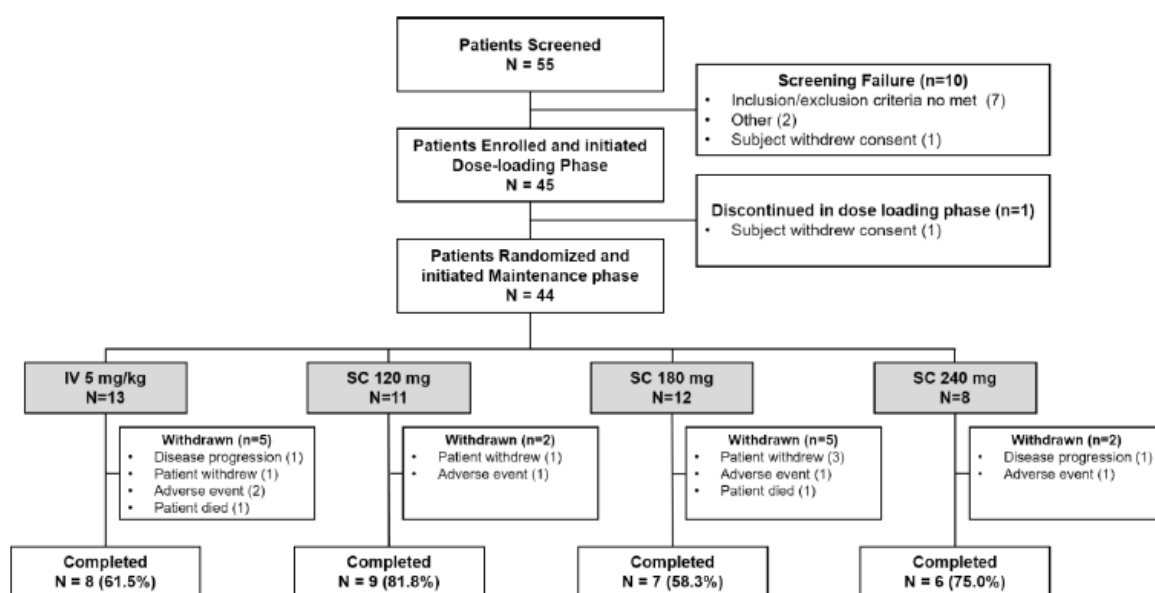
- Primary objective for **Part 2** was revised as C_{trough} at Week 2 which was selected as the most relevant PK parameter predictive of therapeutic efficacy through literatures
- Sample size for Part 1 was revised not to specify the total number of enrolled patients to a certain number, and sample size for Part 2 was revised to allow minimum of 130 patients
- Among the stratification factors for **Part 2**, region deleted and body weight cut-off point adjusted to make balance in number of obese patients between arms
- Revised number of participating countries for Part 1 and clarify that the target number of patients is for randomization
- Revision of inclusion and exclusion criteria
- Loss of response criteria added for **Part 2** to allow dose escalation
- Revised definition of study population
- Updated optimal dose of CT-P13 SC for **Part 2**
- Added dose escalation posology in **Part 2**
- Revised visit window and pharmacodynamics assessment time points
- Revised clinical remission definition of partial Mayo score
- Mayo Scoring System revised to exclude mild friability from Mayo endoscopic subscore of 1 per FDA guidance.

At least some amendments appear to relate only to Part 2 of the study CT P13 3.5; this is highlighted in **bold** above.

Patient disposition/ participant flow

Patient disposition is summarized for the all-randomized population in the figure below.

Figure 15 - Patient Disposition of Study CT-P13 1.6 Part 1: All-Randomized Population



Abbreviation: IV, intravenous; SC, subcutaneous

Demographic Characteristics

The mean (SD) age of patients was 39.5 (12.39), 36.9 (13.35), 38.3 (10.82) and 42.4 (10.20) years in the IV 5 mg/kg, SC 120 mg, SC 180 mg and SC 240 mg cohorts, respectively. In total, there was a higher proportion of male patients than female patients (24 [54.5%] male patients and 20 [45.5%] female patients).

The number (proportion %) of patients with current use of treatment with AZA or 6-MP or MTX was: 9 (69.2%) in the IV 5 mg/kg-group, 7 (63.6%) in the SC 120 mg-group, 6 (50.0%) in the SC 180 mg group and 2 (25.0%) in the SC 240 mg-group.

PK data

Please refer to the section 3.3.1 Pharmacokinetics of this AR for summary and assessment of PK results. The MAH states that Remsima SC 120 mg every 2 weeks for patients with body weights of < 80 kg and 240 mg every 2 weeks in patients with body weights of ≥ 80 kg was determined as the optimal dose.

Clinical Efficacy data

The proportions of patients achieving the relevant clinical outcomes (clinical response according to the CDAI-100 criteria and Endoscopic Remission According to the SES-CD Criteria) are summarized for the efficacy population in the tables below.

Table 15 - Proportions of Patients Achieving Clinical Response According to the CDAI-100 Criteria in Study CT-P13 1.6 Part 1: Efficacy Population

| | IV 5 mg/kg (N=12) | SC 120 mg (N=11) | SC 180 mg (N=12) | SC 240 mg (N=7) |
|---------|------------------------|---------------------|---------------------|--------------------|
| Visit | Number (%) of patients | | | |
| Week 2 | 3 (25.0) | 5 (45.5) | 2 (16.7) | 3 (42.9) |
| Week 6 | 7 (58.3) | 6 (54.5) | 5 (41.7) | 3 (42.9) |
| Week 14 | 6 (50.0) | 6 (54.5) | 6 (50.0) | 3 (42.9) |
| Week 22 | 8 (66.7) | 7 (63.6) | 7 (58.3) | 4 (57.1) |
| Week 30 | 7 (58.3) | 9 (81.8) | 10 (83.3) | 5 (71.4) |
| Week 54 | 6 (50.0) | 9 (81.8) | 7 (58.3) | 5 (71.4) |

Abbreviations: CDAI, Crohn's Disease Activity Index; IV, intravenous; SC, subcutaneous.

Note: A patient was defined as having a CDAI-100 response if there was a decrease in CDAI score of 100 points or more from the baseline value. The baseline value was considered to be the last non-missing value before the first administration.

Table 16 - Proportion of Patients Achieving Endoscopic Remission According to the SES-CD Criteria in Study CT-P13 1.6 Part 1: Efficacy Population

| | IV 5 mg/kg (N=12) | SC 120 mg (N=11) | SC 180 mg (N=12) | SC 240 mg (N=7) |
|----------------|------------------------|---------------------|---------------------|--------------------|
| Visit | Number (%) of patients | | | |
| Week 30 | 3/7 (42.9) | 3/8 (37.5) | 3/9 (33.3) | 1/6 (16.7) |
| Week 54 | 3/7 (42.9) | 6/9 (66.7) | 1/4 (25.0) | 2/6 (33.3) |

Abbreviations: IV, intravenous; SC, subcutaneous; SES-CD, Simplified Endoscopic Activity Score for Crohn's Disease.

Note: Endoscopic remission was defined as an absolute overall SES-CD score of 2 points or less without inaccessible or missing. Percentages were calculated by using the number of patients who had confirmed mucosal abnormalities (overall SES-CD score greater than 0) regardless of exploration result or overall SES-CD score of 0 with inaccessible exploration result or with missing exploration result at baseline as the denominator.

The results for changes from baseline in CDAI score and overall SES-CD score, CDAI-70 response, Clinical remission, Endoscopic response, Short Inflammatory Bowel Disease Questionnaire (SIBDQ) were also reported (not reported here).

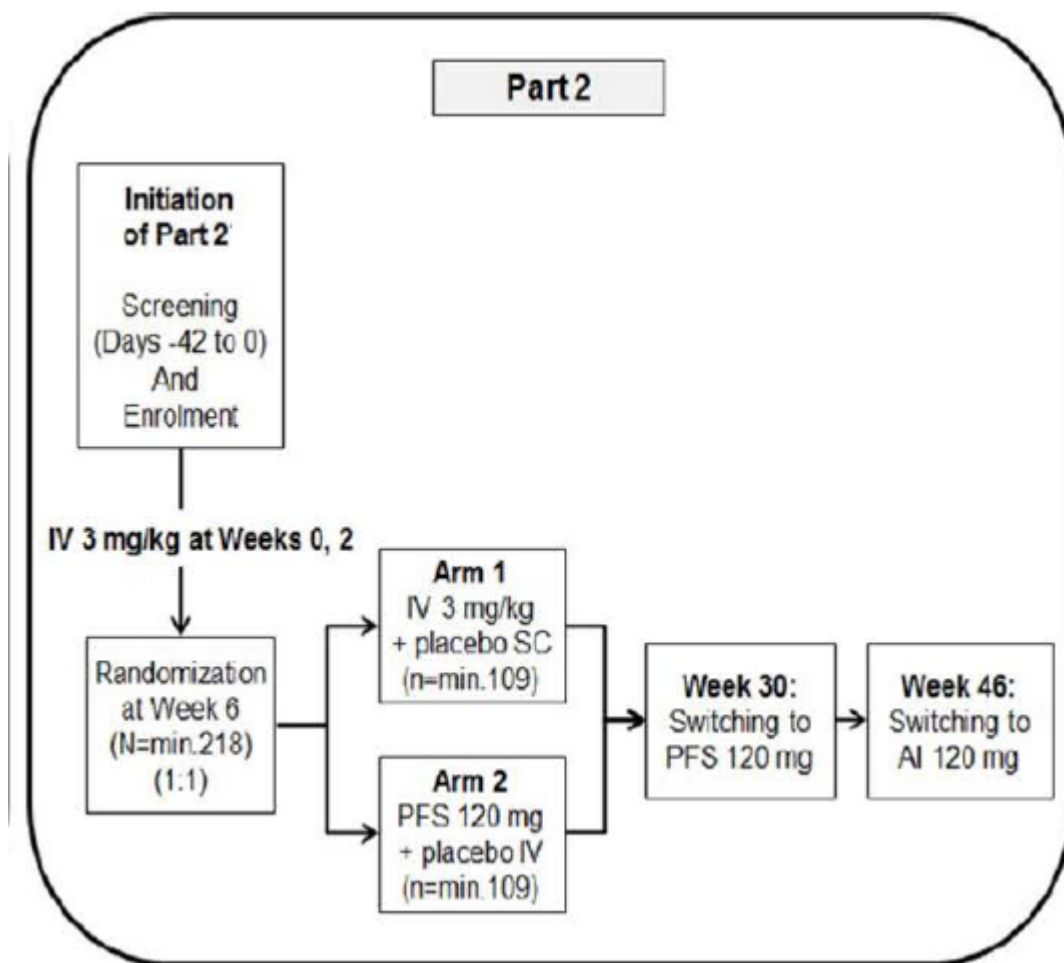
2.7.2. Main study

Study CT-P13 3.5 Part 2

The main efficacy study is Part 2 of Study CT-P13 3.5, i.e. a randomised, placebo-controlled, double-dummy, parallel group study. It was designed to demonstrate therapeutic non-inferiority of Remsima SC to Remsima IV in efficacy in patients with active RA who were concomitantly treated with methotrexate (MTX) and folic acid during the entire study period.

Non-inferiority in efficacy of Remsima SC to Remsima IV was assessed in terms of mean change from baseline of DAS28 (CRP) with a pre-specified non-inferiority margin of -0.6 at Week 22 in Part 2 of the CT-P13 3.5 study. From week 30 onward all patients received Remsima SC.

Figure 16 - Overall Study Design of Study CT-P13 3.5 Part 2



Methods

Study Participants

Male or female patients, aged 18 to 75 years old, with active RA (the presence of 6 or more swollen joints of 28 assessed, 6 or more tender joints of 28 assessed and a serum CRP concentration greater than 0.6 mg/dL at screening; diagnosed according to the 2010 ACR/EULAR classification criteria for at least 6 months prior to the first administration of the study drug), despite previous treatment with MTX over at least 3 months were included. Patient who had previously received a biological agent for the treatment of RA and/or a TNF α inhibitor for the treatment of other disease were excluded.

Treatments

All enrolled patients initially received Remsima IV 3mg/kg infusion at Weeks 0 and 2. At week 6, patients who received 2 full doses and for whom there were no safety concerns based on the investigator's discretion were randomly assigned to receive either 120mg Remsima SC with placebo IV or 3mg/kg Remsima IV with placebo SC starting on Day 42, Week 6.

- **Arm 1:** Further 3 doses of 3mg/kg Remsima IV were administered at Week 6 and every 8 weeks thereafter up to Week 22 (Weeks 14 and 22) with placebo SC at Week 6 and every 2 weeks thereafter up to Week 28.

- **Arm 2:** First 120mg Remsima SC was administered by PFS at Week 6 and every 2 weeks thereafter up to Week 28 with placebo IV at Weeks 6, 14, and 22.

From Week 30, both arms received Remsima SC every 2 weeks up to Week 54 either via PFS up to Week 54 or, for patients in Bulgaria, Poland and Russia, PFS up to Week 44 and subsequently via AI every 2 weeks from Week 46 to 54. In Bulgaria, Poland and Russia patients who agreed with further administration were switched back to CT-P13 SC via PFS at Week 56. Further doses of study treatment CT-P13 SC via PFS every 2 weeks were given up to Week 64. From week 56 to week 64 only usability and safety was assessed and no efficacy data was recorded per protocol.

All patients were treated with MTX on stable dosing throughout the study.

Objectives

Primary Objective

- To demonstrate that Remsima SC is non-inferior to Remsima IV at Week 22, in terms of efficacy, as determined by clinical response according to change from baseline in disease activity measured by Disease Activity Score using 28 joint counts (DAS28) (CRP).

Secondary Objectives

- To evaluate efficacy, PK, PD, and overall safety of Remsima SC in comparison with Remsima IV (over the first 30 weeks).
- To evaluate efficacy, PK, PD, and overall safety of Remsima SC up to Week 54.

Outcomes/endpoints

The primary efficacy endpoint in Part 2 of Study CT-P13 3.5 was the mean change from baseline in disease activity measured by DAS28 (CRP) at Week 22.

Secondary efficacy endpoints were DAS28 (CRP and ESR), individual components of the DAS28, ACR 20% improvement criteria (ACR20), ACR 50% improvement criteria (ACR50), ACR 70% improvement criteria (ACR70), individual components of the ACR, hybrid ACR response, European League Against Rheumatism (EULAR) response criteria, clinical disease activity index (CDAI), simplified disease activity index (SDAI) and Health assessment questionnaire (HAQ) and the 36-item short form health survey (SF-36) questionnaire.

All endpoints were evaluated at Weeks 0, 2, 6, 14, 22, 30, 38, 46 and 54.

Randomisation and blinding (masking)

At week 6, the patients were randomly assigned with ratio 1:1 to receive either 120 mg Remsima SC with placebo IV or 3mg/kg Remsima IV with placebo SC. The randomization was stratified by country, Week 2 serum CRP concentration (≤ 0.6 mg/dL vs > 0.6 mg/dL) and Week 6 body weight (≤ 100 kg vs > 100 kg).

A double-dummy design was used to maintain blinding during the maintenance phase up to Week 30. The study was un-blinded at Week 30 for reporting purposes. The un-blinded teams were predefined prior to performing the analyses. The study remained blinded to the investigators, patients, and predefined blinded team from the sponsor until all patients had completed the study and the database had been finalized for study termination.

Statistical methods

A number of analysis populations were pre-defined whereof the All-Randomised and the Efficacy populations were used for the analysis of the primary and secondary efficacy endpoints. The all-

randomized population consisted of all randomly assigned patients at Week 6, regardless of whether or not any study drug dosing was completed. Analysis of all-Randomized population was performed according to the treatment they were randomized to at Week 6.

The efficacy population consisted of the all-randomized population who received at least one full dose of study drug (CT-P13 IV, CT-P13 SC) at Week 6 or thereafter and who had at least one efficacy evaluation result after Week 6 or thereafter treatment, and had no major protocol deviation. Analysis of efficacy population was performed according to actual treatment received.

Primary endpoint was a change in DAS28(CRP) score from baseline to Week 22. It was analysed using ANCOVA in All-Randomized and Efficacy populations as well as repeated on the Efficacy population by the "adjusted treatment arm" defined based on the actual treatment received between Week 6 (inclusive) and Week 22 (exclusive).

Regarding the different definitions above the following example was found in the SAP; a patient receiving CT-P13 IV up to Week 22 and CT-P13 SC at Week 24 was assigned to CT-P13 SC treatment arm for the *actual treatment arm*, and, CT-P13 IV treatment arm for the *adjusted treatment arm*.

In the ANCOVA model, treatment was considered as fixed effect, and country, Week 2 serum CRP concentration (≤ 0.6 mg/dL vs. > 0.6 mg/dL), and Week 6 body weight (≤ 100 kg vs. > 100 kg) were considered as covariates. The least squares mean and corresponding standard error of the change (decrease) from baseline in DAS28(CRP) at Week 22 was presented for each treatment arm. A point estimate and 2-sided 95% CI for the treatment difference (CT-P13 SC 120mg – CT-P13 IV 3mg/kg) was also provided.

The descriptive summary and ANCOVA were repeated for DAS28 (CRP) at Week 22 on all-randomized population by imputing missing values based on the Multiple Imputation (MI) under the missing at random (MAR) assumption.

The following secondary efficacy parameters were summarized using descriptive statistics: individual components of the DAS28, DAS28 (ESR/CRP), individual components of the ACR, ACR 20/50/70, hybrid ACR score, EULAR response criteria, SDAI, CDAI, HAQ and SF-36. The Efficacy population was used for secondary efficacy analysis. For the evaluation of ACR20/50/70 criteria, any patient with a missing component or not satisfying the responder criteria was to be considered as non-responder.

Pharmacokinetic Analyses: The secondary PK variables were presented in listings and summarized in tables.

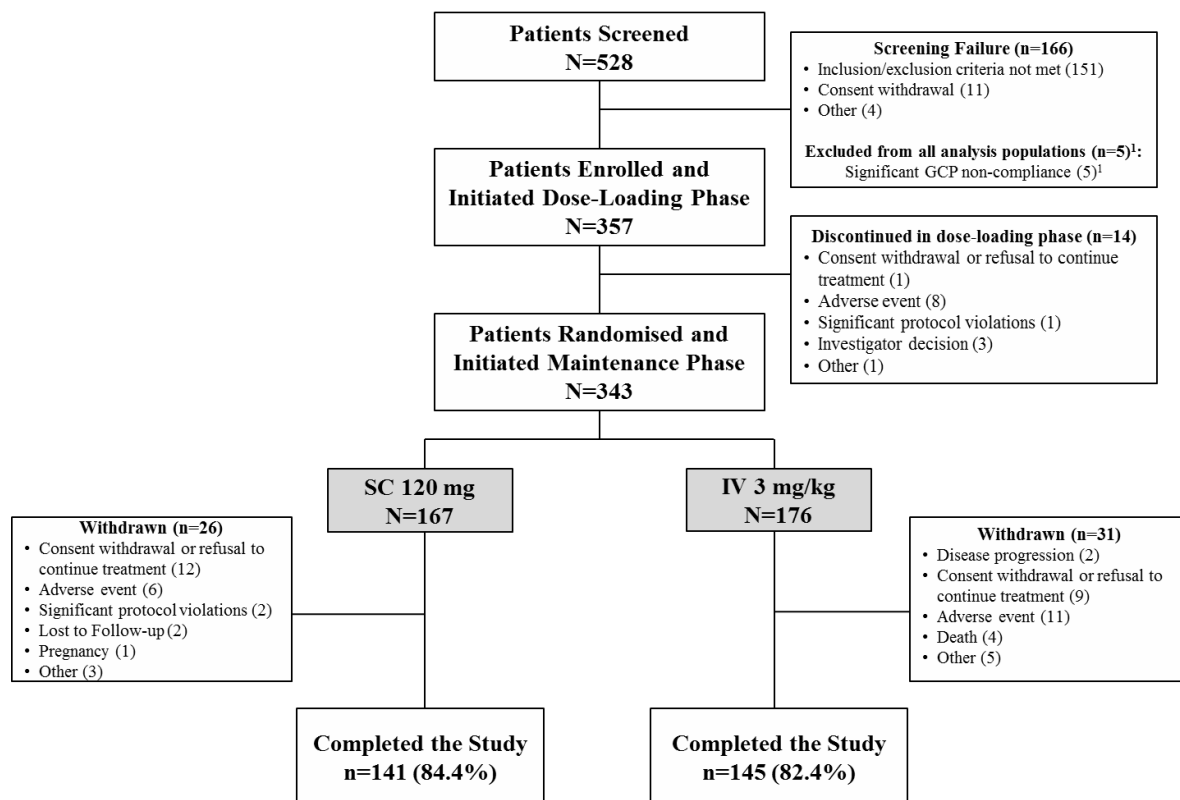
PD Analyses: The following PD parameters were summarized using descriptive statistics: RF, anti-CCP, CRP, and ESR.

Safety Analyses: Analyses were performed on the observed cases. All safety data were listed and summarized by treatment arm as appropriate.

Results

Participant flow

Figure 17 - Patient Disposition in of Study CT-P13 3.5 Part 2: All-Randomised Population



Abbreviation: IV, intravenous; SC, subcutaneous

1. Five patients were excluded in all analysis populations due to the significant GCP non-compliance of one site.

Baseline data

There was a higher percentage of female patients than male patients (269 [78.4%] female patients compared with 74 [21.6%] male patients). The majority of patients were White/Caucasian (296 [86.3%] patients) (

Table 17).

The mean (SD) time since RA diagnosis (year) was similar between the two treatment arms (6.82 [7.153] years and 6.41 [6.390] years in the SC 120 mg and IV 3 mg/kg treatment arms, respectively). A total of 126 (36.7%) patients had taken at least 1 prior medication (61 [36.3%] and 65 [37.1%] in SC 120 mg and IV 3 mg/kg treatment arms, respectively). The most commonly reported prior medications by drug class were anti-inflammatory and antirheumatic products (41 [24.4%] and 46 [26.3%] in SC 120 mg and IV 3 mg/kg treatment arms, respectively). The second most frequently reported prior medication was corticosteroid for systemic use (36 [21.4%] and 40 [22.9%] in SC 120 mg and IV 3 mg/kg treatment arms, respectively).

Immunosuppressants (leflunomide, ciclosporin, tofacitinib, mizoribine, peficitinib) had been taken by 16 (9.5%) and 13 (7.4%) patients in the SC and IV arms, respectively.

Table 17 - Demographic Characteristics in Study CT-P13 3.5 Part 2: All-Randomised Population

| Parameter Statistics | SC 120 mg (N=167) | IV 3 mg/kg (N=176) | Total (N=343) |
|---|--------------------------|---------------------------|----------------------|
| Age (years) | | | |
| n | 167 | 176 | 343 |
| Mean (SD) | 50.9 (12.17) | 51.9 (12.42) | 51.4 (12.29) |
| Median | 52.0 | 53.0 | 53.0 |
| min, max | 19, 74 | 18, 74 | 18, 74 |
| Sex, n (%) | | | |
| Male | 37 (22.2) | 37 (21.0) | 74 (21.6) |
| Female | 130 (77.8) | 139 (79.0) | 269 (78.4) |
| Female fertility status¹, n (%) | | | |
| Surgically sterilised | 6 (4.6) | 12 (8.6) | 18 (6.7) |
| Post-menopausal | 75 (57.7) | 76 (54.7) | 151 (56.1) |
| Potentially able to bear children | 49 (37.7) | 51 (36.7) | 100 (37.2) |
| Race, n (%) | | | |
| Asian/Oriental | 1 (0.6) | 2 (1.1) | 3 (0.9) |
| White/Caucasian | 145 (86.8) | 151 (85.8) | 296 (86.3) |
| Other | 21 (12.6) | 23 (13.1) | 44 (12.8) |
| Ethnicity, n (%) | | | |
| Hispanic or Latino | 27 (16.2) | 32 (18.2) | 59 (17.2) |
| Non-hispanic or Latino | 140 (83.8) | 144 (81.8) | 284 (82.8) |
| Screening Height (cm) | | | |
| n | 167 | 176 | 343 |
| Mean (SD) | 164.73 (9.198) | 164.33 (9.313) | 164.52 (9.246) |
| Median | 164.00 | 165.00 | 164.00 |
| min, max | 142.0, 191.0 | 137.0, 186.0 | 137.0, 191.0 |
| Screening Weight (kg) | | | |
| n | 167 | 176 | 343 |
| Mean (SD) | 73.01 (15.134) | 72.75 (14.402) | 72.87 (14.742) |
| Median | 71.00 | 72.00 | 71.40 |
| min, max | 42.0, 120.5 | 38.2, 119.3 | 38.2, 120.5 |
| Screening BMI (kg/m²) | | | |
| n | 167 | 176 | 343 |
| Mean (SD) | 26.794 (4.4233) | 26.820 (4.1330) | 26.807 (4.2706) |
| Median | 26.620 | 26.135 | 26.400 |
| min, max | 17.26, 35.09 | 16.53, 34.81 | 16.53, 35.09 |

| Parameter Statistics | SC 120 mg (N=167) | IV 3 mg/kg (N=176) | Total (N=343) |
|--|-------------------|--------------------|---------------|
| Country, n (%) | | | |
| Bosnia and Herzegovina | 10 (6.0) | 11 (6.3) | 21 (6.1) |
| Bulgaria | 11 (6.6) | 9 (5.1) | 20 (5.8) |
| Chile | 4 (2.4) | 4 (2.3) | 8 (2.3) |
| Estonia | 0 | 3 (1.7) | 3 (0.9) |
| Hungary | 6 (3.6) | 6 (3.4) | 12 (3.5) |
| Korea, Republic of | 1 (0.6) | 2 (1.1) | 3 (0.9) |
| Latvia | 0 | 2 (1.1) | 2 (0.6) |
| Peru | 21 (12.6) | 23 (13.1) | 44 (12.8) |
| Poland | 46 (27.5) | 46 (26.1) | 92 (26.8) |
| Russia | 39 (23.4) | 39 (22.2) | 78 (22.7) |
| Spain | 2 (1.2) | 2 (1.1) | 4 (1.2) |
| Ukraine | 27 (16.2) | 29 (16.5) | 56 (16.3) |
| Week 6 body weight, n (%) | | | |
| >100 kg | 7 (4.2) | 10 (5.7) | 17 (5.0) |
| ≤100 kg | 160 (95.8) | 166 (94.3) | 326 (95.0) |
| Week 2 serum CRP concentration, n (%) | | | |
| >0.6 mg/dL | 34 (20.4) | 47 (26.7) | 81 (23.6) |
| ≤0.6 mg/dL | 133 (79.6) | 129 (73.3) | 262 (76.4) |

Abbreviations: BMI, body mass index; CRP, C-reactive protein; IV, intravenous; SC, subcutaneous; max, maximum; min, minimum; SD, standard deviation.

1. Percentages were based on the number of female patients

Numbers analysed

The ITT population consisted of all enrolled patients. The all-randomized population consisted of all randomly assigned patients at Week 6, regardless of whether or not any study drug dosing was completed.

The efficacy population consisted of the all-randomized population who received at least one full dose of study drug at Week 6 or thereafter and who had at least one efficacy evaluation result after Week 6 or thereafter treatment. See Table 18.

Sample size calculations gave at hand that a minimum of 218 patients (including a 20% drop-out rate) were needed to show non-inferiority. However, 348 patients were randomized. The MAH explained this was due to fast recruitment and lower than expected retention rate on study, which is acceptable.

Table 18 - Populations of Analysis in Study CT-P13 3.5 Part 2

| | SC 120 mg | IV 3 mg/kg | Total |
|-----------------------------|--------------------|------------|-------|
| | Number of patients | | |
| Intent-to-treat population | | | 357 |
| All-randomised population | 167 | 176 | 343 |
| Efficacy population | 165 | 174 | 339 |
| Pharmacokinetics population | 166 | 174 | 340 |
| Pharmacodynamics population | 168 | 175 | 343 |
| Safety population | 168 | 175 | 343 |
| Usability population | 86 | 82 | 168 |

Note. The randomised treatment at Week 6 was used for all-randomised population. Actual treatment was used for efficacy, pharmacokinetics, pharmacodynamics, safety, and usability populations.

Outcomes and estimation

In general, the clinical response to Remsima SC was comparable to Remsima IV and the results for secondary efficacy endpoints were consistent with the primary endpoint.

The 2-sided 95% CI for difference in the mean change from baseline for DAS 28 (CRP) at Week 22 was above the pre-defined non-inferiority margin of -0.6 and hence, according to the pre-defined criteria approved by the CHMP, non-inferiority of Remsima SC 120 mg compared to Remsima IV 3 mg/kg was shown.

The mean decrease from baseline in DAS28 (CRP) at Week 22 was 2.21 and 1.94 in SC 120 mg and IV 3 mg/kg treatment arms, respectively. This level of improvement was comparable to that seen in previous trials with Remsima IV and Remicade in RA patients.

DAS scores were similar in the two groups at baseline. However, at week 6 the mean DAS (CRP) score was 3.98 in the SC group and 4.11 in the IV group. The difference in change from baseline (-2.03 vs. -1.75 respectively) seen at week 6 cannot be attributed to difference in treatment.

Primary outcome

The primary efficacy endpoint (mean change from baseline of DAS28 [CRP] at Week 22) is summarized for the efficacy and all-randomized populations in Table 19. Non-inferiority was met according to the pre-defined criteria (lower limit of the two-sided 95% CI was 0.02, which was greater than the pre-specified non-inferiority margin of -0.6).

Table 19 - Analysis of Change (decrease) From Baseline of DAS28 (CRP) at Week 22 (ANCOVA) in Study CT-P13 3.5 Part 2: Efficacy and All-Randomised Population

| Treatment | n | LS Mean (SE) | Estimate of Treatment Difference | 95% CI of Treatment Difference |
|----------------------------------|-----|--------------|----------------------------------|--------------------------------|
| Efficacy Population | | | | |
| SC 120 mg | 162 | 2.21 (0.221) | 0.27 | (0.02, 0.52) |
| IV 3 mg/kg | 168 | 1.94 (0.209) | | |
| All-Randomised Population | | | | |
| SC 120 mg | 162 | 2.13 (0.211) | 0.27 | (0.02, 0.53) |
| IV 3 mg/kg | 170 | 1.85 (0.198) | | |

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; CRP, C-reactive protein; DAS28, Disease Activity Score using 28 joint counts; IV, intravenous; LS, least squares; SC, subcutaneous; SE, standard error.

Note: Change (decrease) from baseline for this primary analysis was defined as decrease from baseline and calculated as (DAS28 [CRP] at baseline – DAS28 [CRP] at Week 22). An ANCOVA comparing the change (decrease) from baseline of DAS28 (CRP) at Week 22 between the two treatment arms, CT-P13 SC and CT-P13 IV, was conducted considering the treatment as fixed effect and country, Week 2 serum CRP concentration (≤ 0.6 mg/dL versus > 0.6 mg/dL), and Week 6 body weight (≤ 100 kg versus > 100 kg) as covariates. The LS means, SEs, estimate of treatment difference (CT-P13 SC 120 mg – CT-P13 IV 3 mg/kg), and 2-sided 95% CI obtained from the ANCOVA were displayed

Main secondary outcomes

Secondary efficacy endpoints were assessed by the evaluation of the mean change from baseline in DAS28 (individual components, DAS28 [CRP/ESR]), EULAR response criteria, ACR criteria (individual components, ACR20, ACR50, ACR70, and hybrid ACR score), CDAI, SDAI, HAQ and SF-36 at Weeks 0, 2, 6, 14, 22, 30, 38, 46 and 54. Only ESR and CRP were assessed at Week 38 and Week 46.

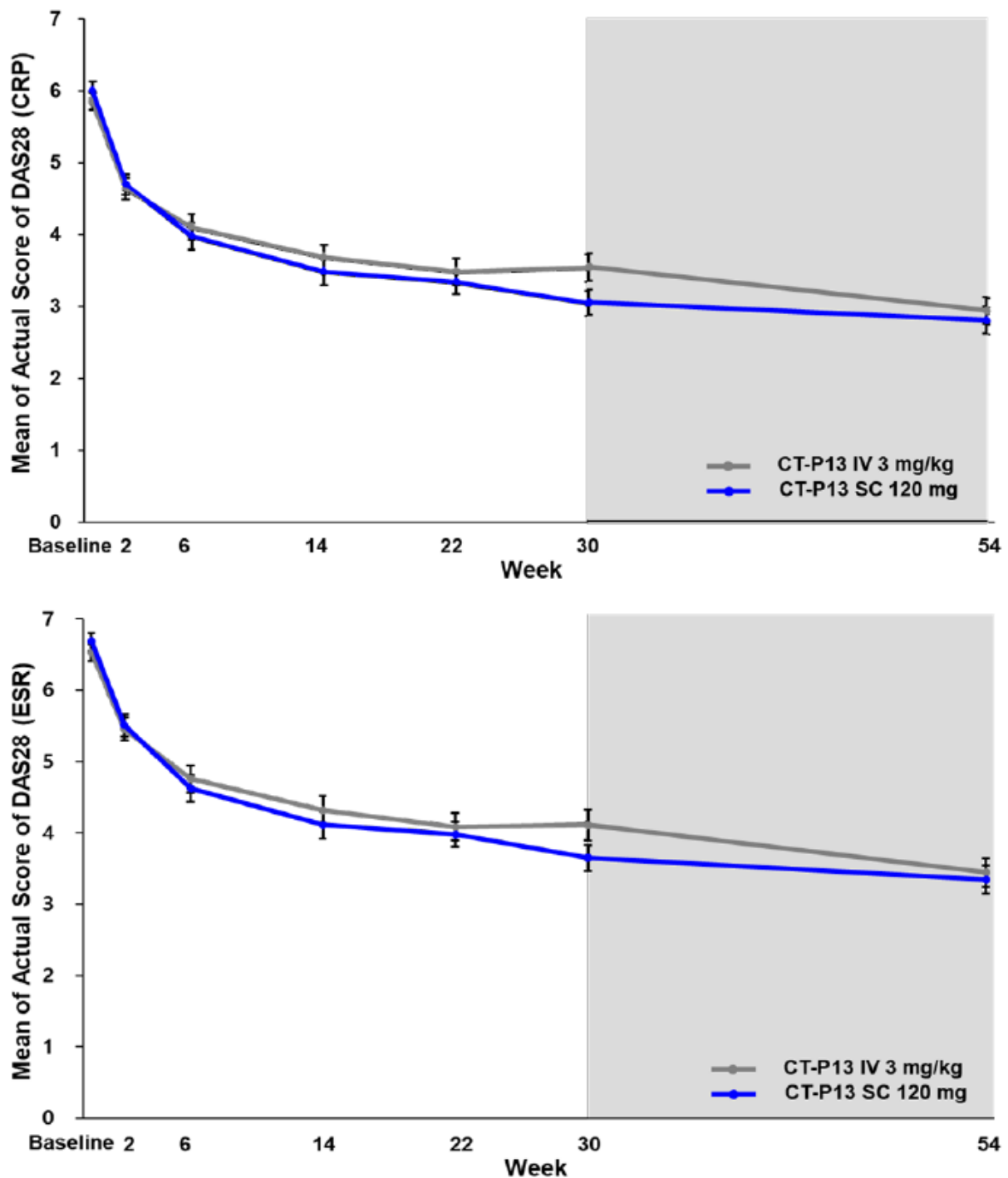
The mean scores for DAS28 (CRP) decreased from baseline until Week 54 in each treatment arm. Numerically, the results were consistently slightly in favour of the SC arm, but the differences were not clinically significant even if a statistically significant difference was recorded at week 30 (Figure 18).

There were decreases in mean score of each individual DAS28 and ACR component from baseline until Week 30 in each treatment arm. The mean decreases from baseline in all individual DAS28 and ACR components were slightly higher in SC 120 mg at Week 30.

Each secondary outcome improved in both treatment arms. Mean changes from baseline were generally in favour of the SC 120mg treatment arm at each time point but with confidence intervals generally overlapping.

Efficacy was maintained and slightly improved over the whole 54 week treatment period in the SC treatment arm and also among patients who switched from IV to SC formulation at week 30 (Figure 18).

Figure 18 - Mean of Actual Score of DAS28 (CRP/ ESR) (95% CI) up to Week 54 in Study CT-P13 3.5 Part 2: Efficacy Population



Note: Shaded area represents patients in the CT-P13 IV 3 mg/kg arm switched to CT-P13 SC 120 mg at Week 30. CRP: C-reactive protein, DAS28: Disease activity score using 28 joint counts, ESR: Erythrocyte sedimentation rate, IV: Intravenous, SC: Subcutaneous EULAR response criteria and ACR Criteria

By week 30 92.7% in the SC 120mg arm and 83.3% in the IV 3mg/kg arm had achieved moderate or good clinical response according to EULAR response criteria (based on DAS28 [CRP]) (Table 20). At week 6 27.3% and 25.9% had achieved good clinical response in the SC 120 mg and IV 3mg/kg treatment

arms respectively. At week 30 50.9% and 35.6% of patients had achieved good clinical response in the SC 120 mg and IV 3mg/kg treatment arms respectively.

Of note, more than 80% of all patients achieved good or moderate response already by week 6.

Table 20 - Proportion of Patients Achieving EULAR(CRP) Response in Study CT-P13 3.5 Part 2: Efficacy Population

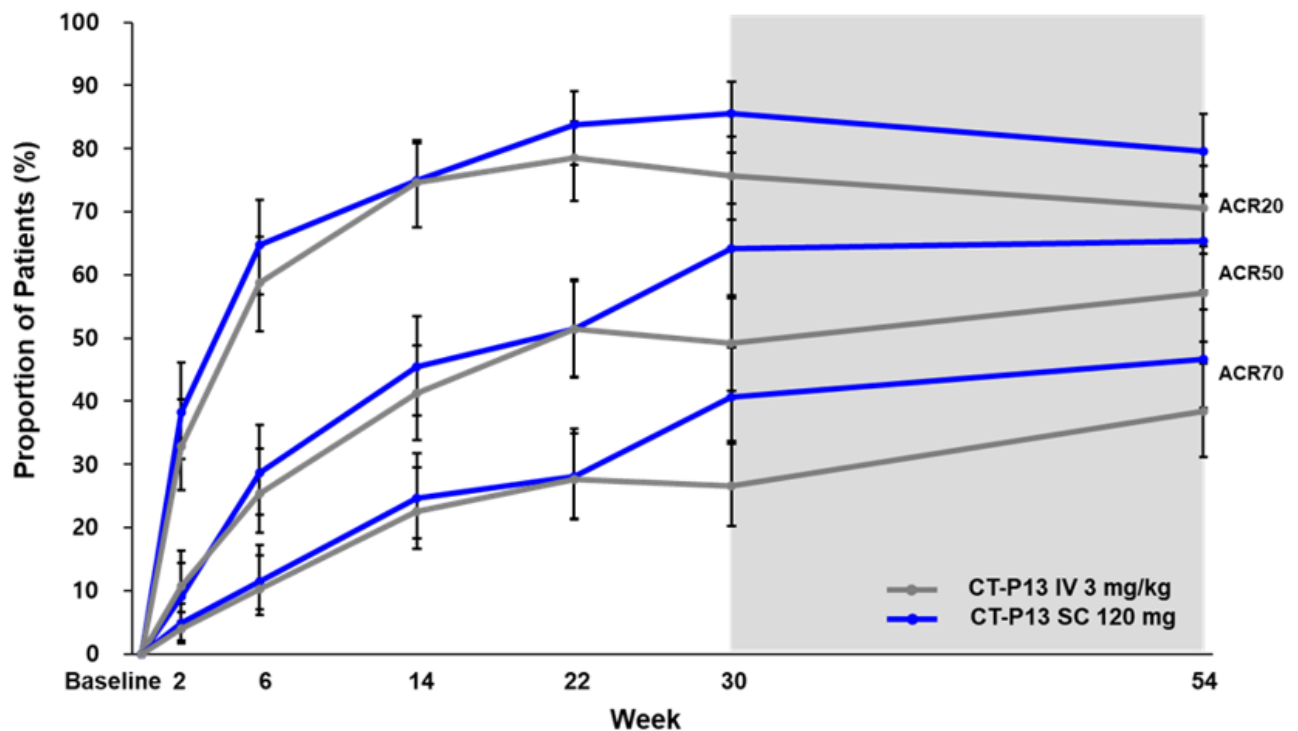
| Visit | SC 120 mg (N=165) | IV 3 mg/kg (N=174) |
|-------------------|------------------------|-----------------------|
| Category | Number (%) of patients | |
| Week 2 | | |
| No Response | 58 (35.2) | 69 (39.7) |
| Moderate Response | 97 (58.8) | 85 (48.9) |
| Good Response | 9 (5.5) | 18 (10.3) |
| Week 6 | | |
| No Response | 29 (17.6) | 35 (20.1) |
| Moderate Response | 91 (55.2) | 94 (54.0) |
| Good Response | 45 (27.3) | 45 (25.9) |
| Week 14 | | |
| No Response | 17 (10.3) | 23 (13.2) |
| Moderate Response | 72 (43.6) | 86 (49.4) |
| Good Response | 75 (45.5) | 63 (36.2) |
| Week 22 | | |
| No Response | 6 (3.6) | 12 (6.9) |
| Moderate Response | 80 (48.5) | 91 (52.3) |
| Good Response | 76 (46.1) | 65 (37.4) |
| Week 30 | | |
| No Response | 4 (2.4) | 14 (8.0) |
| Moderate Response | 69 (41.8) | 83 (47.7) |
| Good Response | 84 (50.9) | 62 (35.6) |
| Week 54 | | |
| No Response | 6 (3.6) | 3 (1.7) |
| Moderate Response | 46 (27.9) | 57 (32.8) |
| Good Response | 93 (56.4) | 85 (48.9) |

Abbreviations: CRP, C-reactive protein; EULAR, European League Against Rheumatism; IV, intravenous; SC, subcutaneous.

The proportions of patients in the IV 3 mg/kg and SC 120 mg arms achieving clinical response according to the ACR20 criteria were similar at each time point until Week 22. A slightly higher response rate was observed in favour of the SC 120 mg arm at Week 30 (133 [76.4%] patients and 142 [86.1%] patients in the IV 3 mg/kg and SC 120 mg arms, respectively). The results of ACR50 and ACR70 were consistent with those of the ACR20

Figure 19.

Figure 19 - Proportion of Patients Achieving Clinical Response according to the ACR Criteria up to Week 54 in Study CT-P13 3.5 Part 2: Efficacy Population



Note: Shaded area represents patients in the CT-P13 IV 3 mg/kg arm switched to CT-P13 SC 120 mg at Week 30. ACR: American College of Rheumatology, ACR20: ACR 20% improvement criteria, ACR50: ACR 50% improvement criteria, ACR70: ACR 70% improvement criteria, IV: Intravenous, SC: Subcutaneous

ACR20 from Week 6 was similar between the CT-P13 IV 3 mg/kg and CT-P13 SC 120 mg arm up to Week 54. The 95% CI for proportion of patients achieving ACR20 from Week 6 overlapped between the 2 arms up to Week 54 (

Table **21**).

Table 21 - Proportion of Patients Achieving Clinical Response according to the ACR 20 Criteria from Week 6 (95% CI) up to Week 54 in Study CT-P13 3.5 Part 2: Efficacy Population

| Parameter Visit | CT-P13 IV 3 mg/kg (N=177) | CT-P13 SC 120 mg (N=167) |
|----------------------------|------------------------------|-----------------------------|
| Week 22 | | |
| Number of Patients | 60 (33.9) | 66 (39.5) |
| Exact 95% CI of Proportion | 26.97, 41.38 | 32.05, 47.37 |
| Week 30 | | |
| Number of Patients | 60 (33.9) | 74 (44.3) |
| Exact 95% CI of Proportion | 26.97, 41.38 | 36.64, 52.19 |
| Week 54 | | |
| Number of Patients | 68 (38.4) | 79 (47.3) |
| Exact 95% CI of Proportion | 31.22, 46.01 | 39.54, 55.17 |

A patient was defined as a responder according to the ACR20 criteria from Week 6 if the percentage decrease of at least 20% from Week 6 in the number of tender joints (assessment of 68 joints), and the number of swollen joints (assessment of 66 joints) and on three of the following: patient's assessment of pain (VAS Scale, mm), patient's global assessment of disease activity (VAS scale, mm), physician's global assessment of disease activity (VAS scale, mm), HAQ estimate of physical ability and serum CRP (mg/dL) concentration or ESR (mm/h).

ACR: American College of Rheumatology, ACR20: ACR 20% improvement criteria, CI: Confidence interval, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, HAQ: Health assessment questionnaire, IV: Intravenous, SC: Subcutaneous, VAS: Visual analogue score

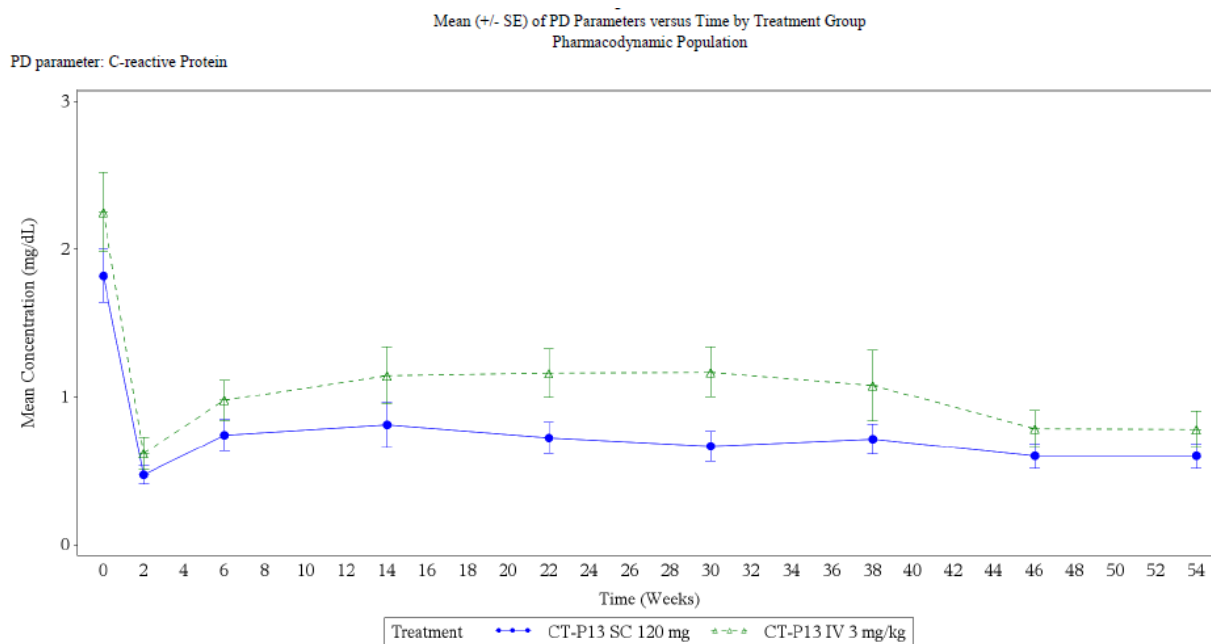
PD parameters and concomitant medication

The following PD parameters were also assessed: Rheumatoid factor (RF), Anti-cyclic citrullinated peptide (anti-CCP), CRP, ESR.

Mean concentration of RF decreased from baseline at each time point measured up to Week 54 in each treatment arm. Although mean (SD) concentration of RF at Week 54 was slightly higher in SC 120 mg treatment arm (170.60 [481.903] IU/mL and 115.17 [321.857] IU/mL in SC 120 mg and IV 3 mg/kg treatment arms, respectively), mean decrease from baseline was similar between two treatment arms (94.92 IU/mL and 100.93 IU/mL in SC 120 mg and IV 3 mg/kg treatment arms, respectively).

One of the inclusion criteria was a serum CRP concentration greater than 0.6 mg/dL at screening. At week 2 (after one dose of IV Remsima 76,7% of patients already had a serum CRP concentration \leq than 0.6 mg/dL. CRP concentration generally maintained a consistent level from Week 14 to Week 54 in the two treatment arms (Figure 20). Patients in the SC group had a slightly lower average CRP at baseline and week 2. This difference was accounted for in the analysis of the outcome by including CRP at week 2 as a covariate.

Figure 20 - Mean (+/-SE) CRP in Study CT-P13 3.5 Part 2: Efficacy Population



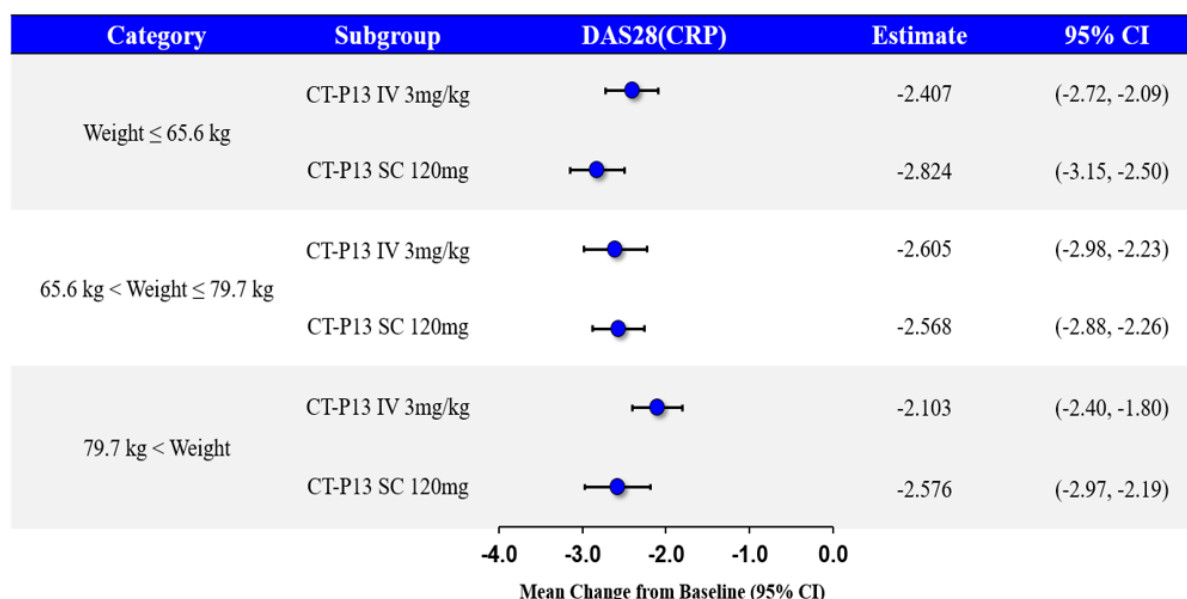
During the comparative maintenance phase (weeks 6-30), 339 (98.8%) patients had taken at least 1 concomitant medication (167 [99.4%] patients and 172 [98.3%] patients in the SC 120 mg and IV 3 mg/kg treatment arms, respectively). The most frequently reported concomitant medications by drug class during the maintenance phase were analgesics and antihistamines for systemic use (128 [76.2%] patients and 135 [77.1%] in SC 120 mg and IV 3 mg/kg treatment arms, respectively).

The use of analgesics was similar or less common if anything in the SC treatment arm (129 [76.8%] patients and 140 [80.0%] in SC 120 mg and IV 3 mg/kg treatment arms, respectively). The use of concomitant corticosteroids was similar in the two treatment arms (124 (72.9%) 131 (73.6%) for SC and IV arms, respectively).

Ancillary analyses

In Study CT-P13 3.5 Part 2, post-hoc analysis was performed for 95% CI for the mean change from baseline of DAS28 (CRP) at Week 22 by subgroups according to tertiles of body weight at Week 6 in the efficacy population (Figure 21). The mean changes from baseline of DAS28 (CRP) were generally similar between the CT-P13 IV 3 mg/kg and CT-P13 SC 120 mg arms at Week 22 in each subgroup.

Figure 21 - Plot of 95% CI for the Mean Change from Baseline of DAS28 (CRP) at Week 22 by Body Weight in Study CT-P13 3.5 Part 2: Efficacy Population



Note: Patients were categorised using the 33rd and 67th percentile of body weight at Week 6 on the efficacy population.
CI: Confidence interval, CRP: C-reactive protein, DAS28: Disease activity score in 28 joints, IV: Intravenous, SC: Subcutaneous

Data on usability of the auto-injector (AI) and pre-filled syringe (PFS)

In Study CT-P13 3.5 Part 2, usability of CT-P13 SC via auto-injector (AI) and pre-filled syringe (PFS) was evaluated in Bulgaria, Poland and Russia only as per the country specific protocol. Patients self-administered CT-P13 SC via AI every 2 weeks from Weeks 46 to 54. Patients who agreed with further administration switched back to CT-P13 SC via PFS at Week 56 and continued up to Week 64. Usability was assessed via self-injection assessment questionnaires on weeks 46 to 64.

A total of 168 patients were included in the usability population, 86 and 82 patients from the original SC and IV arms respectively. Patients from one Site were excluded from the usability population due to non-compliance with Good Clinical Practice (GCP).

According to the self-assessment questionnaires completed by the patients, scores on feeling about injections, self-confidence, satisfaction of self-injection, ease of self-injection, pain and skin reactions were acceptable.

A majority of patients completed successful self-injection with both AI and PFS device. Of the patients with valid usability assessment performed, all patients were able to successfully complete all instructions for both devices. No specifics regarding the nature of the failures could be found.

Only a few patients experienced a hazard during self-administration. A needle stick in non-critical area was the only form of hazard recorded. Almost 5% (9/167) of patients experienced a hazard during the first self-injection with the AI device. However, the number decreased by two thirds (3/165) by the second hazard assessment at Week 54. There was one patient each at Week 54 (1/164) and Week 64 (1/159) experienced a hazard during the self-injection with the PFS device. The number of patients experiencing a hazard is too small to allow conclusion regarding the difference in hazard rate between the two devices. However, a needle stick in a non-critical area is considered not serious and the rate of hazard is acceptable since it seems that patients learned to be more careful with more experience.

According to the data provided, there was no recording of incomplete dose administration.

Four patients from one Site were excluded from the usability analyses because of non-compliance with GCP standards. However, sensitivity analyses were performed also including patients from this Site and these results are also in line with the results above.

The usability of both AI and PSF devices are acceptable in terms of patient satisfaction and rate of successfully and appropriately completed self-administration.

Summary of main efficacy results

Table 22 summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 22 - Summary of Efficacy for Trial CT-P13 3.5 Part 2

| Title: A Randomised, Parallel-Group, Phase I/III Study to Evaluate Efficacy, Pharmacokinetics and Safety between Subcutaneous CT-P13 and Intravenous CT-P13 in Patients with Active Rheumatoid Arthritis | | |
|---|--|--|
| Study identifier | Project code: CT-P13 SC EudraCT number: 2016-002125-11 | |
| Design | Randomised, parallel-group, double-blind for Part 2, multicentre study | |
| | Duration of main phase: | 54 weeks <u>Dose-Loading Phase:</u> 6 weeks (all patients received CT-P13 IV 3 mg/kg at weeks 0 and 2) <u>Maintenance Phase:</u> 48 weeks (patients were randomised 1:1 ratio into CT-P13 IV 3 mg/kg or CT-P13 SC 120 mg) |
| | Duration of Run-in phase: | not applicable |
| | Duration of Extension phase: | not applicable |
| Hypothesis | To demonstrate that CT-P13 SC is noninferior to CT-P13 IV | |
| | CT-P13 IV 3 mg/kg | <u>Dose-loading Phase:</u> CT-P13 IV (3 mg/kg) at Weeks 0 and 2 <u>Maintenance Phase:</u> CT-P13 IV (3 mg/kg) at Week 6 and every 8 weeks up to Week 22 with placebo SC at Week 6 and every 2 weeks up to Week 28. CT-P13 IV was switched to CT-P13 SC 120 mg via PFS at Week 30 and thereafter further doses of CT-P13 SC via PFS were administered up to Week 54 (in Bulgaria, Poland and Russia, patients were switched to CT-P13 SC via AI at Week 46 and every 2 weeks thereafter up to Week 54 and then administered CT-P13 SC via PFS at Week 56 up to Week 64 for usability assessment) Number of randomised=176 |
| | CT-P13 SC 120 mg | <u>Dose-loading Phase:</u> CT-P13 IV (3 mg/kg) at Weeks 0 and 2 <u>Maintenance Phase:</u> CT-P13 SC 120 mg by PFS at Week 6 and every 2 weeks up to Week 54 with placebo IV at Weeks 6, 14 and 22 (in Bulgaria, Poland and Russia, patients were switched to CT-P13 SC via AI at Week 46 and every 2 weeks thereafter up to Week 54 and then administered CT-P13 SC via PFS at Week 56 up to Week 64 for usability assessment) Number of randomised=167 |

| | | | | |
|---|--|------------------------------------|--|--|
| Endpoints and definitions | Primary endpoint | DAS28 (CRP) | Change from baseline of DAS28 (CRP) at Week 22 | |
| | Secondary endpoint | Individual components of the DAS28 | Number of tender and swollen joints with a total of 28 joints assessed for tenderness and 28 joints assessed for swelling, ESR measurement, CRP measurement | |
| | | DAS28 (CRP) | $(0.56 \times \sqrt{TJC28}) + (0.28 \times \sqrt{SJC28}) + (0.36 \times \ln(CRP+1)) + (0.014 \times GH) + 0.96$ | |
| | | DAS28 (ESR) | $(0.56 \times \sqrt{TJC28}) + (0.28 \times \sqrt{SJC28}) + (0.70 \times \ln(ESR)) + (0.014 \times GH)$ | |
| | | Individual components of the ACR | Number of tender and swollen joints with a total of 68 joints assessed for tenderness and 66 for swelling, patient's assessment of pain measured on VAS, patient's and physician's global disease activity measured on VAS, HAQ estimate of physical ability, ESR, CRP | |
| | | ACR20 | 20% responses, as defined by the American College of Rheumatology | |
| | | ACR50 | 50% responses, as defined by the American College of Rheumatology | |
| | | ACR70 | 70% responses, as defined by the American College of Rheumatology | |
| | | hybrid ACR score | an outcome measure that combines the ACR20, the ACR50 and the ACR70 and a continuous score of the mean improvement in core set measures | |
| | | EULAR response criteria | Response criteria according to European League Against Rheumatism | |
| | | SDAI | SDAI= SJC28+TJC28+PGA+EGA+CRP | |
| | | CDAI | CDAI = SJC28+TJC28+PGA+EGA | |
| | | HAQ | HAQ has 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip and activities | |
| | | SF-36 | Short-form health survey assesses 8 aspects of health status: general and mental health, physical function, social function, physical and emotional health, pain, vitality | |
| Database lock | 16 July 2018 as the last patient's Week 30 visit for Week 30 CSR 10 January 2019 as the last patient's End-of-Study (EOS) visit for Week 54 CSR 15 April 2019 as the last patient's last visit for final CSR | | | |
| Results and Analysis | | | | |
| Analysis description | Primary Analysis | | | |
| Analysis population and time point description | <ul style="list-style-type: none">All-randomised population: All randomly assigned patients at Week 6, regardless of whether or not any study drug dosing was completed.Efficacy population: All-randomized population who receive at least one full dose of study drug (CT-P13 IV, CT-P13 SC) at Week 6 or thereafter and who have at least one efficacy evaluation result after Week 6 or thereafter treatmentPrimary endpoint was analysed at Week 22 | | | |
| Descriptive statistics and estimate variability | Treatment group | CT-P13 IV 3 mg/kg | CT-P13 SC 120 mg | |
| | Number of subject | | | |
| | Efficacy population | 174 | 165 | |
| | All-randomised population | 176 | 167 | |
| | Change from baseline of | | | |
| | DAS28 (CRP) LS mean (SE) | | | |
| | Efficacy population | 1.94 (0.209) | 2.21 (0.221) | |
| | All-randomised | 1.85 (0.198) | 2.13 (0.211) | |

| | | | |
|---|---|---|--------------------------------------|
| | population | | |
| Effect estimate per comparison | Primary endpoint: change from baseline of DAS28 (CRP) | Comparison groups | CT-P13 SC 120 mg – CT-P13 IV 3 mg/kg |
| | | Estimate of Treatment Difference Efficacy population All-randomised population | 0.27 0.27 |
| | | 95% CI of Treatment Difference Efficacy population All-randomised population | (0.02, 0.52) (0.02, 0.53) |
| Notes | Pre-defined noninferiority margin was -0.6. The primary analysis for DAS28 (CRP) is an ANCOVA comparing the change from baseline of DAS28 (CRP) at Week 22 of treatment between the 2 arms, CT-P13 IV and CT-P13 SC. The LS mean and corresponding SE of the change from baseline in DAS28 (CRP) at Week 22 are presented for each arm. A point estimate and 2-sided 95% CI for the treatment difference (CT-P13 SC 120 mg arm - CT-P13 IV 3 mg/kg arm) are provided. | | |
| Analysis description | Secondary analysis | | |
| Analysis population and time point description | <ul style="list-style-type: none">Efficacy population: All-randomized population who receive at least one full dose of study drug (CT-P13 IV, CT-P13 SC) at Week 6 or thereafter and who have at least one efficacy evaluation result after Week 6 or thereafter treatmentSecondary endpoints were analysed at Weeks 0, 2, 6, 14, 22, 30 and 54 | | |
| Descriptive statistics and estimate variability | Treatment group | CT-P13 IV 3 mg/kg | CT-P13 SC 120 mg |
| | DAS28 (CRP/ESR) (Mean [SD]) | | |
| | Number of subject | 174 | 165 |
| | Mean (SD) of DAS28 (CRP) at Baseline | 5.863 (0.8090) | 6.008 (0.7541) |
| | Number of subject | 174 | 165 |
| | Mean (SD) of DAS28 (CRP) at Week 6 | 4.112 (1.2105) | 3.983 (1.2021) |
| | Number of subject | 168 | 162 |
| | Mean (SD) of DAS28 (CRP) at Week 22 | 3.482 (1.2329) | 3.338 (1.0958) |
| | Number of subject | 159 | 157 |
| | Mean (SD) of DAS28 (CRP) at Week 30 | 3.521 (1.2339) | 3.047 (1.1272) |
| | Number of subject | 145 | 145 |
| | Mean (SD) of DAS28 (CRP) at Week 54 | 2.913 (1.1648) | 2.796 (1.1414) |
| | Number of subject | 173 | 165 |
| | Mean (SD) of DAS28 (ESR) at Baseline | 6.557 (0.7843) | 6.695 (0.7889) |
| | Number of subject | 174 | 165 |
| | Mean (SD) of DAS28 (ESR) at Week 6 | 4.784 (1.2982) | 4.637 (1.2339) |
| | Number of subject | 169 | 163 |
| | Mean (SD) of DAS28 (ESR) at Week 22 | 4.097 (1.3308) | 3.984 (1.1229) |
| | Number of subject | 160 | 161 |
| | Mean (SD) of DAS28 (ESR) at Week 30 | 4.115 (1.3465) | 3.658 (1.1951) |
| Number of subject | 146 | 146 | |
| Mean (SD) of DAS28 (ESR) at Week 54 | 3.449 (1.2766) | 3.357 (1.2254) | |
| ACR 20, 50 and 70 (number [%] of patients) | | | |
| Number of subject | 174 | 165 | |
| ACR 20 at Week 6 | 103 (59.2) | 107 (64.8) | |

| | | | |
|--|-------------------|------------|------------|
| | ACR 20 at Week 22 | 137 (78.7) | 139 (84.2) |
| | ACR 20 at Week 30 | 133 (76.4) | 142 (86.1) |
| | ACR 20 at Week 54 | 125 (71.8) | 132 (80.0) |
| | ACR 50 at Week 6 | 45 (25.9) | 47 (28.5) |
| | ACR 50 at Week 22 | 90 (51.7) | 85 (51.5) |
| | ACR 50 at Week 30 | 87 (50.0) | 106 (64.2) |
| | ACR 50 at Week 54 | 101 (58.0) | 108 (65.5) |
| | ACR 70 at Week 6 | 18 (10.3) | 19 (11.5) |
| | ACR 70 at Week 22 | 49 (28.2) | 46 (27.9) |
| | ACR 70 at Week 30 | 47 (27.0) | 68 (41.2) |
| | ACR 70 at Week 54 | 68 (39.1) | 77 (46.7) |

Analysis performed across trials (pooled analyses and meta-analysis)

The MAH compared Efficacy data from Studies CT-P13 3.1 (CT-P13 or Remicade IV infusion) and CT-P13 3.5 (CT-P13 IV or SC injection). Study CT-P13 3.1 was a randomised, double-blind, parallel-group, pivotal Phase III study to demonstrate equivalence in efficacy and safety of CT-13 IV compared with Remicade when co-administered with MTX in patients with active RA. The MAH remarked that in Study CT-P13 3.5 the change from baseline of DAS28 (CRP) at Week 22 was the primary efficacy endpoint whereas, in Study CT-P13 3.1, the proportion of patients who achieved clinical response according to ACR20 was the primary endpoint but both endpoints were reported either as a primary or secondary endpoint in both studies. Results for both endpoints across these studies show similar responses up to Week 54, regardless of route of administration (CT-P13 IV vs. CT-P13 SC).

The MAH also compared efficacy data from Studies CT-P13 3.4 (CT-P13 or Remicade IV infusion) and CT-P13 1.6 Part 1 (CT-P13 IV infusion or CT-P13 SC injection). Study CT-P13 3.4 was a randomised, double-blind, parallel-group, Phase III study to demonstrate non-inferiority in efficacy and to assess safety of CT-P13 IV compared to Remicade in patients with active CD. According to the MAH, results from the CT-P13 IV 5 mg/kg cohort in study CT-P13 1.6 were slightly lower than those of the 2 treatment groups (CT-P13 5 mg/kg and Remicade 5 mg/kg maintenance groups) in Study CT-P13 3.4 but the overall results across all the treatment groups, including the CT-P13 SC cohorts, between Studies CT-P13 3.4 and CT-P13 1.6 were broadly similar.

Clinical studies in special populations

Not applicable.

2.7.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Design and conduct of the two dose-finding studies in RA and IBD

The proposed posology for the **RA**-population was supported by PK-data from Part 1 of study CT-P13 3.5. It was a randomised open-label study that compared CT-P13 SC (in 3 different dose levels) and CT-P13 IV when co-administered with MTX in patients with active RA who were not adequately responding to MTX. The study included a dose-loading phase during which all enrolled patients initially were to receive a 2-hour CT-P13 IV infusion at Weeks 0 and 2.

The proposed posology for the **IBD** population (indications not sought at present) was supported by PK-data from Part 1 of study CT-P13 1.6. The study was an open-label, randomised, multicentre, parallel group, Phase I study that compared CT-P13 SC (in three different dose-levels) and CT-P13 IV in patients with active CD. The study included a dose-loading phase during which all enrolled patients initially received a 2-hour CT-P13 IV infusion at Weeks 0 and 2.

Overall, the designs of the two dose-finding studies are acceptable including the patient population and comparator. Comments with regards to PK assessments can be found in the separate PK-section.

Design and conduct of the pivotal clinical study in RA

The primary objective of CT-P13 3.5, Part 2 was to demonstrate that CT-P13 SC is *non-inferior* to CT-P13 IV at Week 22, in terms of efficacy, as determined by clinical response according to change from baseline in disease activity as measured by Disease Activity Score using DAS28 (CRP). Overall, the study was a randomized, parallel group, Phase I/III study; in which CT-P13 SC and CT-P13 IV were compared when co-administered with MTX in patients with active RA who were not adequately responding to MTX. The clinical development program was discussed and agreed with the CHMP through Scientific Advice (SA) meetings. The primary and secondary endpoints are validated endpoints and broadly used in RA studies. The clinical setting (RA patients not adequately controlled with methotrexate, and with no prior biological treatment), the primary endpoint (DAS28(CRP)), and the non-inferiority margin of 0.6 points are in line with the CHMP guidance. The CHMP concluded that 54-week data are required for assessment of immunogenicity.

The eligibility criteria for the pivotal study were clinically relevant and similar to those in previous infliximab trials. However, there was a discrepancy regarding the cut-off point of CRP. In the pivotal therapeutic equivalence trial for Remsima IV (CT-P13 3.1) a CRP concentration of >2mg/dL was set as cut-off for inclusion, while the present study (Study CT-P13 3.5) has included patients with a CRP concentration >0.6 mg/dL. Enrolment of patients with a lower CRP might lead to enrolment of a population with less severe disease. In such a population the difference between treatments could be more difficult to detect, especially considering that the primary endpoint DAS28(CRP) includes CRP as a component. The MAH has provided data to confirm that the patients enrolled in Study CT-P13 3.1 had a similar disease activity as patients in Study CT-P13 3.5 Part 2 (according to DAS28(CRP) scores) in spite of slightly different inclusion criteria regarding CRP. Moreover, Study CT-P13 3.5 Part 2 results showed that CRP concentration at screening did not affect the efficacy results.

After randomisation up to Week 64, 26 patients in the SC group (15.6%) and 31 patients in the IV group (17.6%) discontinued in the maintenance phase. The withdrawal rates are acceptable.

The primary analysis was performed based on both the Efficacy population (defined in line with a per-protocol approach) and the All-Randomised population, which is endorsed given the primary non-inferiority objective. The difference between the two populations was however negligible due to few patients with major protocol deviations; in total only four patients were excluded in the Efficacy population (two in each arm). Major protocol violations were rare and do not have significant impact on the validity of the results.

Regarding the statistical analysis plan nothing specific has been found on how missing data was to be handled in the primary analysis of the primary endpoint. With support from reported outcomes patients with missing assessments were seemingly excluded and hence, both the Efficacy and All-randomised population analysis seems to have been performed on observed cases. One sensitivity analysis in the All-Randomised population was planned and has been performed in which missing data was replaced using a method of multiple imputation and assuming missing at random. Given primary outcomes and that it was few with missing assessments at week 22 (less than 5%, more patients in the IV than in the SC arm) the primary approach could be accepted. However, for confirmation, an additional analysis was requested. The MAH conducted mixed-effect model repeated measures (MRMM) for the absolute values of the primary endpoint, including weeks 14, 22 and 30 data in the both efficacy and all randomized populations, and provide appropriate point and interval estimates for treatment effect primarily at Week 22, but also at weeks 14 and 30. The model included week 6 values of DAS28 (CRP) as a covariate as the last observed value prior randomization, as well as stratification factors at randomization, treatment and week and their interaction as fixed effects. This sensitivity analysis confirmed the primary analysis.

The original study protocol was amended 17 times during the course of the study whereof four were global amendments and 13 were country specific. The amendments included deletion of primary PK objective for Part 2 and decision that DAS28 (CRP) would only be considered as primary endpoint for Part 2, update of the study design for Part 2 including double-blind and double-dummy design, addition of breaking the blind for Part 2 as per the updated design (double-blind), update of the statistical analysis plan as per the updated design, revision of the posology for part 2 from 'every 4 weeks' to 'every 2 weeks' as per the result of interim PK-PD modelling analysis, modification of the time point of EOS and revision of the study population for Part 2. Most of the amendments were implemented during Part 1 and before the initiation of part 2.

The MAH has provided a comprehensive list of amendments with brief justifications. The amendments were mostly clarifying changes and of editorial nature or in direct relation to scientific advice by the CHMP. For Study CT-P13 3.5 Part 2, all patients were enrolled and randomised based on the global protocol version 3.0. Five patients were enrolled after minor country specific amendments. None of the protocol amendments were data-driven and the amendments had no impact on the overall outcome of the Study CT-P13 3.5 Part 1 and Part 2. The amendments implemented after the part 2 study initiation were minor and had no impact on outcome.

During the assessment, the MAH reported a major scientific misconduct in the pivotal study CT-P13 3.5 Part 2 at one Site (with 5 enrolled subjects), which was found as a result of a GCP audit conducted by the MAH/CRO. The misconduct seemed to concern only the usability part of the pivotal study CT-P13 3.5 Part 2. The MAH undertook appropriate measures in performing a sensitivity analysis for the primary efficacy endpoint excluding the patients from the Site. The study results (primary endpoint, as well as usability results), with/ without the site were similar so the misconduct does not change the scientific conclusions.

Appropriate follow-up action was taken upon exposure of the scientific misconduct and two additional audits were conducted. The MAH provided all audit certificates. No new concerns emerged in relation to these audits.

The MAH also provided results from new sensitivity analyses of the efficacy data in the pivotal study CT-P13 3.5 part 2. The MAH performed sensitivity analysis of the primary endpoint, excluding one site at a time, to show that the results remain unchanged even after removing any one of the sites. All sites are relatively small, with only eight sites having 10 or more patients and only one site having more than 20 patients (32 patients). Therefore, it is clear that excluding any one site will not have a significant impact on the efficacy outcome. Also, the study was overpowered so exclusion of one site would not compromise the overall power to detect a difference.

The MAH also presented a table showing that the primary efficacy result is positive, i.e. non-inferiority holds, even when the top 21 sites (31.5% [51/162] patients in the CT-P13 SC 120 mg group, 38.7% [65/168] patients in the CT-P13 IV 3mg/kg group) along with the Site with the major scientific misconduct were excluded simultaneously among the total 64 sites.

In conclusion, the efficacy results of the pivotal trial are robust and any remaining uncertainties regarding GCP compliance are not considered to have severe impact on data quality of the pivotal trial. Based on these considerations the CHMP considers that the non-compliance reported by the MAH may be seen as an indication of improved procedures of the sponsor.

To support data integrity the MAH has further submitted 3rd party independent audit results from four additional site audits and an integrated audit report by the independent consultants. All mock inspections were dated in July or August 2019 and performed at the request of Celltrion and at several sites including the site which were major scientific misconduct had been reported. No additional concerns were raised based on findings from these audits.

Efficacy data and additional analyses

Clinical (efficacy/safety) data from the dose-finding study in RA (Part 1 of study CT-P13 3.5)

CT-P13 **120 mg by SC injection every 2 weeks after loading dose** was determined as the optimal dose for the **RA** indication based on PK-data from Part 1 of study CT-P13 3.5. Regarding the clinical data, the CHMP agrees that the outcome of the clinical efficacy measures in the 120 mg dose sc cohort does not appear to be consistently weaker than in the iv cohort. Moreover, there were no apparent differences in the clinical safety outcomes between the iv cohort and the SC cohort but CT-P13 SC appeared to be less immunogenic. Thus, there is nothing in the clinical data from this small open label study that clearly contradicts the SC dose that was selected for the RA population based on PK data.

Clinical efficacy did not appear to improve with increasing dose in the investigated dose intervals. Hence, if anything, e.g. the 90mg dose could have been enough for RA patients. However, the small number of patients (N = 7 to 13) in each cohort and the open-label design of the study strongly limit the interpretation of the efficacy results of study CT-P13 3.5 Part 1.

Discussion on the efficacy data from the pivotal clinical efficacy study (Part 2 of study CT-P13 3.5)

The baseline characteristics and prior treatment histories of patients in the pivotal study can be considered typical for patients with moderate to severe RA. The following aspects of the baseline characteristics were addressed in the LoQ.

Patients over 75 years of age were not included in the study. However, the MAH has shown that AUC and efficacy is similar for patients < 65 years and patients ≥ 65 years in Study CT-P13 3.5 Part 2 in both IV and SC treated patients. Moreover, AUC, clearance and volume of distribution does not seem to be strongly age related. Efficacy data from other infliximab or TNF α products in patients over 75 is very limited and actual PK data in this age group could not be found. The PK modelling does not take altered absorption into account and is not suitable for drawing conclusions on absorption in the elderly. However, the available data on patients ≥ 65 years does not suggest any dramatic age related difference in PK or efficacy and as the MAH states, the concerns around the impact of a thinner hypodermis and impaired lymphatic drainage in the elderly are mitigated by the location of injection site areas in abdomen, upper limbs or upper parts of lower limbs. Thus, no upper age limit is warranted despite absence of data in this age group.

Patients with a BMI ≥35 were not included in the study and there were only 7 patients weighing over 100kg in the Remsima SC 120mg group in the pivotal study. Thus, data on the exposure and efficacy in the highest weighing population is very limited.

However, subgroup analyses showed that there was no trend in efficacy results in CT-P13 SC 120 mg Q2W across the bodyweight subgroups and patients in the highest body weight subgroup (>88.2kg) demonstrated similar efficacy as the other patients. Moreover, predicted C_{trough} levels were maintained well-above the efficacy threshold of 1 μ g/mL. Other TNF-alpha products with subcutaneous administration are also indicated without upper weight limit no upper weight limit is warranted for Remsima SC, despite the limited data.

Initially it was unclear how similar the IV and SC groups were at baseline with regard to details of previous DMARD usage (disease-modifying anti-rheumatic drugs; e.g. duration of methotrexate treatment). The MAH has clarified that the dosage of MTX and duration of prior MTX usage at baseline were similar between the 2 arms and history of previous DMARDS usage, other than MTX, was balanced between the 2 arms.

Overall, there seemed to be no apparent asymmetry in baseline characteristics of interest.

The primary efficacy endpoint was defined as the change from baseline in disease activity measured by DAS28 (CRP) at Week 22. According to the pre-defined criteria approved by the CHMP, non-inferiority of Remsima SC 120 mg compared to Remsima IV 3 mg/kg was shown. Both treatment arms reached clinically significant response already by week 6. The mean difference in treatment response (0.27 points in DAS 28 (CRP)) in favour of Remsima SC is not considered clinically significant according to EULAR response criteria, where an improvement in DAS28(CRP) score of ≤ 0.6 is considered negligible.

It is noted that, even though efficacy was measured in terms of change **from baseline** to week 22, the treatment arms were identical until week 6. At week 6, more than 80% of all patients in both treatment arms had already reached at least a moderate clinical response. Therefore, the pivotal study (study CT-P13 3.5 Part 2) is in effect more suitable to show the efficacy of maintenance treatment and the results should be interpreted with focus on the change from week 6, rather than change from baseline. While the present study design is technically suitable to assess, whether the full potential of treatment with infliximab is reached equally well by week 22, regardless of a switch in formulation at week 6, from a clinical point of view, the relevant question is whether the achieved response will persist. It is unclear how long the achieved treatment response would persist if treatment were to be discontinued at week 6. This is essential because any non-inferiority between treatments can only be shown if there is a possibility to detect an effect compared to placebo. The sensitivity of the design is not optimal. DAS28(CRP) scores were similar in the two groups at baseline. However, at week 6 the mean DAS28 (CRP) score was 3.98 in the SC group and 4.11 in the IV group. The difference in change from baseline (-2.03 vs. -1.75 respectively) seen at week 6 cannot be attributed to difference in treatment.

The design where efficacy is measured as change from baseline despite a 6 weeks identical induction phase blurs the sensitivity to detect difference. The decrease from week 14 to week 22 is limited in both arms, thus the sensitivity to demonstrate non-inferiority at week 22 is not optimal, as it seems that the plateau has been reached. However, the decline in DAS28(CRP) scores continued after week 6 up until week 54. The mean difference in DAS28(CRP) from week 6 to week 22 is clinically significant and similar in both treatment arms. Since the SC formulation was consistently shown to give rise to slightly better results than the IV formulation, there is no reason to question the non-inferiority. The results of the secondary outcome endpoints were in line with the primary outcome and supported the observation of equal, if not even better efficacy of Remsima SC compared to Remsima IV up to week 54.

Discussion on the appropriateness of the selected doses for RA indication

The maintenance dosage regimen was proposed based on the Population PK and PK-PD modelling data from the original Remsima IV Studies (CT-P13 1.1, CT-P13 1.4, CT-P13 3.1, and CT-P13 3.4) and the studies from the Remsima SC programme in healthy volunteers (Study CT-P13 1.5) and RA patients (CT-P13 3.5 [Part 1 up to Week 54 and Part 2 up to Week 30]). The method of dose selection was endorsed in CHMP Scientific Advice. The objective was to exceed a target C_{trough} threshold of 1 $\mu\text{g/mL}$ and to generate a steady state AUC over 8 weeks ($AUC_{8\text{weeks,ss}}$) that aligned as closely as possible to that achieved following 3 mg/kg IV administration.

It is generally believed that C_{trough} is the driver for efficacy. However, the role of AUC and initial peak concentration in driving efficacy is not known. The high initial concentration of infliximab achieved only with IV administration might be crucial to the induction of response and this is adequately reflected in the SmPC since Remsima SC is only indicated after a loading dose comprising two intravenous infusions of infliximab.

The proportion of patients with observed $C_{trough} > 1 \mu\text{g/mL}$ at Week 30 was 81.8% (126/154) in the SC 120 mg treatment arm. Of note, the target C_{trough} of $> 1 \mu\text{g/mL}$ at Week 22 was achieved by only 28.5 % in the IV arm with a significant number of patients with virtually no detectable concentrations of infliximab at week 30. Nevertheless, significant clinical response was achieved also among these

patients, possibly because of high initial concentrations and a slow re-activation of symptoms even without treatment.

Regarding efficacy, the higher C_{trough} seen following SC administration supports the demonstrated clinical non-inferiority. Regarding safety, the C_{max} will be lower following the proposed SC dosing regimen, but the total exposure (AUC over 8 weeks) will be higher in most patients, though slightly lower in patients with high body weight. In addition, the C_{trough} -levels were indeed 12-fold higher in the SC-group. There are differences in exposure between the approved IV drug and the SC drug and these differences could potentially translate into clinical (safety) differences but the observed week 54 data from CT-P13 3.5, Part 2 supports that the safety profile of CT-P13 SC up to 1 year in the proposed posology for the RA indication is acceptable.

The observed data from Study CT-P13 3.5 Part 2 predicted no major differences in efficacy and safety between the selected 120 mg CT-P13 SC Q2W fixed-dosage regimen and the 3 mg/kg CT-P13 IV Q8W weight-based dosage regimen. Of note, neither was any remarkable improvement in efficacy seen in spite of the significantly higher C_{trough} concentrations in the SC treatment arm.

However, since a trend for better efficacy of the SC formulation is observable in the pivotal study, the question arises whether 120mg Remsima SC could in fact be more potent than 3mg/kg Remsima IV. Based on the dose-finding study (CT-P13 3.5 Part 1) a 90mg SC dose might be equally efficient as 120mg, even though the small number of patients in each cohort limits the interpretation of the efficacy results. In study CT-P13 3.5 Part 1 the mean pre-dose concentration was substantially greater (above 8 µg/mL) in the 90 mg SC cohort than in the IV 3mg/kg cohort (~0.6 to 1.0 mg/mL) and in terms of AUC over 8 weeks at steady state, exposure was 1,5-fold greater in the SC 90mg cohort compared to the IV 3mg/kg cohort ($AUC_{ss8W} = 11860 \text{ h} \cdot \mu\text{g/mL}$). The mean change from baseline of DAS28 (CRP/ ESR) was greater in the CT-P13 SC 90 mg cohort than other cohorts but this was explained by the higher baseline DAS28 (CRP/ ESR) score in the CT-P13 SC 90 mg cohort which resulted in a larger decrease in DAS28 (CRP/ ESR).

Based on the submitted data, and the reviewed literature, it remains slightly unclear whether a lower dose could have been more appropriate (with similar/ more efficacious profile, and similar safety profile, but with uncertainties related to the immunogenicity profile) than CT-P13 SC 120mg Q2W. Nevertheless, it can be concluded that the benefit/risk of the 120 mg dose seems overall similar to that of IV 3mg/kg dose.

Subgroup analyses showed that there are no apparent differences in efficacy among subjects according to body weight when subjects were divided into tertiles of body weight and patients categorised into the highest tertile of body weight (> 79.7 kg) were further divided into 2 groups using median weight (88.2kg). In all these weight bands, mean C_{trough} values remain above the threshold of 1 µg/mL. The proportion of patients who had at least one TEAE, treatment-emergent serious adverse event (TESAE) and Infection at Week 30 in Study CT-P13 3.5 Part 2 did not appear to be affected by the patient weight. The proportion of patients who were ADA and NAb positive at Week 30 in Study CT-P13 3.5 Part 2 did not appear to be affected by the patient weight.

To conclude, focusing on the clinical data, it is agreed with the MAH that the selected SC posology resulted in only marginal differences in clinical efficacy as measured by DAS28 change/ACR 20 response across the selected weight bands in the RA-study Study CT-P13 3.5 Part 2 and that this applies also for safety. Thus, for the RA-indication, there are no signals from the clinical data that the benefit/risk of the proposed posology would be unfavourable.

2.7.4. Conclusions on clinical efficacy

The primary efficacy endpoint was defined as the change from baseline in disease activity measured by DAS28 (CRP) at Week 22. According to the pre-defined criteria approved by the CHMP, non-inferiority of Remsima SC 120 mg compared to Remsima IV 3 mg/kg was shown. The results of the secondary outcome endpoints were in line with the primary outcome and supported the observation of non-inferior, if not even better efficacy of Remsima SC compared to Remsima IV up to week 54.

In the sought **RA** indication, with proposed doses, mean C_{trough} levels of infliximab were well above the target levels of 1 µg/mL in all weight bands.

Therefore, the CHMP concluded that the efficacy profile of Remsima subcutaneous formulation compared to Remsima intravenous formulation in RA patients was generally comparable in terms of disease activity measured by DAS28 (CRP and ESR) and ACR response up to week 54.

2.8. Clinical safety

Patient exposure

The originator IV infliximab, Remicade, has been approved in the EU since 1999. The safety profile of infliximab has been well characterised by more than 15 years of clinical use. Remsima IV was developed as an infliximab biosimilar and was approved by the EMA in September 2013. According to information provided by the MAH, to date Remsima has been approved in 80 countries and launched in 60 countries worldwide.

Based on information provided by the MAH in the original submission, a total of 846 RA patients, 212 AS patients and 166 CD patients have been exposed to Remsima IV in 9 completed clinical studies (CT-P13 1.1, CT-P13 1.2, CT-P13 1.3, CT-P13 3.1, CT-P13 3.2, CT-P13 3.3, CT-P13 3.4, B1P13101 and B2P13111). In addition, 10 non-interventional studies have been completed or are ongoing. Post-marketing exposure to Remsima in countries where it is launched is estimated at 370,108 patient-years up to 20 January 2018.

Across the 4 clinical studies included in the original application with Remsima SC, the safety population consisted of 693 subjects: 396 patients with rheumatoid arthritis, 44 patients with Crohn's disease and 253 healthy subjects. 633 subjects (367 RA patients, 31 CD patients and 235 healthy subjects) received at least 1 dose of Remsima SC. It is noteworthy, that in this group of 367 patients in RA were included also 162 RA patients who switched to Remsima SC at Week 30 in Study CT-P13 3.5 Part 2.

In the original submission, in total, only 26 RA patients and only 22 CD patients received Remsima SC treatment up to Week 54 in Study CT-P13 3.5 Part 1 and Study CT-P13 1.6 Part 1, respectively, and 162 RA patients received Remsima SC treatment up to Week 30 in Study CT-P13 3.5 Part 2. In total, 8 patients (with IBD) were exposed to the 240 mg with every other week posology. In studies with RA and CD patients, in total 398 patients have been exposed to at least one dose of CT-P13 SC and 196 patients have received the drug long-term.

According to updated safety data, including the five patients from the site where major scientific misconduct was reported, a total of 633 subjects (235 HVs, 367 RA and 31 CD patients) received at least 1 dose of CT-P13 SC and 576 subjects received at least 1 dose of 120 mg of CT-P13 SC in the overall CT-P13 SC program (Studies CT-P13 1.5 and CT-P13 1.9 in healthy volunteers [HVs] and Studies CT-P13 3.5 Parts 1 and 2 in RA patients and Study CT-P13 1.6 Part 1 in CD patients).

From Week 6 to Week 30, 220 patients overall (194 RA and 26 CD patients) received CT-P13 SC and 181 patients (172 RA and 9 CD patients) received 120 mg of CT-P13 SC.

From Week 6 to Week 54, 196 patients overall (174 RA and 22 CD patients) received CT-P13 SC and 166 patients (157 RA and 9 CD patients) received 120 mg of CT-P13 SC.

In study CT-P13 3.5 Part 2 a total of 148 patients have received CT-P13 SC from Week 6 to Week 54. In addition, 81 of these 148 RA patients received 120 mg of CT-P13 SC up to Week 64 (patients in Bulgaria, Poland and Russia for clinical usability assessment).

The number of patients exposed to CT-P13 SC over all studies is summarized in Table 23.

Table 23 - Number of Patients Exposed to CT-P13 SC in All Studies

| Study | Subjects | Dose (CT-P13 SC) | Study Duration | Number of Patients Receiving | | | |
|---|----------|----------------------------|----------------|--|--|--|--|
| | | | | At Least 1 Dose of CT-P13 SC | Treatment up to Week 30 in CT-P13 SC arm | Treatment up to Week 54 in CT-P13 SC arm | Treatment up to Week 64 in CT-P13 SC arm |
| Study CT-P13 1.5 | HV | 120 mg 180 mg 240 mg | 12 Weeks | 6 (120 mg) 7 (180 mg) 7 (240 mg) | | | |
| Study CT-P13 1.9 | HV | 120 mg | 12 Weeks | 215 (120 mg) | | | |
| Total in Healthy Volunteers | | | | 235 | | | |
| Study CT-P13 3.5 Part 1 | RA | 90 mg 120 mg 180 mg | 54 Weeks | 11 (90 mg) 12 (120 mg) 12 (180 mg) | 10 (90 mg) 11 (120 mg) 12 (180 mg) | 9 (90 mg) 9 (120 mg) 8 (180 mg) | N/A |
| Study CT-P13 3.5 Part 2 | RA | 120 mg | 64 Weeks | 332 ¹ (120 mg) | 161 ² (120 mg) | 148 ² (120 mg) | 81 (120 mg) |
| Total in Rheumatoid Arthritis Patients | | | | 367 | 194 | 174 | 81 |
| Study CT-P13 1.6 Part 1 | CD | 120 mg 180 mg 240 mg | 54 Weeks | 11 (120 mg) 12 (180 mg) 8 (240 mg) | 9 (120 mg) 11 (180 mg) 6 (240 mg) | 9 (120 mg) 7 (180 mg) 6 (240 mg) | N/A |
| Total in Crohn's Disease Patients | | | | 31 | 26 | 22 | N/A |
| Total | | | | 633 (576 exposed to SC 120 mg) | 220 (181 exposed to SC 120 mg) | 196 (166 exposed to SC 120 mg) | 81 (120 mg) |

¹ Including 162 patients in the CT-P13 IV arm who switched to CT-P13 SC 120 mg treatment at Week 30

² Excluding Patient who was randomised to the CT-P13 IV arm at Week 6 but received 120 mg of CT-P13 SC instead of the placebo SC at Week 14
CD: Crohn's disease, HV: Healthy volunteer, IV: Intravenous, RA: Rheumatoid arthritis, SC: Subcutaneous

In conclusion, the long-term safety database in patients with RA has been extended; however, the numbers are still limited to identify potential rare adverse events.

No paediatric indications are proposed for CT-P13 SC in this line extension indication and no paediatric data is submitted.

Exposure by subject

All healthy subjects received a single dose of CT-P13 SC that was \leq 240 mg.

The MAH has proposed a fixed maintenance dose 120 mg SC q2w. However, the proposed dose (and the other simulated dosing regimens) results in high plasma C_{trough} levels. The MAH has submitted updated results of the Study CT-P13 3.5 in patients with RA. The database is still limited, however, no safety concerns in relation to high C_{trough} levels were observed.

In the original submission, the MAH indicated that most RA patients in Study CT-P13 3.5 Parts 1 and 2 received a cumulative SC dose between 1320 to 1860 mg. The mean (SD) of total administered doses up to (and including) Week 30 of SC 120 mg treatment arm was greater than that of IV 3 mg/kg treatment arm; 1515.53 (203.423) mg and 646.11 (141.891) mg in SC 120 mg and IV 3 mg/kg treatment arms, respectively. Among 167 patients who received \leq 240 mg dose of Remsima SC, 162 RA patients received only 1 dose of SC 120 mg after switching to CT-P13 SC at Week 30. Most CD patients in Study CT-P13 1.6 Part 1 received a cumulative subcutaneous dose above 2400 mg.

Based on updated data from Study CT-P13 3.5 Part 2 up to Week 54, the number of RA patients who had received at least one Remsima SC treatment was 332. The number of doses and total amount of

Remsima SC administered from Week 30 to Week 54 for the Remsima IV arm and Week 6 to Week 54 for the Remsima SC arm are provided in Table 24. The mean (SD) total dose of CT-P13 SC administered was 1473.33 (300.04) mg in the IV 3 mg/kg and 2829.18 (510.58) mg in the SC 120 mg arm.

Table 24 - Descriptive Statistics for Number of Subcutaneous Doses and Total Amount of Study Drug Received in Study CT-P13 3.5 Part 2: Safety Population (Original safety data, including patients from the site where major scientific misconduct was reported)

| | CT-P13 IV ¹ 3 mg/kg | CT-P13 SC 120 mg |
|--|-----------------------------------|---------------------|
| Maintenance phase (up to Week 54) | | |
| Total number of doses received | | |
| Number of Patients | 162 | 170 |
| Mean | 12.3 | 23.6 |
| SD | 2.50 | 4.25 |
| Median | 13.0 | 25.0 |
| Minimum, maximum | 1, 13 | 2, 25 |
| Total administered dose (mg) | | |
| Number of Patients | 162 | 170 |
| Mean | 1473.33 | 2829.18 |
| SD | 300.04 | 510.58 |
| Median | 1560 | 3000 |
| Minimum, maximum | 120, 1560 | 240, 3000 |

¹ Patients switched to CT-P13 SC 120 mg treatment at Week 30
IV: Intravenous, SC: Subcutaneous, SD: Standard deviation.

Table 25 - Descriptive Statistics for Number of Subcutaneous Doses and Total Amount of Study Drug Received in Study CT-P13 3.5 Part 2: Safety Population (Updated safety data, excluding five patients from the site where major scientific misconduct was reported)

| | SC 120 mg (N=168) | IV 3 mg/kg (N=175) |
|--|-------------------------|-------------------------|
| Maintenance Phase (SC) (up to Week 54) | | |
| Total number of doses received | | |
| n | 168 | 160 ¹ |
| Mean (SD) | 23.6 (4.28) | 12.3 (2.51) |
| Median (min, max) | 25.0 (2, 25) | 13.0 (1, 13) |
| Total administered dose (mg) | | |
| n | 168 | 160 ¹ |
| Mean (SD) | 2827.14 (513.284) | 1472.25 (301.760) |
| Median (min, max) | 3000.00 (240.0, 3000.0) | 1560.00 (120.0, 1560.0) |
| Maintenance Phase (IV) (up to Week 54) | | |
| Total number of doses received | | |
| n | 1 ² | 175 |
| Mean (SD) | 3.0 | 2.9 (0.27) |
| Median (min, max) | 3.0 (3, 3) | 3.0 (1, 3) |
| Total administered dose (mg) | | |
| n | 1 ² | 175 |
| Mean (SD) | 598.80 | 644.40 (141.797) |
| Median (min, max) | 598.80 (598.8, 598.8) | 635.40 (224.4, 1016.4) |
| Maintenance Phase (SC) (Week 56 to Week 64)³ | | |
| Total number of doses received | | |
| n | 83 | 82 |
| Mean (SD) | 5.0 (0.19) | 5.0 (0.11) |
| Median (min, max) | 5.0 (4, 5) | 5.0 (4, 5) |
| Total administered dose (mg) | | |
| n | 83 | 82 |
| Mean (SD) | 595.66 (22.534) | 598.54 (13.252) |
| Median (min, max) | 600.00 (480.0, 600.0) | 600.00 (480.0, 600.0) |

Abbreviations: IV, intravenous; Max, maximum; Min, minimum; SC, subcutaneous; SD, standard deviation.

1. Patients in the IV 3 mg/kg treatment arm who were ongoing with the study at Week 30 were switched to receive CT-P13 SC treatment from Week 30.
2. Patient in the IV 3 mg/kg treatment arm was administered with both CT-P13 IV and CT-P13 SC treatments at Week 14. According to the SAP (Version 4.0), this patient was analysed as CT-P13 SC 120 mg treatment arm for safety population.
3. Visits from Week 56 to Week 64 were only made by patients from Bulgaria, Poland, and Russia.

In conclusion, the total administered dose for patients in the Remsima SC arm was on average 2-fold compared to IV arm, AUC-levels were higher, and C_{trough} concentrations after SC administration were > 12-fold in comparison to IV. The data concerning potential long-term effects of this on patient safety, particularly concerning serious infections (including TB and other opportunistic infections) is still limited, and data concerning cancer still unknown.

Adverse events

The safety assessments of Remsima SC included monitoring of adverse events (AEs), serious adverse events (SAEs), treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs) and deaths; vital signs measurements (including blood pressure, heart rate, respiratory rate [RR] and body temperature); hypersensitivity monitoring; 12-lead electrocardiogram (ECG); physical examination; clinical laboratory tests (including liver function tests, Hepatitis B, C and HIV screening); recording concomitant medications, monitoring for signs and symptoms of TB, chest x-ray and interferon- γ release assay (IGRA); and pregnancy tests. The immunogenicity of Remsima was assessed by measuring anti-drug antibodies (ADA) and neutralising antibodies (NAb) at pre-defined endpoints. Local site pain was measured using Visual Analogue Scale (VAS).

The following events were monitored as adverse events of special interest (AESIs) in the Remsima SC studies: Administration-related reactions (ARR), which included infusion-related reactions (IRRs) (for IV) and systemic injection reaction (for SC), hypersensitivity and anaphylactic reactions, injection site reactions, intended to capture local injection site reactions; as well as infections (including TB), and malignancies.

The selection of safety assessments can be considered adequate.

Adverse events in healthy volunteers

Study CT-P13 1.5

In Study CT-P13 1.5 the most commonly reported TEAE was fatigue (3 [7.9%] subjects overall; 1 subject each in the SC 120 mg, SC 180 mg and IV 5 mg/kg cohorts).

At least 1 TEAE considered to be related to study drug was reported for 4 (10.5%) subjects overall (1 subject in each of the SC 120 mg [ISR], SC 180 mg [fatigue], IV 3 mg/kg [herpes zoster] and IV 5 mg/kg [fatigue] cohorts). These events were of grade 1 and 2, and no Grade 3 - 5 events or SAEs considered as related to study medication were observed.

Study CT-P13 1.9

In Study CT-P13 1.9 at least 1 TEAE considered to be related to study drug was reported for 72 (33.5%) subjects overall (37 [33.9%] subjects in the Remsima SC AI arm and 35 [33.0%] subjects in the Remsima SC PFS arm).

The most commonly reported TEAEs ($\geq 5\%$ subjects overall) were blood creatine phosphokinase (CPK) increased (20 [9.3%] subjects overall; 7 [6.4%] subjects in the Remsima SC AI arm, and 13 [12.3%] subjects in the Remsima SC PFS arm) and ISR (14 [6.5%] subjects overall; 5 [4.6%] in the AI arm and 9 [8.5%] subjects in the PFS arm). After SC dosing, ARR were seen in 2.8% in study CT-P13 1.9. The incidence of TEAEs in Study CT-P13 1.9 was generally similar to the incidence reported in other single-dose anti-TNF studies conducted in healthy volunteers.

Table 26 - A Summary of Adverse Events in Healthy Volunteer Studies: Safety Population

| | Study CT-P13 1.5 | | | | | Study CT-P13 1.9 | |
|--|---------------------------------|---------------------------------|---------------------------------|-----------------------------------|----------------------------------|--------------------------------------|---------------------------------------|
| | CT-P13 SC 120 mg (N=6) | CT-P13 SC 180 mg (N=7) | CT-P13 SC 240 mg (N=7) | CT-P13 IV 3 mg/kg (N=10) | CT-P13 IV 5 mg/kg (N=8) | CT-P13 SC AI 120 mg (N=109) | CT-P13 SC PFS 120 mg (N=106) |
| Total number of TEAEs | 5 | 4 | 1 | 4 | 3 | 115 | 89 |
| Number (%) of patients with ≥ 1 TEAE | 3 (50.0) | 3 (42.9) | 1 (14.3) | 4 (40.0) | 2 (25.0) | 55 (50.5) | 54 (50.9) |
| Related | 1 (16.7) | 1 (14.3) | 0 | 1 (10.0) | 1 (12.5) | 37 (33.9) | 35 (33.0) |
| Unrelated | 3 (50.0) | 2 (28.6) | 1 (14.3) | 3 (30.0) | 2 (25.0) | 32 (29.4) | 26 (24.5) |
| Number (%) of patients with ≥ 1 TEAE leading to death | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Number (%) of patients with ≥ 1 TESAE | 0 | 0 | 0 | 0 | 0 | 2 (1.8) ¹ | 0 |
| Related | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Unrelated | 0 | 0 | 0 | 0 | 0 | 2 (1.8) ¹ | 0 |
| Number (%) of patients with ≥ 1 TEAE leading to permanent discontinuation from study drug | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Number (%) of patients with ≥ 1 TEAE classified as IRR/SIR ² | 0 | 0 | 0 | 0 | 0 | 3 (2.8) | 3 (2.8) |
| Related | 0 | 0 | 0 | 0 | 0 | 3 (2.8) | 3 (2.8) |
| Unrelated | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Number (%) of patients with ≥ 1 TEAE classified as localised ISR ³ | 1 (16.7) | 1 (14.3) | 0 | 0 | 0 | 5 (4.6) | 9 (8.5) |
| Related | 1 (16.7) | 0 | 0 | 0 | 0 | 5 (4.6) | 9 (8.5) |
| Unrelated | 0 | 1 (14.3) | 0 | 0 | 0 | 0 | 0 |
| Number (%) of patients with ≥ 1 TEAE classified as infection | 0 | 0 | 0 | 1 (10.0) | 1 (12.5) | 9 (8.3) | 7 (6.6) |
| Related | 0 | 0 | 0 | 1 (10.0) | 0 | 8 (7.3) | 5 (4.7) |
| Unrelated | 0 | 0 | 0 | 0 | 1 (12.5) | 1 (0.9) | 2 (1.9) |

¹ Both TESAEs were road traffic accidents considered by the Investigator to be unrelated to study drug.

² In Study CT-P13 1.5, IRR/SIR was reported as infusion-related reaction in the eCRF and in Study CT-P13 1.9, SIR was reported as administration-related reaction in the eCRF.

³ In Studies CT-P13 1.5 and CT-P13 1.9, localised ISR was reported as injection site reaction in the eCRF.

eCRF: Electronic case report form, IRR: Infusion-related reaction, ISR: Injection site reaction, IV: Intravenous, SC: Subcutaneous, SIR: Systemic injection reaction, TEAE: Treatment-emergent adverse event; TESAE: Treatment-emergent serious adverse event

Adverse events in patients with RA

AEs in Study CT-P13 3.5 Part 1

For baseline characteristics of Study CT-P13 3.5 patients, see Section 3.3 of the Clinical AR.

In Part 1, a total of 50 patients were enrolled in the study and 48 patients were randomly assigned to study treatment at Week 6. Among the randomised patients, 41/48 (85.4%) patients completed the study and 7/48 (14.6%) patients discontinued the study. However, long-term data of SC treatment up to 54 weeks from the maintenance phase of this Part 1 is only available from 26 subjects.

During the Maintenance Phase of Study CT-P13 3.5 Part 1, at least 1 TEAE was reported for 9 (69.2%) patients in the IV 3 mg/kg cohort, 7 (63.6%) patients in the SC 90 mg cohort, 8 (66.7%) patients in the SC 120 mg cohort and 9 (75.0%) patients in the SC 180 mg cohort.

The most commonly reported TEAEs were ISR (5 [10.4%] patients overall; 2 [18.2%] patients in the SC 90 mg cohort, 1 [8.3%] patient in the SC 120 mg cohort and 2 [16.7%] patients in the SC 180 mg cohort) and upper respiratory tract infection (5 [10.4%] patients overall; 1 [7.7%] patient in the IV 3 mg/kg cohort, 1 [9.1%] patient in the SC 90 mg cohort, 1 [8.3%] patient in the SC 120 mg cohort and 2 [16.7%] patients in the SC 180 mg cohort). No deaths were reported during Part 1 of Study CT-P13 3.5.

Study CT-P13 3.5 Part 2

After D120 the MAH reported a major scientific misconduct in the pivotal study CT-P13 3.5 Part 2 at one Site. According to standard praxis, the main results have been updated, excluding the five patients from the non-compliant site. However, these patients have been exposed to the study drug and have also experienced some adverse events. Therefore, in order not to omit any relevant data on recorded adverse events, listings of adverse events are mostly presented here with the patients from the site where major scientific misconduct was reported included.

In RA study Part 2, a total of 362 patients were enrolled for the study and 348 patients were randomly assigned to study treatment at Week 6. Among the randomised patients, at Week 30, 325/348 (93.4%) patients were continuing in the study and 23 (6.6%) patients had discontinued the study.

During the Maintenance Phase of Study CT-P13 3.5 Part 2 up to Week 30, at least 1 TEAE was reported for 76 (42.7%) patients in the IV 3 mg/kg arm and 62 (36.5%) patients in the SC 120 mg Arm (Table 3.3.8.4). The most commonly reported TEAEs were ISR (15 [4.3%] patients overall; 4 [2.2%] patients in the IV 3 mg/kg arm and 11 [6.5%] patients in the SC 120 mg arm), followed by viral upper respiratory tract infection (13 [3.7%] patients overall; 6 [3.4%] patients in the IV 3 mg/kg arm and 7 [4.1%] patients in the SC 120 mg arm), latent TB (11 [3.2%] patients overall; 7 [3.9%] patients in the IV 3 mg/kg arm and 4 [2.4%] patients in the SC 120 mg arm) and upper respiratory tract infection (11 [3.2%] patients overall; 6 [3.4%] patients in the IV 3 mg/kg arm and 5 [2.9%] patients in the SC 120 mg). These numbers include patients from the site where major scientific misconduct was reported.

In study CT-P13 3.5 Part 2, up to week 30, a total of 3 deaths were reported during the treatment period up to and including Week 30; 1 patient in SC 120 mg treatment arm and 2 patients in IV 3 mg/kg treatment arm. With the updated safety data, two additional deaths were reported in those patients who switched from Remsima IV to SC at Week 30.

The overview of adverse events in Study CT-P13 3.5 is provided in the below tables.

Table 27 - Overview of Adverse Events in Study CT-P13 3.5 Part 1 up to Week 54 and Part 2 up to Week 30 (Maintenance Phase): Safety Population. (Original safety data, including patients from the site where major scientific misconduct was reported)

| | Study CT-P13 3.5 Part 1 | | | | Study CT-P13 3.5 Part 2 | |
|---|-----------------------------------|---------------------------------|----------------------------------|----------------------------------|------------------------------------|-----------------------------------|
| | CT-P13 IV 3 mg/kg (N=13) | CT-P13 SC 90 mg (N=11) | CT-P13 SC 120 mg (N=12) | CT-P13 SC 180 mg (N=12) | CT-P13 IV 3 mg/kg (N=178) | CT-P13 SC 120 mg (N=170) |
| Total number of TEAEs | 27 | 24 | 17 | 41 | 143 | 120 |
| Number (%) of patients with ≥ 1 TEAE | 9 (69.2%) | 7 (63.6%) | 8 (66.7%) | 9 (75.0%) | 76 (42.7%) | 62 (36.5%) |
| Related | 4 (30.8%) | 5 (45.5%) | 7 (58.3%) | 7 (58.3%) | 38 (21.3%) | 43 (25.3%) |
| Unrelated | 9 (69.2%) | 5 (45.5%) | 2 (16.7%) | 4 (33.3%) | 52 (29.2%) | 27 (15.9%) |
| Number (%) of patients with ≥ 1 TEAE leading to death | 0 | 0 | 0 | 0 | 2 (1.1%) | 1 (0.6%) |
| Related | 0 | 0 | 0 | 0 | 0 | 0 |
| Unrelated | 0 | 0 | 0 | 0 | 2 (1.1%) | 1 (0.6%) |
| Number (%) of patients with ≥ 1 TESAE | 1 (7.7%) | 2 (18.2%) | 0 | 3 (25.0%) | 7 (3.9%) | 3 (1.8%) |
| Related | 0 | 0 | 0 | 2 (16.7%) | 4 (2.2%) | 1 (0.6%) |
| Unrelated | 1 (7.7%) | 2 (18.2%) | 0 | 1 (8.3%) | 5 (2.8%) | 2 (1.2%) |
| Number (%) of patients with ≥ 1 TEAE leading to permanent discontinuation from study drug | 0 | 2 (18.2%) | 2 (16.7%) | 2 (16.7%) | 9 (5.1%) | 1 (0.6%) |
| Related | 0 | 1 (9.1%) | 2 (16.7%) | 2 (16.7%) | 8 (4.5%) | 0 |
| Unrelated | 0 | 1 (9.1%) | 0 | 0 | 1 (0.6%) | 1 (0.6%) |
| Number (%) of patients with ≥ 1 TEAE classified as ARR ¹ | 1 (7.7%) | 1 (9.1%) | 2 (16.7%) | 0 | 8 (4.5%) | 1 (0.6%) |
| Related | 1 (7.7%) | 1 (9.1%) | 2 (16.7%) | 0 | 8 (4.5%) | 1 (0.6%) |
| Unrelated | 0 | 0 | 0 | 0 | 0 | 0 |
| Number (%) of patients with ≥ 1 TEAE classified as ISR | 0 | 2 (18.2%) | 1 (8.3%) | 2 (16.7%) | 4 (2.2%) | 11 (6.5%) |
| Related | 0 | 2 (18.2%) | 1 (8.3%) | 2 (16.7%) | 4 (2.2%) | 11 (6.5%) |
| Unrelated | 0 | 0 | 0 | 0 | 0 | 0 |
| Number (%) of patients with ≥ 1 TEAE classified as infection | 5 (38.5%) | 4 (36.4%) | 3 (25.0%) | 6 (50.0%) | 32 (18.0%) | 34 (20.0%) |
| Related | 2 (15.4%) | 1 (9.1%) | 3 (25.0%) | 3 (25.0%) | 13 (7.3%) | 18 (10.6%) |
| Unrelated | 4 (30.8%) | 4 (36.4%) | 0 | 3 (25.0%) | 20 (11.2%) | 18 (10.6%) |
| Number (%) of patients with ≥ 1 TEAE classified as malignancy | 0 | 0 | 0 | 0 | 0 | 0 |
| Related | 0 | 0 | 0 | 0 | 0 | 0 |
| Unrelated | 0 | 0 | 0 | 0 | 0 | 0 |

¹ In Study CT-P13 3.5 Part 1, ARR was reported as IRR in the eCRF.

ARR: Administration-related reaction, eCRF: Electronic Case Report Form, IRR: Infusion-related reaction, ISR: Injection site reaction, IV: Intravenous, SC: Subcutaneous, TEAE: Treatment-emergent adverse event, TESAE: Treatment-emergent serious adverse event

Table 28 - Overview of Adverse Events in Study CT-P13 3.5 Part 2 up to Week 54 (Maintenance Phase): Safety Population (Week 54 Clinical Study Report, including five patients from the site where major scientific misconduct was reported)

| | SC 120 mg (N=170) | IV 3 mg/kg (N=178) | Total (N=348) |
|--|------------------------------|-------------------------------|--------------------------|
| Total number of TEAEs | 265 | 283 | 548 |
| Number (%) of patients with at least 1 TEAE | 92 (54.1) | 113 (63.5) | 205 (58.9) |
| Related to the study drug | 71 (41.8) | 70 (39.3) | 141 (40.5) |
| Unrelated to the study drug | 46 (27.1) | 73 (41.0) | 119 (34.2) |
| Total number of TESAEs | 8 | 15 | 23 |
| Number (%) of patients with at least 1 TESA | 6 (3.5) | 13 (7.3) | 19 (5.5) |
| Related to the study drug | 3 (1.8) | 4 (2.2) | 7 (2.0) |
| Unrelated to the study drug | 3 (1.8) | 11 (6.2) | 14 (4.0) |
| Total number of TEAEs leading to discontinuation of study drug | 5 | 14 | 19 |
| Number (%) of patients with at least 1 TEAE leading to discontinuation of study drug | 5 (2.9) | 14 (7.9) | 19 (5.5) |
| Related to the study drug | 4 (2.4) | 10 (5.6) | 14 (4.0) |
| Unrelated to the study drug | 1 (0.6) | 4 (2.2) | 5 (1.4) |
| Total number of TEAEs classified as IRR | 0 | 7 | 7 |
| Number (%) of patients with at least 1 TEAE classified as IRR | 0 | 7 (3.9) | 7 (2.0) |
| Total number of TEAEs classified as SIR | 2 | 3 | 5 |
| Number (%) of patients with at least 1 TEAE classified as SIR | 2 (1.2) | 3 (1.7) | 5 (1.4) |
| Total number of TEAEs classified as delayed hypersensitivity | 2 | 0 | 2 |
| Number (%) of patients with at least 1 TEAE classified as delayed hypersensitivity | 2 (1.2) | 0 | 2 (0.6) |
| Total number of TEAEs classified as localised ISR | 91 | 48 | 139 |
| Number (%) of patients with at least 1 TEAE classified as localised ISR | 28 (16.5) | 22 (12.4) | 50 (14.4) |
| Total number of TEAEs classified as infections | 71 | 72 | 143 |
| Number (%) of patients with at least 1 TEAE classified as infections | 48 (28.2) | 54 (30.3) | 102 (29.3) |
| Total number of TEAEs classified as malignancy | 1 | 0 | 1 |
| Number (%) of patients with at least 1 TEAE classified as malignancy | 1 (0.6) | 0 | 1 (0.3) |

Abbreviations: IRR, infusion related reaction; ISR, injection site reaction; IV, intravenous; SC, subcutaneous; SIR, systemic injection reaction; TEAE, treatment-emergent adverse event; TESA, treatment-emergent serious adverse event.

Note: The total number of TEAEs included all-patient events. At each level of summarisation, a patient was counted once if they reported 1 or more events. Only the most severe event was counted. The event was considered to be related to the study drug by the investigator if the relationship was defined as "possible", "probable", or "definite".

Table 29 - Overview of Adverse Events in Study CT-P13 3.5 Part 2 up to Week 54 (up to Week 64 for patients in Bulgaria, Poland and Russia) (Maintenance phase): Safety Population (Final Clinical Study Report, excluding five patients from the site where major scientific misconduct was reported)

| | SC 120 mg (N=168) | IV 3 mg/kg (N=175) | Total (N=343) |
|--|------------------------------|-------------------------------|--------------------------|
| Total number of TEAEs | 309 | 313 | 622 |
| Number (%) of patients with at least 1 TEAE | 92 (54.8) | 117 (66.9) | 209 (60.9) |
| Related to the study drug | 73 (43.5) | 72 (41.1) | 145 (42.3) |
| Unrelated to the study drug | 46 (27.4) | 77 (44.0) | 123 (35.9) |
| Total number of TESAEs | 8 | 15 | 23 |
| Number (%) of patients with at least 1 TESA | 6 (3.6) | 13 (7.4) | 19 (5.5) |
| Related to the study drug | 3 (1.8) | 4 (2.3) | 7 (2.0) |
| Unrelated to the study drug | 3 (1.8) | 11 (6.3) | 14 (4.1) |
| Total number of TEAEs leading to discontinuation of study drug | 6 | 14 | 20 |
| Number (%) of patients with at least 1 TEAE leading to discontinuation of study drug | 6 (3.6) | 14 (8.0) | 20 (5.8) |
| Related to the study drug | 5 (3.0) | 10 (5.7) | 15 (4.4) |
| Unrelated to the study drug | 1 (0.6) | 4 (2.3) | 5 (1.5) |
| Total number of TEAEs classified as IRR | 0 | 7 | 7 |
| Number (%) of patients with at least 1 TEAE classified as IRR | 0 | 7 (4.0) | 7 (2.0) |
| Total number of TEAEs classified as SIR | 2 | 3 | 5 |
| Number (%) of patients with at least 1 TEAE classified as SIR | 2 (1.2) | 3 (1.7) | 5 (1.5) |
| Total number of TEAEs classified as delayed hypersensitivity | 4 | 0 | 4 |
| Number (%) of patients with at least 1 TEAE classified as delayed hypersensitivity | 4 (2.4) | 0 | 4 (1.2) |
| Total number of TEAEs classified as localised ISR | 118 | 61 | 179 |
| Number (%) of patients with at least 1 TEAE classified as localised ISR | 30 (17.9) | 22 (12.6) | 52 (15.2) |
| Total number of TEAEs classified as infections | 78 | 83 | 161 |
| Number (%) of patients with at least 1 TEAE classified as infections | 49 (29.2) | 60 (34.3) | 109 (31.8) |
| Total number of TEAEs classified as malignancy | 1 | 0 | 1 |
| Number (%) of patients with at least 1 TEAE classified as malignancy | 1 (0.6) | 0 | 1 (0.3) |

Abbreviations: IRR, infusion related reaction; ISR, injection site reaction; IV, intravenous; SC, subcutaneous; SIR, systemic injection reaction; TEAE, treatment-emergent adverse event; TESA, treatment-emergent serious adverse event.

Note: The total number of TEAEs included all-patient events. At each level of summarisation, a patient was counted once if they reported 1 or more events. Only the most severe event was counted. The event was considered to be related to the study drug by the investigator if the relationship was defined as "possible", "probable", or "definite". Treatment-emergent AEs occurred in maintenance phase were summarised.

Table 30 - Treatment-Emergent Adverse Events Reported during the Maintenance Phase for at Least 3% of Patients in Any Treatment Arm by System Organ Class and Preferred Term in Study CT-P13 3.5 Part 2 up to Week 54: Safety Population (Updated safety data, including five patients from the site where major scientific misconduct was reported)

| System Organ Class ¹ Preferred Term ¹ | SC 120 mg (N=170) | IV 3 mg/kg (N=178) | Total (N=348) |
|--|------------------------|-----------------------|------------------|
| | Number (%) of patients | | |
| Infections and infestations | 30 (17.6) | 36 (20.2) | 66 (19.0) |
| Viral upper respiratory tract infection | 10 (5.9) | 10 (5.6) | 20 (5.7) |
| Upper respiratory tract infection | 6 (3.5) | 13 (7.3) | 19 (5.5) |
| Latent tuberculosis | 8 (4.7) | 10 (5.6) | 18 (5.2) |
| Urinary tract infection | 9 (5.3) | 7 (3.9) | 16 (4.6) |
| General disorders and administration site conditions | 28 (16.5) | 22 (12.4) | 50 (14.4) |
| Localised injection site reaction ² | 28 (16.5) | 22 (12.4) | 50 (14.4) |
| Investigations | 7 (4.1) | 9 (5.1) | 16 (4.6) |
| Alanine aminotransferase increased | 7 (4.1) | 9 (5.1) | 16 (4.6) |
| Aspartate aminotransferase increased | 2 (1.2) | 6 (3.4) | 8 (2.3) |
| Injury, poisoning and procedural complications | 3 (1.8) | 10 (5.6) | 13 (3.7) |
| Infusion related reaction ³ | 0 | 7 (3.9) | 7 (2.0) |
| Musculoskeletal and connective tissue disorders | 6 (3.5) | 6 (3.4) | 12 (3.4) |
| Rheumatoid arthritis | 6 (3.5) | 6 (3.4) | 12 (3.4) |
| Nervous system disorders | 5 (2.9) | 7 (3.9) | 12 (3.4) |
| Headache | 5 (2.9) | 7 (3.9) | 12 (3.4) |
| Blood and lymphatic system disorders | 6 (3.5) | 4 (2.2) | 10 (2.9) |
| Neutropenia | 6 (3.5) | 4 (2.2) | 10 (2.9) |

Abbreviations: IV, intravenous; PT, preferred term; SC, subcutaneous.

Note: At each level of summarisation, patients were counted once if they reported 1 or more events. Only the most severe event was counted.

1. From MedDRA, Version 20.0
2. Localised injection site reaction: PT reported as "injection site reaction".
3. Infusion related reaction: PT reported as "administration related reaction" and occurred between start of administration and 24 hours from the end of IV infusion (including placebo).

Table 31 - Treatment-Emergent Adverse Events Reported during the Maintenance Phase for at Least 3% of Patients in Any Treatment Arm by System Organ Class and Preferred Term in Study CT-P13 3.5 Part 2 up to Week 54 (up to Week 64 for patients in Bulgaria, Poland and Russia): Safety Population (Updated safety data, excluding five patients from the site where major scientific misconduct was reported)

| System Organ Class ¹ Preferred Term ¹ | SC 120 mg (N=168) | IV 3 mg/kg (N=175) | Total (N=343) |
|--|------------------------|-----------------------|------------------|
| | Number (%) of patients | | |
| Infections and infestations | 30 (17.9) | 40 (22.9) | 70 (20.4) |
| Viral upper respiratory tract infection | 10 (6.0) | 14 (8.0) | 24 (7.0) |
| Upper respiratory tract infection | 8 (4.8) | 13 (7.4) | 21 (6.1) |
| Latent tuberculosis | 8 (4.8) | 10 (5.7) | 18 (5.2) |
| Urinary tract infection | 9 (5.4) | 7 (4.0) | 16 (4.7) |
| General disorders and administration site conditions | 30 (17.9) | 22 (12.6) | 52 (15.2) |
| Localised injection site reaction ² | 30 (17.9) | 22 (12.6) | 52 (15.2) |
| Investigations | 7 (4.2) | 9 (5.1) | 16 (4.7) |
| Alanine aminotransferase increased | 7 (4.2) | 9 (5.1) | 16 (4.7) |
| Aspartate aminotransferase increased | 2 (1.2) | 6 (3.4) | 8 (2.3) |
| Injury, poisoning and procedural complications | 5 (3.0) | 10 (5.7) | 15 (4.4) |
| Infusion related reaction ³ | 0 | 7 (4.0) | 7 (2.0) |
| Musculoskeletal and connective tissue disorders | 7 (4.2) | 6 (3.4) | 13 (3.8) |
| Rheumatoid arthritis | 7 (4.2) | 6 (3.4) | 13 (3.8) |
| Nervous system disorders | 6 (3.6) | 7 (4.0) | 13 (3.8) |
| Headache | 6 (3.6) | 7 (4.0) | 13 (3.8) |
| Blood and lymphatic system disorders | 6 (3.6) | 3 (1.7) | 9 (2.6) |
| Neutropenia | 6 (3.6) | 3 (1.7) | 9 (2.6) |

Abbreviations: IV, intravenous; SC, subcutaneous.

Note: At each level of summarisation, patients were counted once if they reported 1 or more events. Only the most severe event was counted. Treatment-emergent AEs occurred in maintenance phase were summarised.

4. From MedDRA, Version 20.0

5. Localised injection site reaction: preferred term reported as "injection site reaction".

6. Infusion related reaction: preferred term reported as "administration related reaction" and occurred between start of administration and 24 hours from the end of IV infusion (including placebo).

The TEAEs by severity and in relation to the study medication in the updated safety population in patients with RA is presented in Table 32. There were no obvious differences in the number of adverse events in general, in the number of patients with AEs, and in the number of AEs in relation to study drug, or in the number of Grade 3 and 4 events between the treatment arms.

Table 32 - Treatment-Emergent Adverse Events by Severity by System Organ Class and Preferred Term for patients with at least 1 Grade 3 event or higher in Study CT-P13 3.5 Part 2 (Maintenance Phase) up to Week 54: Safety Population (Updated safety data, including five patients from the site where major scientific misconduct was reported.)

| | CT-P13 IV 3 mg/kg (N=178) | CT-P13 SC 120 mg (N=170) | Total (N=348) |
|--|--|---|--------------------------|
| Number (%) of patients with at least 1 TEAE | 113 (63.5) | 92 (54.1) | 205 (58.9) |
| Severity | | | |
| Grade 1 | 27 (15.2) | 22 (12.9) | 49 (14.1) |
| Grade 2 | 67 (37.6) | 54 (31.8) | 121 (34.8) |
| Grade 3 | 14 (7.9) | 14 (8.2) | 28 (8.0) |
| Grade 4 | 1 (0.6) | 1 (0.6) | 2 (0.6) |
| Grade 5 | 4 (2.2) | 1 (0.6) | 5 (1.4) |
| Grade 3 or higher TEAEs by SOC and PT | | | |
| Number (%) of patients with at least 1 Grade 3 or higher TEAE | 19 (10.7) | 16 (9.4) | 35 (10.1) |
| Blood and lymphatic system disorders | 2 (1.1) | 5 (2.9) | 7 (2.0) |
| Leukopenia - Grade 3 | 0 | 1 (0.6) | 1 (0.3) |
| Neutropenia - Grade 3 | 1 (0.6) | 3 (1.8) | 4 (1.1) |
| Neutropenia - Grade 4 | 1 (0.6) | 1 (0.6) | 2 (0.6) |
| Cardiac disorders | 4 (2.2) | 0 | 4 (1.1) |
| Atrial fibrillation - Grade 3 | 1 (0.6) | 0 | 1 (0.3) |
| Cardiac arrest - Grade 5 | 1 (0.6) | 0 | 1 (0.3) |
| Myocardial infarction - Grade 5 | 2 (1.1) | 0 | 2 (0.6) |
| Congenital, familial and genetic disorders | 0 | 1 (0.6) | 1 (0.3) |
| Hereditary haemochromatosis - Grade 5 | 0 | 1 (0.6) | 1 (0.3) |
| Ear and labyrinth disorders | 2 (1.1) | 0 | 2 (0.6) |
| Vertigo positional - Grade 3 | 2 (1.1) | 0 | 2 (0.6) |
| Gastrointestinal disorders | 0 | 2 (1.2) | 2 (0.6) |
| Duodenal ulcer haemorrhage - Grade 3 | 0 | 1 (0.6) | 1 (0.3) |
| Inguinal hernia - Grade 3 | 0 | 1 (0.6) | 1 (0.3) |
| General disorders and administration site conditions | 2 (1.1) | 1 (0.6) | 3 (0.9) |
| Localised injection site reaction - Grade 3 | 1 (0.6) | 1 (0.6) | 2 (0.6) |
| Sudden death - Grade 5 | 1 (0.6) | 0 | 1 (0.3) |
| Infections and infestations | 0 | 6 (3.5) | 6 (1.7) |
| Asymptomatic bacteriuria - Grade 3 | 0 | 1 (0.6) | 1 (0.3) |
| Bronchitis haemophilus - Grade 3 | 0 | 1 (0.6) | 1 (0.3) |
| Pneumonia - Grade 3 | 0 | 2 (1.2) | 2 (0.6) |
| Tracheobronchitis - Grade 3 | 0 | 1 (0.6) | 1 (0.3) |
| Urinary tract infection - Grade 3 | 0 | 1 (0.6) | 1 (0.3) |
| Injury, poisoning and procedural complications | 2 (1.1) | 1 (0.6) | 3 (0.9) |
| Infusion-related reaction - Grade 3 | 1 (0.6) | 0 | 1 (0.3) |
| Hip fracture - Grade 3 | 1 (0.6) | 0 | 1 (0.3) |
| Synovial rupture - Grade 3 | 0 | 1 (0.6) | 1 (0.3) |
| Investigations | 2 (1.1) | 0 | 2 (0.6) |
| Transaminases increased - Grade 3 | 2 (1.1) | 0 | 2 (0.6) |
| Musculoskeletal and connective tissue disorders | 3 (1.7) | 2 (1.2) | 5 (1.4) |

| | CT-P13 IV 3 mg/kg (N=178) | CT-P13 SC 120 mg (N=170) | Total (N=348) |
|---|--|---|--------------------------|
| Connective tissue inflammation - Grade 3 | 0 | 1 (0.6) | 1 (0.3) |
| Intervertebral disc protrusion - Grade 3 | 1 (0.6) | 0 | 1 (0.3) |
| (Worsening of) Rheumatoid arthritis - Grade 3 | 1 (0.6) | 1 (0.6) | 2 (0.6) |
| Spinal osteoarthritis - Grade 3 | 1 (0.6) | 0 | 1 (0.3) |
| Nervous system disorders | 2 (1.1) | 0 | 2 (0.6) |
| Cerebral infarction - Grade 3 | 1 (0.6) | 0 | 1 (0.3) |
| Dementia Alzheimer's type - Grade 3 | 1 (0.6) | 0 | 1 (0.3) |
| Product issues | 0 | 1 (0.6) | 1 (0.3) |
| Device loosening - Grade 3 | 0 | 1 (0.6) | 1 (0.3) |
| Vascular disorders | 2 (1.1) | 1 (0.6) | 3 (0.9) |
| Deep vein thrombosis - Grade 3 | 1 (0.6) | 0 | 1 (0.3) |
| Hypertension - Grade 3 | 1 (0.6) | 1 (0.6) | 2 (0.6) |

Note: At each level of summarisation, patients are counted once if they reported one or more events. Only the most severe event is counted. The severity is defined as Grade 3 = Severe, 4 = Life-threatening, 5 = Death.

IV: Intravenous, PT: Preferred term, SC: Subcutaneous, SOC: System organ class, TEAE: Treatment-emergent adverse event

Table 33 - Treatment-Emergent Adverse Events Considered by the Investigator to be Related to the Study Drug, Reported during the Maintenance Phase in Any Treatment Arm by System Organ Class and Preferred Term in Study CT-P13 3.5 Part 2 up to Week 54: Safety Population (Updated safety data, including five patients from the site where major scientific misconduct was reported)

| | SC 120 mg (N=170) | IV 3 mg/kg (N=178) | Total (N=348) |
|--|-------------------------------|-----------------------|------------------|
| System Organ Class¹ Preferred Term¹ | Number (%) of patients | | |
| Total number of TEAEs | 163 | 135 | 298 |
| Number of patients with at least 1 treatment-related TEAE | 57 (33.5) | 48 (27.0) | 105 (30.2) |
| General disorders and administration site conditions | 28 (16.5) | 22 (12.4) | 50 (14.4) |
| Localised injection site reaction ² | 28 (16.5) | 22 (12.4) | 50 (14.4) |
| Infections and infestations | 17 (10.0) | 17 (9.6) | 34 (9.8) |
| Latent tuberculosis | 8 (4.7) | 7 (3.9) | 15 (4.3) |
| Upper respiratory tract infection | 2 (1.2) | 8 (4.5) | 10 (2.9) |
| Urinary tract infection | 6 (3.5) | 3 (1.7) | 9 (2.6) |
| Injury, poisoning and procedural complications | 3 (1.8) | 10 (5.6) | 13 (3.7) |
| Infusion related reaction ³ | 0 | 7 (3.9) | 7 (2.0) |
| Blood and lymphatic system disorders | 6 (3.5) | 4 (2.2) | 10 (2.9) |
| Neutropenia | 6 (3.5) | 4 (2.2) | 10 (2.9) |
| Investigations | 6 (3.5) | 4 (2.2) | 10 (2.9) |
| Alanine aminotransferase increased | 6 (3.5) | 4 (2.2) | 10 (2.9) |
| Musculoskeletal and connective tissue disorders | 2 (1.2) | 2 (1.1) | 4 (1.1) |
| Rheumatoid arthritis | 2 (1.2) | 2 (1.1) | 4 (1.1) |
| Nervous system disorders | 0 | 1 (0.6) | 1 (0.3) |
| Headache | 0 | 1 (0.6) | 1 (0.3) |

Abbreviations: IV, intravenous; PT, preferred term; SC, subcutaneous.

Note: At each level of summarisation, patients were counted once if they reported 1 or more events. Only the most severe event was counted. The event was considered to be related to the study drug by the investigator if the relationship was defined as "possible", "probable", or "definite".

1. From MedDRA, Version 20.0
2. Localised injection site reaction: PT reported as "injection site reaction".
3. Infusion related reaction: PT reported as "administration related reaction" and occurred between start of administration and 24 hours from the end of IV infusion (including placebo).

Overall, the safety profile of Remsima SC was comparable to that of Remsima IV during the maintenance phase even after switching to CT-P13 SC 120 mg in IV 3 mg/kg treatment arm at Week 30. There were no new or unexpected safety findings observed in this trial.

Adverse events in patients with CD

Study CT-P13 1.6 Part 1

Study CP-P13 1.6 Part 1 was a dose-finding study in patients with CD. Overall summaries of TEAEs during the maintenance phases for the safety population are presented in Table 34.

Table 34 - Summary of Treatment-Emergent Adverse Events during the Maintenance Phase in Study CT-P13 1.6 Part 1: Safety Population

| | IV 5 mg/kg (N=13) | SC 120 mg (N=11) | SC 180 mg (N=12) | SC 240 mg (N=8) | Total (N=44) |
|--|-------------------------|---------------------|---------------------|--------------------|-----------------|
| Total number of TEAEs | 36 | 26 | 21 | 31 | 114 |
| Number (%) of patients with at least 1 TEAE | 10 (76.9) | 9 (81.8) | 8 (66.7) | 6 (75.0) | 33 (75.0) |
| Related to the study drug | 3 (23.1) | 5 (45.5) | 3 (25.0) | 3 (37.5) | 14 (31.8) |
| Unrelated to the study drug | 10 (76.9) | 7 (63.6) | 8 (66.7) | 5 (62.5) | 30 (68.2) |
| Total number of TESAEs | 5 | 2 | 1 | 3 | 11 |
| Number (%) of patients with at least 1 TESA | 4 (30.8) | 2 (18.2) | 1 (8.3) | 3 (37.5) | 10 (22.7) |
| Related to the study drug | 0 | 0 | 0 | 0 | 0 |
| Unrelated to the study drug | 4 (30.8) | 2 (18.2) | 1 (8.3) | 3 (37.5) | 10 (22.7) |
| Total number of TEAEs leading to discontinuation of study drug | 3 | 1 | 2 | 1 | 7 |
| Number (%) of patients with at least 1 TEAE leading to discontinuation of study drug | 3 (23.1) | 1 (9.1) | 2 (16.7) | 1 (12.5) | 7 (15.9) |
| Related to the study drug | 1 (7.7) | 0 | 1 (8.3) | 0 | 2 (4.5) |
| Unrelated to the study drug | 2 (15.4) | 1 (9.1) | 1 (8.3) | 1 (12.5) | 5 (11.4) |
| Total number of TEAEs classified as ARRs | 2 | 0 | 0 | 1 | 3 |
| Number (%) of patients with at least 1 TEAE classified as ARRs | 1 (7.7) | 0 | 0 | 1 (12.5) | 2 (4.5) |
| Total number of TEAEs classified as ISRs | 0 | 1 | 4 | 14 | 19 |
| Number (%) of patients with at least 1 TEAE classified as ISRs | 0 | 1 (9.1) | 3 (25.0) | 1 (12.5) | 5 (11.4) |
| Total number of TEAEs classified as infections | 5 | 9 | 2 | 4 | 20 |
| Number (%) of patients with at least 1 TEAE classified as infections | 3 (23.1) | 7 (63.6) | 2 (16.7) | 4 (50.0) | 16 (36.4) |
| Total number of TEAEs classified as malignancy | 1 | 0 | 0 | 0 | 1 |
| Number (%) of patients with at least 1 TEAE classified as malignancy | 1 (7.7) | 0 | 0 | 0 | 1 (2.3) |

Abbreviations: ARR, administration-related reaction; ISR, injection site reaction; IV, intravenous; SC, subcutaneous; TEAE, treatment-emergent adverse event; TESA, treatment-emergent serious adverse event.

Note: The total number of TEAEs included all-patient events. At each level of summarization, a patient was counted once if they reported one or more events. The event was considered to be related to the study drug by the investigator if the relationship was defined as "possible", "probable", or "definite".

During the Maintenance Phase of Study CT-P13 1.6 Part 1, at least 1 TEAE was reported for 10 (76.9%) patients in the IV 5 mg/kg cohort, 9 (81.8%) patients in the SC 120 mg cohort, 8 (66.7%) patients in the SC 180 mg cohort and 6 (75.0%) patients in the SC 240 mg cohort. The most commonly reported TEAEs ($\geq 10\%$ patients overall) were (aggravation of) Crohn's disease (5 [11.4%] patients overall) and ISR (5 [11.4%] patients overall). ISRs were all reported in the SC cohorts. Many of the events observed were related to the underlying disease. Two deaths were reported in Study CT-P13 1.6 Part 1.

Summary of frequently reported AEs across studies and severity of AEs

Frequently reported AEs in the healthy control studies included fatigue, CPK increase and ISR. Frequently reported AEs in the patient populations included ISR, infections and aggravation of underlying disease.

In study CT-P13 1.5 in healthy volunteers, all TEAEs were Grade 1 (mild) or Grade 2 (moderate) in severity. In study CT-P13 1.9, the MAH states that the majority of TEAEs were Grade 1 or Grade 2 in severity and that all ISRs and ARRs were Grade 1 in severity. In study CT-P13 1.9 in healthy volunteers, at least one Grade 3 or higher TEAE was reported for 15 (7.0%) subjects overall (8 [7.3%] subjects in

the CT-P13 SC AI arm and 7 [6.6%] subjects in the CT-P13 SC PFS arm). These included CPK increased and neutropenia.

In study CT-P13 3.5, Part 1, no Grade 4 or higher events were reported up to Week 54 during the maintenance phase. At least one Grade 3 TEAE was reported for 2 (15.4%) patients in the IV 3 mg/kg cohort, 3 (27.3%) patients in the SC 90 mg cohort, 1 (8.3%) patient in the SC 120 mg cohort and 3 (25.0%) patients in the SC 180 mg cohort. The only Grade 3 TEAE reported for more than 1 patient overall was ARR (2 [4.2%] patients overall; 1 [9.1%] patient in the SC 90 mg cohort and 1 [8.3%] patient in the SC 120 mg cohort).

In the original submission in Study CT-P13 3.5 Part 2, most patients were reported to have experienced TEAEs with Grade 1 or 2 in severity (66 [37.1%] patients in the IV 3 mg/kg arm and 51 [30.0%] patients in the SC 120 mg arm) during the maintenance phase up to Week 30. At least one Grade 3 or higher TEAE was reported for 10 (5.6%) patients in the IV 3 mg/kg arm and 11 (6.5%) patients in the SC 120 mg arm. Grade 3 or higher TEAEs reported for more than 1 patient were neutropenia (5 [1.4%] patients overall; 2 [1.1%] patients in the IV 3 mg/kg arm and 3 [1.8%] patients in the SC 120 mg arm) and vertigo positional (2 [0.6%] patients overall, both in the IV 3 mg/kg arm).

According to updated study results in Study CT-P13 3.5 up to Week 64, excluding the five patients from the site where major scientific misconduct was reported, the proportion of patients who experienced at least 1 TEAE during the maintenance phase was slightly higher in the IV 3 mg/kg treatment arm, compared to the SC 120 mg treatment arm (92 [54.8%] patients and 117 [66.9%] patients in SC 120 mg and IV 3 mg/kg treatment arms, respectively).

The most frequently reported TEAEs during the maintenance phase for patients in the SC 120 mg treatment arm, considered as related to study medical were localised ISR (30 [17.9%] patients) and infections and infestations (30 [17.9%] patients).

The most frequently reported related TEAEs during the maintenance phase for patients in the IV 3 mg/kg treatment arm were localised ISR (22 [12.6%] patients) and infections and infestations (26 [14.9%]). The incidence of related TB was 8 (4.8%) patients in the SC arm and 7 (4.0%) patients in the IV arm.

The proportion of patients who experienced at least 1 TEAE on or after Week 30 was similar between two treatment arms after switching from IV 3 mg/kg to SC 120 mg.

The most frequently reported TEAEs on or after Week 30 for patients in the SC 120 mg treatment arm were localized ISR (24 [14.3%] patients) followed by latent TB and urinary tract infection (7 [4.2%] patients each). The most frequently reported TEAEs on or after Week 30 for patients in the IV 3 mg/kg treatment arm were localized ISR (20 [11.4%] patients) followed by latent TB and viral upper respiratory tract infection (9 [5.1%] patients).

The majority of TEAEs in the maintenance phase of Study CT-P13 3.5 Part 2 were CTCAE grade 1 or 2 in intensity. The number of patients who experienced at least one grade 3 TEAE considered by the investigator to be related to study drug during the maintenance phase was reported for 18 (5.2%) patients (11 [6.5%] patients and 7 [4.0%] patients in SC 120 mg and IV 3 mg/kg treatment arms, respectively).

Four grade 4 TEAEs during the maintenance phase were reported for 3 patients (2 [1.2%] patients and 1 [0.6%] patient in the SC 120 mg and IV 3 mg/kg treatment arms, respectively). All grade 4 TEAEs were neutropenia and were considered by the investigator to be related to the study drug. Of these, the grade 4 TEAE in the SC 120 mg treatment arm was reported as TESAE. Deaths are discussed later in this document.

In the dose-finding study CT-P13 1.6 Part 1 in patients with CD, at least one Grade 3 or higher TEAE was reported for 2 (15.4%) patients in the IV 5 mg/kg cohort, 2 (18.2%) patients in the SC 120 mg

cohort, 1 (8.3%) patient in the SC 180 mg cohort and 3 (37.5%) patients in the SC 240 mg cohort during the maintenance phase. Grade 3 or higher TEAEs reported for more than 1 patient were anaemia (2 [4.5%] patients overall; 1 [7.7%] patient in the IV 5 mg/kg cohort and 1 [12.5%] patient in the SC 240 mg cohort) and (aggravation of) Crohn's disease (2 [4.5%] patients overall; 1 [7.7%] patient in the IV 5 mg/kg cohort and 1 [9.1%] patient in the SC 120 mg cohort).

Adverse events of special interest

During the development programme of Remsima SC, the following events were evaluated as protocol-defined AESIs:

- ARRr (IRRs/hypersensitivity/anaphylactic reactions)
- ISRs
- Infections (including TB)
- Malignancy (only in Study CT-P13 3.5 Parts 1 and 2 and Study CT-P13 1.6 Part 1).

Administration related reactions and injection site reactions

Healthy volunteer studies

In Study CT-P13 1.5, an ISR was reported for 2 (5.3%) subjects overall. Both events were Grade 1 in severity; one subject in the SC 120 mg cohort and one subject in SC 180 mg cohort experienced an ISR with a sign and symptom of bruise that was considered by the Investigator to be unlikely related to study drug. No TEAEs classified as IRRs (ARRs), hypersensitivity or anaphylactic reactions were reported.

In Study CT-P13 1.9, at least 1 ISR was reported for 5 (4.6%) subjects in the CT-P13 SC AI arm and 9 (8.5%) subjects in the CT-P13 SC PFS arm. All ISRs were Grade 1 in intensity. The most common sign and symptom was erythema. Most subjects did not receive treatment for the ISR and all subjects recovered.

In Study CT-P13 1.9, ARRr occurring within 24 hours from study drug administration were reported for 3 (2.8%) subjects in each treatment arm; all ARRr were Grade 1 in intensity and all subjects recovered. In addition, after 24 hours from study drug administration, serum sickness-like reactions were reported for 3 (2.8%) subjects in the CT-P13 SC AI arm and 1 (0.9%) subject in the CT-P13 SC PFS arm. All subjects recovered after receiving treatment for the events.

The MAH has performed literature review and re-analysis of the serum sickness-like reactions (SSLR). The MAH has concluded that based on additional investigation of the cases and based on systematical review of the literature, the reported cases of SSLR in healthy volunteers in Study CT-P13 1.9, which is a single dose study, cannot qualify as serum sickness events. As the MAH indicates, serum sickness typically occurs in patients who received repeated doses of infliximab or have preexisting hypersensitivity to murine products and therefore were able to form immune complexes and ADA from previous exposure. Secondly, published literature clearly indicate that the most important risk factor for emergence of serum sickness is episodic treatment, so prolonged drug free period which enables for immune complexes to be formed to trigger serum sickness. Based on analysis, the MAH concludes, the events in Study CT-P13 1.9 can be categorized as delayed injection reactions and severe injection site reactions, but not as serum sickness events, in line with literature on infliximab related safety and infusion-related events.

Patients with RA in study CT-P13 3.5

Part 1

During the Maintenance Phase of Study CT-P13 3.5 Part 1, at least 1 ISR was reported for 2 (18.2%) patients in the SC 90 mg cohort, 1 (8.3%) patient in the SC 120 mg cohort and 2 (16.7%) patients in

the SC 180 mg cohort, and no patients in the IV cohort. All events were Grade 1 or 2 in intensity and all patients recovered; no action was taken with study drug for 4 of the 5 patients. The most commonly reported sign and symptom was injection site erythema, which was reported for all 5 patients who experienced an ISR.

During the Maintenance Phase at least 1 TEAE classified as ARR and occurring within 24 hours of study drug administration was reported for 1 (7.7%) patient in the IV 3 mg/kg cohort, 1 (9.1%) patient in the SC 90 mg cohort, 1 (8.3%) patient in the SC 120 mg cohort and no patients in the SC 180 mg cohort. ARR occurring more than 24 hours after study drug administration were reported for 2 (16.7%) patients in the SC 120 mg cohort and no patients in the other cohorts. For both patients, the ARRs were reported as an IRR in the eCRF. Both patients recovered.

Part 2

The MAH has also reclassified the ARR, as the terminology used in the SmPC was somewhat confusing. The following new terminology has been used in the classification of events (Table 35 below).

Table 35 – Comparison of Terms of Systemic and Localised Reactions Used between Week 30 and Week 54 CSR CT-P13 3.5 Part 2

| Previous (Week 30 CSR CT-P13 3.5 Part 2) | | Current (Week 54 CSR CT-P13 3.5 Part 2) | |
|---|-------------------------|---|-------------------------|
| Terms | Treatment | Terms | Treatment |
| Administration related reaction that occurred within 24 hours from study drug administration | CT-P13 IV and CT-P13 SC | Infusion related reaction that occurred within 24 hours from study drug administration | CT-P13 IV only |
| | | Systemic injection reaction that occurred within 24 hours from study drug administration | CT-P13 SC only |
| Injection site reaction | CT-P13 IV and CT-P13 SC | Localised injection site reaction | CT-P13 IV and CT-P13 SC |
| Delayed hypersensitivity (ARR that occurred after 24 hours from study drug administration) | CT-P13 IV and CT-P13 SC | Delayed hypersensitivity (IRR or SIR that occurred after 24 hours from study drug administration) | CT-P13 IV and CT-P13 SC |

ARR: Administration related reaction, IRR: Infusion related reaction, IV: Intravenous, SC: Subcutaneous, SIR: Systemic injection reaction

Original submission

During the Maintenance Phase of Study CT-P13 3.5 Part 2, at least 1 TEAE classified as ISR was reported for 4 (2.2%) patients in the IV 3 mg/kg arm and 11 (6.5%) patients in the SC 120 mg arm. Among the 4 patients who experienced at least 1 TEAE classified as ISR in the IV 3 mg/kg arm, 3 patients experienced the events after injection of placebo SC and 1 patient experienced the event after injection of Remsima SC when switching to SC 120 mg at Week 30. All these events were Grade 1 or 2 in intensity and all the patients recovered. No action was taken with study drug for except for 1 patient in the IV 3 mg/kg arm for whom the study drug was interrupted after the SC injection at Week 30.

During the Maintenance Phase of Study CT-P13 3.5 Part 2, Treatment-emergent AEs classified as ARRs were reported in 9 (2.6%) patients in total, with lower proportion of patients in the SC 120 mg treatment arm compared to the IV 3 mg/kg treatment arm (1 [0.6%] patient and 8 [4.5%] patients in SC 120 mg and IV 3 mg/kg treatment arms, respectively). Among these patients, TEAE classified as delayed hypersensitivity (ARRs that occurred after 24 hours from the study drug administration) was reported for 1 (0.6%) patient in SC 120 mg treatment arm only, with no signs of serum sickness. Five patients

were ADA and NAb positive when ARR occurred who were all from IV 3 mg/kg treatment arm. Most of the patients who experienced at least 1 TEAE classified as ARRs during the maintenance phase had received pre-medications of antihistamine, hydrocortisone, paracetamol, and/or non-sedating antihistamine prior to the study drug administration when ARR occurred.

In cases of delayed hypersensitivity which occurred after 24 hours of study drug administration, including serum sickness-like reactions (myalgia with fever or rash, arthralgia, lymphadenopathy, skin eruption, or edema), the following assessments were additionally performed to determine serum sickness during the study period: immunogenicity, clinical laboratory analyses, complement (C3, C4) and total hemolytic complement. In Study CT-P13 3.5 Parts 1 and 2 and in Study CT-P13 1.6 Part 1, these additional assessments were performed on patients experiencing ARRs more than 24 hours after study drug administration. No confirmed cases of serum sickness were reported in the CT-P13 SC studies in RA and CD.

Exploratory analyses revealed that there were more acute ARR (< 24 hours) in Remsima IV group and more delayed ARR (> 24 hours) in the Remsima SC group. However, the numbers are small and 3 out of 4 events in the SC arm occurred in study CT- P13 3.5 Part 1 and only 1 in 170 patients in the study CT-P13 3.5 Part 2 in Remsima SC 120 mg arm.

Updated safety data, excluding the five patients from the site where major scientific misconduct was reported

The MAH has now revised the terminology concerning IRR to make these distinctions clearer in CT-P13 3.5 Part 2 Statistical Analysis Plan. Only the terminology has been revised and the corresponding capture logics have not been changed. Specifically, ARR was revised to IRR and systemic injection reaction (SIR) for the CT-P13 IV and CT-P13 SC arms, respectively, to distinguish systemic reactions as per the route of administration. ISR was revised to localised ISR to specify that these reactions occurred around the injection site only, and to differentiate from systemic reactions (IRR and SIR). Of note, IRR or SIR that occurred after 24 hours from study drug administration were maintained as “delayed hypersensitivity”. All delayed hypersensitivity cases were examined to determine if these cases were serum sickness or not. Based on these new classifications, the MAH has performed updated analysis with more mature data from Study CT-P13 3.5. While evaluating the results, it needs to be considered, that patients in the IV arm were actually treated with IV Remsima only until week 30 and were thereafter switched to Remsima SC for weeks 30-54.

Treatment-emergent AEs classified as IRR during the treatment period were reported for 2 (1.2%) patients in SC 120 mg treatment arm and 10 (5.7%) patients in IV 3 mg/kg treatment arm. Treatment-emergent AEs classified as SIR during the treatment period were reported for 2 (1.2%) patients in SC 120 mg treatment arm and 3 (1.7%) patients in IV 3 mg/kg treatment arm.

Treatment-emergent AEs classified as delayed hypersensitivity during the treatment period were reported for 5 (3.0%) patients in SC 120 mg treatment arm and 1 (0.6%) patient in IV 3 mg/kg treatment arm. Treatment-emergent AEs classified as localised ISR during the treatment period were reported for 30 (17.9%) patients in SC 120 mg treatment arm and 22 (12.6%) patients in IV 3 mg/kg treatment arm.

In the SPC the safety data is reported as incidence per 100 patient years, excluding patients from the non-compliant site. The incidence of systemic injection reactions (e.g. rash, pruritus, flushing and oedema) was 1.2 per 100 patient-years in the Remsima subcutaneous group (from Week 6) and 2.1 per 100 patient-years in the Remsima intravenous group who switched to Remsima subcutaneous administration (from Week 30). All systemic injection reactions were mild to moderate.

The incidence of localised injection site reactions (e.g. injection site erythema, pain, pruritus and swelling) was 17.6 per 100 patient-years in the Remsima subcutaneous group (from Week 6) and 21.4 per 100 patient-years in those who switched to Remsima subcutaneous administration (from Week 30).

Patients with CD in study CT-P13 1.6

During the Maintenance Phase of Part 1, ISR was reported for 1 (9.1%) patient in the SC 120 mg cohort, 3 (25.0%) patients in the SC 180 mg cohort and 1 (12.5%) patient in the SC 240 mg cohort.

During the Maintenance Phase of Part 1, at least 1 TEAE classified as ARR and occurring within 24 hours of study drug administration was reported for 1 (7.7%) patient in the IV 5 mg/kg cohort and no patients in the SC cohorts. At least 1 TEAE classified as ARR and occurring more than 24 hours after study drug administration was reported for 1 (12.5%) patient in the SC 240 mg cohort and no patients in the other cohorts; no action was taken with study drug and the patient recovered without receiving treatment for the event.

Infections

Healthy volunteer studies

In Study CT-P13 1.5, TEAEs classified as infection were reported for 2 (5.3%) subjects overall, both in the IV arm. One subject in the IV 3 mg/kg cohort experienced the Grade 2, related TEAE of herpes zoster.

In Study CT-P13 1.9, at least 1 TEAE classified as infection was reported for 9 (8.3%) subjects in the Remsima SC AI arm and 7 (6.6%) subjects in the CT-P13 SC PFS arm. All infections were Grade 1 or 2 in intensity. The most commonly reported infection was upper respiratory tract infection (5 [4.6%] subjects in the CT-P13 SC AI arm and 3 [2.8%] subjects in the CT-P13 SC PFS arm). The causality was in in most cases not related.

No events of TB of other opportunistic infections were reported in healthy volunteer studies.

Patients with RA in study CT-P13 3.5

Part 1

During the Maintenance Phase of Study CT-P13 3.5 Part 1, at least 1 TEAE classified as infection was reported for 5 (38.5%) patients in the IV 3 mg/kg cohort, 4 (36.4%) patients in the SC 90 mg cohort, 3 (25.0%) patients in the SC 120 mg cohort and 6 (50.0%) patients in the SC 180 mg cohort. One patient with serious infection in each of the IV arm, SC 90 mg arm and SC 180 mg were reported; there were no patients with serious infection in the SC 120 mg arm.

Part 2

Original submission

During the maintenance phase of study CT-P13 3.5 Part 2, treatment-emergent AEs classified as infections were reported in 66 (19.0%) patients in total (34 [20%] patients and 32 [18.0%] patients in SC 120 mg and IV 3 mg/kg treatment arms, respectively). The majority of TEAEs due to infections were grade 1 or 2 in intensity.

The most commonly reported infection was viral upper respiratory tract infection (6 [3.4%] patients in the IV 3 mg/kg arm and 7 [4.1%] patients in the SC 120 mg arm), followed by latent TB (7 [3.9%] patients in the IV 3 mg/kg arm and 4 [2.4%] patients in the SC 120 mg arm) and upper respiratory tract infection (6 [3.4%] patients in the IV 3 mg/kg arm and 5 [2.9%] patients in the SC 120 mg arm).

There were no obvious differences between IV and SC in the incidence or severity of infections in the study CT-P13 3.5 either in Part I of Part II between the study arms. The summary of infections is provided on Table 36.

Table 36 - Summary of Infections in Study CT-P13 3.5 Part 1 (Maintenance Phase up to 54 weeks) and Part 2 (Maintenance Phase up to 30 weeks): Safety Population (Original safety data, including the five patients from the site where major scientific misconduct was reported)

| | Part 1 | | | | Part 2 | |
|--|--------------------------------|------------------------------|-------------------------------|-------------------------------|---------------------------------|--------------------------------|
| | CT-P13 IV 3 mg/kg (N=13) | CT-P13 SC 90 mg (N=11) | CT-P13 SC 120 mg (N=12) | CT-P13 SC 180 mg (N=12) | CT-P13 IV 3 mg/kg (N=178) | CT-P13 SC 120 mg (N=170) |
| Total number of infections | 7 | 6 | 6 | 8 | 40 | 40 |
| Number (%) of patients with ≥ 1 infection | 5/13 (38.5%) | 4/11 (36.4%) | 3/12 (25.0%) | 6/12 (50.0%) | 32/178 (18.0%) | 34/170 (20.0%) |
| Patients with infections/100PY | 36.071 | 37.988 | 25.057 | 48.852 | 39.462 | 43.704 |
| 95% CI for 100PY | 11.712, 84.177 | 10.350, 97.263 | 5.167, 73.228 | 17.928, 106.330 | 26.992, 55.709 | 30.266, 61.072 |
| Relatedness | | | | | | |
| Related | 2 (40.0%) | 1 (25.0%) | 3 (100.0%) | 3 (50.0%) | 13 (40.6%) | 18 (52.9%) |
| Unrelated | 4 (80.0%) | 4 (100.0%) | 0 | 3 (50.0%) | 20 (62.5%) | 18 (52.9%) |
| Severity | | | | | | |
| Grade 1 | 0 | 0 | 0 | 0 | 4 (12.5%) | 7 (20.6%) |
| Grade 2 | 4 (80.0%) | 4 (100.0%) | 3 (100.0%) | 5 (83.3%) | 28 (87.5%) | 23 (67.6%) |
| Grade 3 | 1 (20.0%) | 0 | 0 | 1 (16.7%) | 0 | 4 (11.8%) |
| Outcome | | | | | | |
| Unknown | 0 | 1 (25.0%) | 0 | 0 | 0 | 0 |
| Recovered | 4 (80.0%) | 3 (75.0%) | 3 (100.0%) | 6 (100.0%) | 25 (78.1%) | 26 (76.5%) |
| Recovering | 0 | 0 | 0 | 0 | 1 (3.1%) | 4 (11.8%) |
| Not recovered | 1 (20.0%) | 0 | 0 | 0 | 6 (18.8%) | 4 (11.8%) |
| Fatal | 0 | 0 | 0 | 0 | 0 | 0 |
| Number (%) of patients with ≥ 1 serious infection | 1 (20.0%) | 1 (25.0%) | 0 | 1 (16.7%) | 1 (3.1%) | 1 (2.9%) |
| Number (%) of patients with ≥ 1 infection leading to permanent study drug discontinuation | 0 | 1 (25.0%) | 0 | 1 (16.7%) | 2 (6.3%) | 0 |

Note: Unless indicated, the denominator is the number of patients with at least one AESI. Only the most severe and serious event is counted.

AESI: Adverse events of special interest, CI: Confidence interval, IV: Intravenous, PY: Patient-years, SC: Subcutaneous

Updated safety data, excluding the five patients from the site where major scientific misconduct was reported

With the updated safety data, the infections by incidence and grade are presented in Table 37. The incidence of infections was 29.22% for SC arm and 34.3% in the IV arm. No clear differences in the severity and in relation to study medication were observed.

The MAH has also calculated the incidence of patients with infections per 100PY Study CT-P13 3.5 Part 2, which were 36.230 (95% CI: 25.509, 49.939) and 32.885 (95% CI: 24.971, 42.511) for the Treatment

Period data up to Week 30 and Week 54, respectively. These incidence results were similar to the range of historical data and especially similar to the CT-P13 IV historical data.

Table 37 - Treatment-Emergent Adverse Events Classified as Infections during the Maintenance Phase by System Organ Class and Preferred Term in Study CT-P13 3.5 Part 2 up to Week 54 (up to Week 64 for patients in Bulgaria, Poland and Russia): Safety Population (Updated safety data, excluding five patients from site the where major scientific misconduct was reported)

| System Organ Class ¹ Preferred Term ¹ | SC 120 mg (N=168) | IV 3 mg/kg (N=175) | Total (N=343) |
|---|------------------------|-----------------------|-------------------|
| | Number (%) of patients | | |
| Total number of TEAEs classified as infections | 78 | 83 | 161 |
| Number of patients with at least 1 TEAE classified as infections | 49 (29.2) | 60 (34.3) | 109 (31.8) |
| Related | 30 (17.9) | 26 (14.9) | 56 (16.3) |
| Unrelated | 27 (16.1) | 38 (21.7) | 65 (19.0) |
| Infections and infestations | 49 (29.2) | 60 (34.3) | 109 (31.8) |
| Viral upper respiratory tract infection | 10 (6.0) | 14 (8.0) | 24 (7.0) |
| Upper respiratory tract infection | 8 (4.8) | 13 (7.4) | 21 (6.1) |
| Latent tuberculosis | 8 (4.8) | 10 (5.7) | 18 (5.2) |
| Urinary tract infection | 9 (5.4) | 7 (4.0) | 16 (4.7) |
| Bronchitis | 5 (3.0) | 4 (2.3) | 9 (2.6) |
| Oral herpes | 4 (2.4) | 3 (1.7) | 7 (2.0) |
| Asymptomatic bacteriuria | 3 (1.8) | 2 (1.1) | 5 (1.5) |
| Pharyngitis | 3 (1.8) | 2 (1.1) | 5 (1.5) |
| Tonsillitis | 1 (0.6) | 3 (1.7) | 4 (1.2) |
| Cystitis | 0 | 3 (1.7) | 3 (0.9) |
| Nasopharyngitis | 2 (1.2) | 1 (0.6) | 3 (0.9) |
| Pneumonia | 2 (1.2) | 1 (0.6) | 3 (0.9) |
| Rhinitis | 1 (0.6) | 2 (1.1) | 3 (0.9) |
| Adenoviral upper respiratory infection | 2 (1.2) | 0 | 2 (0.6) |
| Gingivitis | 0 | 2 (1.1) | 2 (0.6) |
| Influenza | 1 (0.6) | 1 (0.6) | 2 (0.6) |
| Bronchitis haemophilus | 1 (0.6) | 0 | 1 (0.3) |
| Conjunctivitis | 0 | 1 (0.6) | 1 (0.3) |
| Conjunctivitis bacterial | 0 | 1 (0.6) | 1 (0.3) |
| Furuncle | 0 | 1 (0.6) | 1 (0.3) |
| Impetigo | 1 (0.6) | 0 | 1 (0.3) |
| Lower respiratory tract infection | 0 | 1 (0.6) | 1 (0.3) |
| Oral bacterial infection | 0 | 1 (0.6) | 1 (0.3) |
| Paronychia | 0 | 1 (0.6) | 1 (0.3) |
| Pertussis | 0 | 1 (0.6) | 1 (0.3) |
| Pharyngotonsillitis | 1 (0.6) | 0 | 1 (0.3) |
| Pyelonephritis chronic | 0 | 1 (0.6) | 1 (0.3) |
| Salpingo-oophoritis | 1 (0.6) | 0 | 1 (0.3) |
| Sinusitis | 1 (0.6) | 0 | 1 (0.3) |
| Tracheobronchitis | 1 (0.6) | 0 | 1 (0.3) |
| Vaginal infection | 1 (0.6) | 0 | 1 (0.3) |

Abbreviations: IV, intravenous; SC, subcutaneous; TEAE, treatment-emergent adverse event.

Note: At each level of summarisation, patients were counted once if they reported 1 or more events. Only the most severe event was counted. The event was considered to be related if the relationship was defined as "Possible", "Probable" or "Definite". Treatment-emergent AEs occurred in maintenance phase were summarised.

1. From MedDRA, Version 20.0.

In the updated safety results up to 64 weeks, the majority of TEAEs classified as infections during the maintenance phase were grade 1 or 2 in intensity. Four patients (3 [1.8%] patients and 1 [0.6%] patient in SC 120 mg and IV 3 mg/kg treatment arms, respectively) reported TESAEs classified as infections, and 3 events (tracheobronchitis and pneumonia from SC 120 mg treatment arm and pertussis from IV 3 mg/kg treatment arm) were considered related to the study drug by the investigator.

With the updated safety data, the numbers of patients with serious or Grade 3 infections between SC and IV Remsima were 6 vs 1, from which 5 events in the SC arm were considered related, and 1 in SC and 1 in IV were considered unrelated to study medication. The Grade 3 infections for patients in the SC group were mainly respiratory infections (n=3; bronchitis, tracheobronchitis and pneumonia). All other infections were single cases only. No grade 4 or 5 infections were found.

Patients with CD in study CT-P13 1.6

During the Maintenance Phase of Study CT-P13 1.6 Part 1, at least 1 TEAE classified as infection was reported for 3 (23.1%) patients in the IV 5 mg/kg cohort, 7 (63.6%) patients in the SC 120 mg cohort, 2 (16.7%) patients in the SC 180 mg cohort and 4 (50.0%) patients in the SC 240 mg cohort. There was only 1 patient with a serious infection; this patient was in the SC 240 mg arm. The MAH states that the number of patients with infections in this study is comparable to rates in previous studies in which patients were treated with CT-P13 IV and with Remicade.

Latent tuberculosis (TB)

In study CT-P13 3.5 Part 1 during the Maintenance Phase, latent TB was reported for 1 (7.7%) patient in the IV 3 mg/kg cohort and 1 (9.1%) patient in the SC 90 mg cohort.

In the original submission, during the Maintenance Phase of Study CT-P13 3.5 Part 2, latent TB was reported for 7 (3.9%) patients in the IV 3 mg/kg arm and 4 (2.4%) patients in the SC 120 mg arm. All the events were Grade 1 or 2 and non-serious. Four cases in the SC arm and 5 cases in the IV arm were considered not related to the study medication. In most cases, study drug was interrupted due to the event. All patients received treatment for the event, and in 5 of the 11 cases, the patients recovered or were recovering. Except for one patient, none of the events led to permanent discontinuation of study drug.

With the updated safety data, excluding the five patients from the site where major scientific misconduct as reported, in total latent tuberculosis was reported in 8 (4.8%) in the SC arm and 10 (5.7%) in the IV arm in Study CT-P13 3.5 Part 2.

In Study CT-P13 1.6 Part 1 in patients with CD, latent tuberculosis was observed in two patients in the Remsima 180 mg SC arm, and in one patient in 240 mg arm, whereas there were no cases in the IV or SC 120 mg arms.

Active tuberculosis (TB)

During the Maintenance Phase of Study CT-P13 3.5 Part 1, active TB (pulmonary TB) was reported for 1 (8.3%) patient in the SC 180 mg cohort (Grade 3), 16 days after the previous dose of study drug at Week 32. The patient also had a medical history of latent TB. The event was considered to be probably related to study drug by the Investigator. The patient was permanently discontinued from study drug and recovered from the pulmonary TB after treatment. With the updated study data, no new cases of

active tuberculosis were reported. No cases of latent or active tuberculosis were observed in healthy volunteer studies.

Malignancies

In the original submission, no malignancies were reported in Study CT-P13 3.5 Part 1 and Part 2, neither in healthy volunteer studies. With the updated safety data, one TEAE classified as malignancy were reported in 1 (0.6%) patient in SC 120 mg treatment arm (ovarian malignancy classified by the investigator as related) in Study CT-P13 3.5 Part 2. In addition, during the Maintenance Phase of Study CT-P13 1.6 Part 1 in patients with CD, one case of malignant melanoma was reported for 1 patient in the IV 5 mg/kg cohort. The event was considered by the Investigator to be unrelated to study drug.

Serious adverse events and deaths

Serious adverse events in healthy subjects

There were no SAEs reported in study CT-P13 1.5. Two SAEs (1.8%) were reported for two subjects in Study CT-P13 1.9 (traffic accidents, not related).

Serious Adverse events in patients with RA in Study CT-P13 3.5, Part 1

During the Maintenance Phase of Study CT-P13 3.5 Part 1, TESAEs were reported for 1 (7.7%) patient in the IV 3 mg/kg cohort (urinary tract infection), 2 (18.2%) patients in the SC 90 mg cohort (latent TB and intervertebral disc disorder for 1 patient each), no patients in the SC 120 mg cohort and 3 (25.0%) patients in the SC 180 mg cohort (antiphospholipid syndrome, pulmonary TB and spinal compression fracture for 1 patient each).

TESAEs considered by the Investigator to be related to study drug were antiphospholipid syndrome and pulmonary TB in the SC 180 mg cohort.

Serious Adverse events in patients with RA in Study CT-P13 3.5, Part 2

In the original submission, during the Maintenance Phase of Study CT-P13 3.5 Part 2 up to Week 30, TESAEs were reported for 7 (3.9%) patients in the IV 3 mg/kg arm and 3 (1.8%) patients in the SC 120 mg arm. The most commonly reported TESAE was vertigo positional (2 [0.6%] patients overall, both in the IV 3 mg/kg arm). All other TESAEs were reported for only 1 patient each.

With the updated safety data, during the Maintenance Phase of Study CT-P13 3.5 Part 2 up to Week 54, TESAEs were reported for 13 (7.3%) patients in the IV 3 mg/kg arm and 6 (3.5%) patients in the SC 120 mg arm. The most commonly reported TESAE were cardiac disorders (n=4, all unrelated) for the IV group (two of those were fatal) and vertigo positional (n=2, both related). All other TESAEs were reported for only 1 patient each (Table 38).

Table 38 - Treatment-Emergent Serious Adverse Event in Study CT-P13 3.5 Part 2 (Maintenance Phase) up to Week 54: Safety Population (Updated safety report, including the five patients from the site where major scientific misconduct was reported)

| System Organ Class¹ Preferred Term¹ | SC 120 mg (N=170) | IV 3 mg/kg (N=178) | Total (N=348) |
|--|-------------------------------|-------------------------------|--------------------------|
| | Number (%) of patients | | |
| Total number of TESAEs | 8 | 15 | 23 |
| Number of patients with at least 1 TESA | 6 (3.5) | 13 (7.3) | 19 (5.5) |
| Related | 3 (1.8) | 4 (2.2) | 7 (2.0) |
| Unrelated | 3 (1.8) | 11 (6.2) | 14 (4.0) |
| Cardiac disorders | 0 | 4 (2.2) | 4 (1.1) |
| Myocardial infarction – Grade 5, unrelated | 0 | 2 (1.1) | 2 (0.6) |
| Atrial fibrillation – Grade 3, unrelated | 0 | 1 (0.6) | 1 (0.3) |
| Cardiac arrest – Grade 5, unrelated | 0 | 1 (0.6) | 1 (0.3) |
| Infections and infestations | 3 (1.8) | 1 (0.6) | 4 (1.1) |
| Pertussis – Grade 2, related | 0 | 1 (0.6) | 1 (0.3) |
| Pneumonia – Grade 3, related | 1 (0.6) | 0 | 1 (0.3) |
| Pneumonia – Grade 3, unrelated | 1 (0.6) | 0 | 1 (0.3) |
| Tracheobronchitis – Grade 3, related | 1 (0.6) | 0 | 1 (0.3) |
| Ear and labyrinth disorders | 0 | 2 (1.1) | 2 (0.6) |
| Vertigo positional – Grade 3, related | 0 | 2 (1.1) | 2 (0.6) |
| Gastrointestinal disorders | 2 (1.2) | 0 | 2 (0.6) |
| Duodenal ulcer haemorrhage – Grade 3, unrelated | 1 (0.6) | 0 | 1 (0.3) |
| Inguinal hernia – Grade 3, unrelated | 1 (0.6) | 0 | 1 (0.3) |
| Injury, poisoning and procedural complications | 0 | 2 (1.1) | 2 (0.6) |
| Infusion related reaction ² – Grade 3, related | 0 | 1 (0.6) | 1 (0.3) |
| Hip fracture – Grade 3, unrelated | 0 | 1 (0.6) | 1 (0.3) |
| Musculoskeletal and connective tissue disorders | 0 | 2 (1.1) | 2 (0.6) |
| Intervertebral disc protrusion – Grade 3, unrelated | 0 | 1 (0.6) | 1 (0.3) |
| Spinal osteoarthritis – Grade 3, unrelated | 0 | 1 (0.6) | 1 (0.3) |
| Nervous system disorders | 0 | 2 (1.1) | 2 (0.6) |
| Cerebral infarction – Grade 3, unrelated | 0 | 1 (0.6) | 1 (0.3) |
| Dementia Alzheimer's type – Grade 3, unrelated | 0 | 1 (0.6) | 1 (0.3) |
| Blood and lymphatic system disorders | 1 (0.6) | 0 | 1 (0.3) |
| Neutropenia – Grade 4, related | 1 (0.6) | 0 | 1 (0.3) |
| Congenital, familial and genetic disorders | 1 (0.6) | 0 | 1 (0.3) |
| Hereditary haemochromatosis – Grade 5, unrelated | 1 (0.6) | 0 | 1 (0.3) |
| General disorders and administration site conditions | 0 | 1 (0.6) | 1 (0.3) |
| Sudden death – Grade 5, unrelated | 0 | 1 (0.6) | 1 (0.3) |
| Product issues | 1 (0.6) | 0 | 1 (0.3) |
| Device loosening – Grade 3, unrelated | 1 (0.6) | 0 | 1 (0.3) |
| Vascular disorders | 0 | 1 (0.6) | 1 (0.3) |
| Deep vein thrombosis – Grade 3, unrelated | 0 | 1 (0.6) | 1 (0.3) |

Abbreviations: IV, intravenous; PT, preferred term; SC, subcutaneous; TESAE, treatment-emergent serious adverse event.

Note: At each level of summarisation, patients were counted once if they reported 1 or more events. Only the most severe event was counted. The event was considered to be related to the study drug by the investigator if the relationship was defined as "Possible", "Probable", or "Definite". The intensity was defined as Grade 1=mild, 2=moderate, 3=severe, 4=life-threatening, 5=death.

1. From MedDRA, Version 20.0.
2. Infusion related reaction: PT reported as "administration related reaction" and occurred between start of administration and 24 hours from the end of IV infusion (including placebo).

With the updated safety data, the numbers of SAEs and the numbers of patients with SAEs by intensity and relatedness are reported in the Table 39. The majority of TESAEs were grade 3 or lower in intensity. One grade 4 TESAE (neutropenia) was reported in the SC 120 mg treatment arm. Five grade 5 TESAEs (hereditary haemochromatosis for 1 patient in the SC 120 mg treatment arm and myocardial infarction for 2 patients, cardiac arrest for 1 patient and sudden death for 1 patient in the IV 3 mg/kg treatment arm (discussed elsewhere).

Table 39 - Treatment-Emergent Serious Adverse Events by Intensity in Study CT-P13 3.5 Part 2 (Maintenance Phase) up to Week 54: Safety Population (Updated safety report, including the five patients from the site where major scientific misconduct was reported)

| | SC 120 mg (N=170) | IV 3 mg/kg (N=178) | Total (N=348) |
|--|----------------------|-----------------------|------------------|
| Total number of TESAEs | 8 | 15 | 23 |
| Number of patients with at least 1 TESAE | 6 (3.5%) | 13 (7.3%) | 19 (5.5%) |
| Related | 3 (1.8%) | 4 (2.2%) | 7 (2.0%) |
| Grade 2 | 0 | 1 (0.6%) | 1 (0.3%) |
| Grade 3 | 2 (1.2%) | 3 (1.7%) | 5 (1.4%) |
| Grade 4 | 1 (0.6%) | 0 | 1 (0.3%) |
| Unrelated | 3 (1.8%) | 11 (6.2%) | 14 (4.0%) |
| Grade 3 | 2 (1.2%) | 7 (3.9%) | 9 (2.6%) |
| Grade 5 | 1 (0.6%) | 4 (2.2%) | 5 (1.4%) |

Serious Adverse events in patients with CD in Study CT-P13 1.6, Part 1

During the maintenance phase of the dose-finding study CT-P13 1.6 Part 1 in CD-patients, at least 1 TESAE was reported for 4 (30.8%) patients in the IV 5 mg/kg cohort, 2 (18.2%) patients in the SC 120 mg cohort, 1 (8.3%) patient in the SC 180 mg cohort and 3 (37.5%) patients in the SC 240 mg cohort. The most commonly reported TESAE was (aggravation of) Crohn's disease, which was reported for 1 (7.7%) patient in the IV 5 mg/kg cohort and 2 (18.2%) patients in the SC 120 mg cohort. No TESAEs of ARRs or ISRs were reported.

Deaths in CT-P13 studies

No deaths were reported during Studies CT-P13 1.5 and CT-P13 1.9 conducted with healthy subjects or Study CT-P13 3.5 Part 1 conducted with RA patients.

In the original submission, a total of 5 TEAEs leading to death were reported in the Remsima SC studies. There were 3 deaths up to Week 30 in Study CT-P13 3.5 Part 2 conducted with RA patients (sudden death in the IV arm, myocardial infarction on the day of administration (ARR also reported) in the IV arm, and toxic hepatitis and liver failure due to hereditary haemochromatosis in the SC arm) and 2 deaths (sudden cardiac death in patient in IV 5mg/kg arm and sudden death in SC 180 mg arm) in Study CT-P13 1.6 Part 1 conducted with CD patients.

Of these 5 deaths reported in the original submission in patients who had received at least 1 dose of study drug in Remsima SC studies, 3 patients were in IV treatment group (two patient with RA and one patient with CD) and 2 patients were in SC treatment group (one with RA and one with CD). One death in the RA study IV arm and one in the CD study SC arm occurred on the study drug administration day. In addition, there was one death in study CT-P13 3.5 Part 2 that was due to acute myocardial infarction during the screening period before the first administration of study drug.

With the updated data, two additional death cases were reported in Study CT-P13 3.5 Part 2 in the SC arm after the Week 30 visit in patients who switched from IV to SC at Week 30. Thus, there were in total three deaths in patients receiving SC treatment, and two death in the IV treatment arm in the study CT-P13 3.5. The MAH conducted a comprehensive investigation on all death cases, including two new cases reported in patients switching from CT-P13 IV to SC treatment at Week 30, and evaluated the potential effect of study medication on each fatal case. The causes of death were sudden death (n=2), myocardial infarction (n=2), cardiac arrest (n=1), sudden cardiac death (n=1) and hereditary haemochromatosis (n=1). Please notice, that these numbers (n=7) include also the two deaths reported in the CT-P13 1.6 study, as described above.

There were three deaths that occurred on the CT-P13 administration day (the previously reported two cases, and one additional case after Week 30), but according to MAH, no relationship of the deaths to study medication was detected in terms of their drug serum levels and immunogenicity results. Among the three patients who died on the CT-P13 administration day, only one patient had positive anti-drug antibody (ADA) and neutralising antibody (NAb) at the latest result before death. Also, all of three patients had lower C_{trough} levels at the latest results before deaths than the mean values of the same treatment groups.

Short summaries of deaths in patients treated with Remsima SC are provided below.

Patient 1: A patient with RA, who had no previous relevant medical history, received 2 doses of Remsima IV and 2 doses of 120mg Remsima SC. 67 days since the last SC dose, the patient died due to hereditary haemochromatosis (which was diagnosed during the study). No autopsy was performed. However, the Investigator confirmed that the direct causes of death were toxic hepatitis and liver failure due to hereditary hemochromatosis. The infliximab serum concentration at Week 6 pre-dose was 12 500 ng/mL. The event was considered by the Investigator to be unrelated to the study drug.

As requested, the MAH has provided further information concerning this case in relation to infliximab concentration indicating that Based on the patient's body weight of 80 kg, the loading doses of CT-P13 IV 247.5 mg and 248.4 mg (3 mg/kg) were given at Week 0 and Week 2, respectively. CT-P13 SC 120 mg was then administered subcutaneously at Week 6 and Week 8. The patient presented higher C_{trough} level of 12.5 µg/ml (12500 ng/ml), which was measured before the administration of first SC dose at Week 6, compared to the mean 8.7 µg/ml (8686.8 ng/ml) and geometric mean 5.1 µg/ml (5121.8 ng/ml) level of patients from the same treatment arm. The CT-P13 IV loading dose based on the patient's body weight (80 kg) was correctly calculated and the patient complied with dosing interval well. The patient's C_{trough} level was slightly high compared to the mean level of other patients in the same treatment group at the timepoints tested, but the patient's C_{trough} level remained in the range (0.1 - 25.2 µg/ml) which was not considered an outlier and not extremely high. In comparison to Study CT-P13 3.1, the patient's C_{trough} level (12.5 µg/ml) was similar to the mean C_{trough} levels at Week 2, which were 11.97 µg/ml in the CT-P13 treatment group and 11.61 µg/ml in the Remicade® treatment group (CT-P13 3.1 CSR Post-text Table 14.2.7.1). The MAH has also concluded that while an indirect effect of the patient's drug serum concentration level on the event cannot be fully excluded, there was no convincing temporal association between the death and drug exposure since the death event occurred 67 days after the last dose of the medication. Therefore, it is unlikely that C_{trough} level had a profound impact on the patient's death.

Patient 2: patient with RA received the first CT-P13 IV treatment on Week 0 and the last dose of the CT-P13 SC treatment prior to TESA onset on Week 54. The patient experienced cardiac arrest and subsequently died (approximately 8 hours after the last CT-P13 SC treatment at Week 54). The patient had a relevant medical history of hypertension, aortic valve stenosis, bicuspid aortic valve and aortic valve insufficiency. Upon the diagnosis of aortic valve stenosis, a surgical intervention was proposed from another hospital, but the patient refused. It was later confirmed by the cardiology report from another hospital, after her death, that the patient had a chest pain that radiated to the left arm and resolved when she took nitroglycerin. The investigator thought that the patient might have intentionally hid her cardiac symptoms not to be discontinued from the study. The cause of death provided was bicuspid aortic valve congenital and untreated aortic valve stenosis. The event of cardiac arrest was considered by the investigator to be unrelated to the study drug.

Patient 3, a patient with RA received the first CT-P13 IV treatment on (Week 0) and the last dose of the CTP13 SC treatment prior to TESA onset (Week 34). The patient experienced the symptoms of chest pain and dyspnea on (12 days after the last CT-P13 SC treatment at Week 34), The ECG recording from the emergency room showed diaphragmatic acute ST wave elevated MI. The patient was transferred to another hospital, where at the entrance she lost her consciousness and had no spontaneous respiration. Although the advanced cardiopulmonary resuscitation was done, she died. The patient had medical history of hypertension ongoing. The patient had smoked 2 packs of cigarette per day for decades and was in stressful circumstances such as unemployed state and family relations, which are the risk factors of MI. The investigator confirmed that the death occurred because of the event of MI with ventricular fibrillation and diaphragmatic acute STEMI and assessed the event as unrelated to the study drug.

In addition, a sudden death occurred in study CT-P1.6 Part 1 in the 180 mg SC arm: A patient with CD was treated with two doses of Remsima IV and 13 doses of Remsima SC 180 mg. The patient had a sudden death on the day of SC study drug administration. The Investigator reported that although the exact cause of death was unknown due to a sudden nature of the event, the possible underlying causes of the event would include the patient's pre-existing medical history of cardiovascular disease, Crohn's disease, diabetes mellitus and metabolic syndrome. The investigator reported the causal relationship of the event to the study drug as unrelated considering the possible underlying causes of the event.

Additional information on cardiac events

The MAH was requested to provide further information on serum concentration level of infliximab in all patients with confirmed or potential cardiac events (including cardiac deaths and sudden deaths) in the D120 LoQ. The MAH summarized data from the CT-P13 SC studies, according to which in total 19 confirmed cardiac events and potential cardiac events were reported from 16 patients (including 12 events from 11 [3.2%] RA patients). Based on data presented, there was no indication of increased pre-dose serum concentration, nor increased AUC and C_{trough} levels in those patients with cardiac events compared to overall patients at the same sampling week.

Laboratory findings

Healthy volunteers

In study CT-P13 1.5 there were no clinically significant abnormal laboratory results. The MAH states that safety laboratory parameters outside the reference range were noted for several subjects. However, these were usually just above or below the reference range.

For study CT-P13 1.9 in healthy subjects, the MAH states that in evaluation of haematology, clinical chemistry, coagulation and urinalysis parameters, the mean changes from baseline were small and there were no notable differences between the treatment arms. The most commonly reported TEAEs ($\geq 5\%$

subjects overall) were blood creatine phosphokinase (CPK) increased (20 [9.3%] subjects overall; 7 [6.4%] subjects in the CT-P13 SC AI arm and 13 [12.3%] subjects in the CT-P13 SC PFS arm).

Grade 3 or 4 CPK increased was reported for 6 subjects in the CT-P13 SC AI arm and 9 subjects in the CT-P13 SC PFS arm. All subjects with CPK increased recovered without treatment. The MAH performed analysis of these cases and summarized that the elevations were considered related to physical activity.

Patients with RA in Study CT-P13 3.5

In Part 1 Grade 4 hyperkalemia was reported for 1 (8.3%) patient in the SC 120 mg cohort and Grade 3 hyperkalemia was reported for 1 (8.3%) patient in the SC 180 mg cohort. Grade 3 GGT increased was reported for 1 (7.7%) patient in the IV 3 mg/kg cohort and 1 (9.1%) patient in the SC 90 mg cohort.

According to the CSR, in study CT-P13 3.5, part 2, in laboratory values (haematology, clinical chemistry, and urinalysis laboratory parameters) there were generally no notable differences in the mean change from baseline in the two treatment arms. The majority of patients had laboratory results of no CTCAE grade or CTCAE grade 1 (mild) during the study.

In the initial submission in Study CT-P13 3.5 laboratory results showed numerically more events of Grade 3 or 4 liver enzyme elevations in Remsima SC arm (5 events in 3 patients) than the CT-P13 IV 3 mg/kg arm (1 event in 1 patient) for the data up to Week 30 after beginning of maintenance treatment at Week 6.

For the updated safety data up to Week 54, Grade 3 or 4 liver enzyme elevation was reported for 2 (1.1%) patients (2 events) and 4 (2.4%) patients (6 events) in the CT-P13 IV 3 mg/kg and SC 120 mg arms, respectively. However, the increases in liver enzymes were observed in a small number of patients and were transient in nature and none of these cases fulfilled laboratory and clinical criteria for drug-induced liver injury.

Single cases of other laboratory finding, e.g., hyponatremia and hyperkalemia were reported in both arms. Grade 3 neutropenia were reported in both arms at a relatively low incidence, and Grade 4 neutrophil count decreased was reported for 1 patient in each treatment arm. With the updated data no new safety concerns were observed.

Patients with CD in Study CT-P13 1.6

In study CT-P13 1.6 Part 1, single cases of different post-baseline CTCAE Grade 3 and Grade 4 laboratory results were found in all treatment arms and included Blood bilirubin increased, CPK increased, GGT increased, Anaemia, Lymphocyte count decreased, and Neutrophil count decreased.

In conclusion, in healthy volunteer study CT-P13 1.9, there were relatively high numbers of CPK increases overall, and also in Grade 3 and 4 CPK events. In study CT-P13 3.5, even though the numbers are small, there were numerically more Grade 3 or 4 liver enzyme elevations in the SC arm (5 vs. 1 events).

Vital Signs, ECG. Physical Findings and Local Site Pain

In the studies with healthy subjects, commonly reported clinically notable vital sign were abnormal respiratory rates (both low and high). No individual abnormal ECG value was considered clinically significant or reported as a TEAE by the Investigator.

In study CT-P13 3.5 Part 1, the mean changes from baseline in vital sign values were according to the MAH small, and there were no notable differences among the cohorts at any time point.

In study CT-P13 3.5 Part 2, according to the CSR, in general, mean changes from baseline of vital sign measurements were small, and there were no notable differences between the treatment arms at any

time point. All patients who had ECG results were reported to have had normal or abnormal not clinically significant ECG results at baseline and all scheduled visits except for 1 (0.6%) patient. With the updated data, all patients who had ECG results, had normal or abnormal not clinically significant ECG results during the treatment period except for 2 (1.1%) patients in IV 3 mg/kg treatment arm.

In Study CT-P13 1.6 Part 1, according to the MAH, mean changes from baseline in vital sign values were small, and there were no consistent notable differences among the cohort's post-baseline.

Physical Findings

According to the MAH, in all studies, there were no notable findings with regards to physical examination at baseline or during the study.

Local Site Pain Assessment: Visual Analogue Scale (VAS)

Local pain assessments using VAS were also conducted in the two dose-finding studies and the pivotal RA study without any notable findings.

Safety in special populations

As stated above, in order not to omit any relevant data on recorded adverse events, listings of adverse events are mostly presented here with the patients from the site where major scientific misconduct was reported included.

The incidence of serious infections in infliximab-treated patients 65 years and older has been reported to be greater than those under 65 years of age (Remsima SmPC, 2018).

The MAH analysed the incidence of infections by age group in CT-P13 IV study with RA patients and stated that in Study CT-P13 3.5 Part 2 up to Week 30, TEAEs in the SOC infections and infestations were reported for a lower proportion of patients in the ≥ 18 years to ≤ 64 years subgroup (19.2% [n=151]) compared with the ≥ 65 years subgroup (26.3% [n=19]) for the CT-P13 SC treatment arm. The same trend was not observed for the Remsima IV treatment arm (20.7% [n=150] and 3.6% [n=28] in the ≥ 18 years to ≤ 64 years and ≥ 65 years subgroups, respectively).

However, the MAH acknowledged that the data should be interpreted with caution as the number of patients in each subgroup is small and Study CT-P13 3.5 Part 2 is an ongoing study. No other important reported intrinsic factors are considered by the MAH to influence the safety of infliximab.

The MAH has concluded that besides age, no other important reported intrinsic factors are considered to influence the safety of infliximab.

The MAH has provided a summary AE table including more mature safety data (up to 54 weeks) by age groups <65 years and ≥ 65 (up to 75 years which was the upper limit for inclusion in the study). Only a small subgroup of patients were ≥ 65 years of age (19 patients in the SC 120 mg arm and 28 patients in the IV 3 mg/kg arm). There were no obvious trends in relation to safety observations. However, as the number of patients over 65 years is very limited, no conclusions can be drawn.

The data from the subgroup analyses are presented in Table 40 and Table 41 below. There was no particular trend observed for each category that would indicate an increase in risk of adverse events in older patients treated with Remsima IV or SC. Change in quality of life was also calculated based on short form (36) (SF-36) healthy survey. In general, patients < 65 years old showed higher scores than patients ≥ 65 years old, but it was expected for older patients to score lower on the SF-36 survey. By Week 54, the mean score of each component of the survey was increased for younger and older patients in both treatment arms. An additional analysis of safety data by age from CT-P13 3.5 clinical trial showed a trend for increased treatment-emergent adverse events (TEAEs) in those > 65 years of age.

Table 40 - TEAE by Age in Study CT-P13 3.5 Part 2 up to 54 Weeks (Maintenance Phase): Safety Population

| | CT-P13 IV 3mg/kg (N=178) | | CT-P13 SC 120mg (N=170) | | Total (N=348) | |
|---|-----------------------------|--------------------|----------------------------|--------------------|---------------------|--------------------|
| | Age < 65 (N=150) | Age ≥ 65 (N=28) | Age < 65 (N=151) | Age ≥ 65 (N=19) | Age < 65 (N=301) | Age ≥ 65 (N=47) |
| Total number of TEAE | 247 | 36 | 237 | 28 | 484 | 64 |
| Number of Patients with at least 1 TEAE | 99 (66.0) | 14 (50.0) | 83 (55.0) | 9 (47.4) | 182 (60.5) | 23 (48.9) |
| TEAE leading to drop-out | 11 (7.3) | 3 (10.7) | 4 (2.6) | 1 (5.3) | 15 (5.0) | 4 (8.5) |
| Psychiatric disorders | 1 (0.7) | 0 | 0 | 0 | 1 (0.3) | 0 |
| Nervous system disorders | 11 (7.3) | 3 (10.7) | 6 (4.0) | 2 (10.5) | 17 (5.6) | 5 (10.6) |
| Accidents and injuries | 2 (1.3) | 0 | 3 (2.0) | 0 | 5 (1.7) | 0 |
| Cardiac disorders | 7 (4.7) | 1 (3.6) | 2 (1.3) | 0 | 9 (3.0) | 1 (2.1) |
| Vascular disorders | 4 (2.7) | 2 (7.1) | 0 | 1 (5.3) | 4 (1.3) | 3 (6.4) |
| Cerebrovascular disorders | 2 (1.3) | 1 (3.6) | 0 | 0 | 2 (0.7) | 1 (2.1) |
| Infections and infestations | 51 (34.0) | 3 (10.7) | 46 (27.8) | 6 (31.6) | 93 (30.9) | 9 (19.1) |
| Anticholinergic syndrome | 3 (2.0) | 2 (7.1) | 1 (0.7) | 1 (5.3) | 4 (1.3) | 3 (6.4) |
| Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures | 3 (2.0) | 3 (10.7) | 2 (1.3) | 1 (5.3) | 5 (1.7) | 4 (8.5) |

IV: Intravenous, SC: Subcutaneous, TEAE: Treatment-emergent adverse event

Table 41 - TESAE by Age in Study CT-P13 3.5 Part 2 up to 54 Weeks (Maintenance Phase): Safety Population

| | CT-P13 IV 3mg/kg (N=178) | | CT-P13 SC 120mg (N=170) | | Total (N=348) | |
|--|-----------------------------|--------------------|----------------------------|--------------------|---------------------|--------------------|
| | Age < 65 (N=150) | Age ≥ 65 (N=28) | Age < 65 (N=151) | Age ≥ 65 (N=19) | Age < 65 (N=301) | Age ≥ 65 (N=47) |
| Total Number of TESAE | 11 | 4 | 8 | 0 | 19 | 4 |
| Number of patients with at least 1 TESAE | 9 (6) | 4 (14.3) | 6 (4.0) | 0 | 15 (5.0) | 4 (8.5) |
| Related | 3 (2.0) | 1 (3.6) | 3 (2.0) | 0 | 6 (2.0) | 1 (2.1) |
| Hospitalization: Initial | 3 (2.0) | 1 (3.6) | 2 (1.3) | 0 | 5 (1.7) | 1 (2.1) |
| Important Medical Event | 0 | 0 | 1 (0.7) | 0 | 1 (0.3) | 0 |
| Unrelated | 8 (5.3) | 3 (10.7) | 3 (2.0) | 0 | 11 (3.7) | 3 (6.4) |
| Hospitalization: Initial | 6 (4.0) | 2 (7.1) | 3 (2.0) | 0 | 9 (3.0) | 2 (4.3) |
| Hospitalization: Prolongation | 0 | 0 | 1 (0.7) | 0 | 1 (0.3) | 0 |
| Life-Threatening | 1 (0.7) | 0 | 1 (0.7) | 0 | 2 (0.7) | 0 |
| Important Medical Event | 2 (1.3) | 1 (3.6) | 1 (0.7) | 0 | 3 (1.0) | 1 (2.1) |
| Death | 3 (2.0) | 1 (3.6) | 1 (0.7) | 0 | 4 (1.3) | 1 (2.1) |

IV: Intravenous, SC: Subcutaneous, TESAE: Treatment-emergent serious adverse event

There were no confirmed cases of pregnancy in Studies CT-P13 1.5, CT-P13 1.9, CT-P13 3.5 Part 1 or CT-P13 1.9. In Study CT-P13 3.5 Part 2, one pregnancy was reported; a patient was found to be pregnant at the Week 30 visit on 26 June 2018 by urine pregnancy test. Study drug was discontinued due to the event. During the follow-up, it was confirmed that the patient gave birth at 39 weeks gestation to a healthy female child, by caesarean section without incident.

Immunological events

The infliximab in Remsima IV and SC preparations is manufactured under similar conditions and the only differences in composition of the products is the addition of acetic acid, sodium acetate trihydrate and sorbitol to the SC formulation. None of these excipients have been described as being associated with an impact on the immunogenicity of a therapeutic protein in humans.

The comparison of the immunogenicity profiles of Remsima IV and SC are based on two single dose studies in healthy subjects (CT-P13 1.5. and CT-P13 1.9.) and two multiple dose studies in RA and CD patients (CT-P13 3.5. and CT-P13 1.6.). The studies are described in detail in other sections.

Sampling

In study CT-P13 1.5 (single dose), samples were analysed at days 0, 56 and 84 and in study CT-P13 1.9 (single dose) at days 0, 28, 42, 56 and 84. In study CT-P13 3.5 Part 1 and Part 2 (multiple dose), samples were analysed at weeks 0, 6, 14, 22, 30, 38, 46 and 54, and in study CT-P13 1.6 part 1 at weeks 0, 6, 14, 22, 30, 38, 46 and 54.

Results

Frequency of ADA and NAb

In study CT-P13 1.5 (healthy individuals, single dose), ADA levels were overall comparable between the SC and IV groups (70-100% at the end of study visit), with no clear differences between the timing of ADA-positivity, titers, or NAb frequencies. However, numerically these frequencies were slightly higher, in the SC 120 mg group (proposed SC dose for RA) compared to the IV group (3mg/kg, used in RA), i.e. 100% ADA-positive patients at EOS with 50% Nabs in the SC group compared to 70% and 14% in the IV group.

In study CT-P13 1.9 (healthy individuals, single dose), ADA levels were comparable in the autoinjector vs. pre-filled syringe groups (93.6% vs. 90.6% at the end of study visit), with no clear differences between the timing of ADA-positivity, titers, or Nab frequencies.

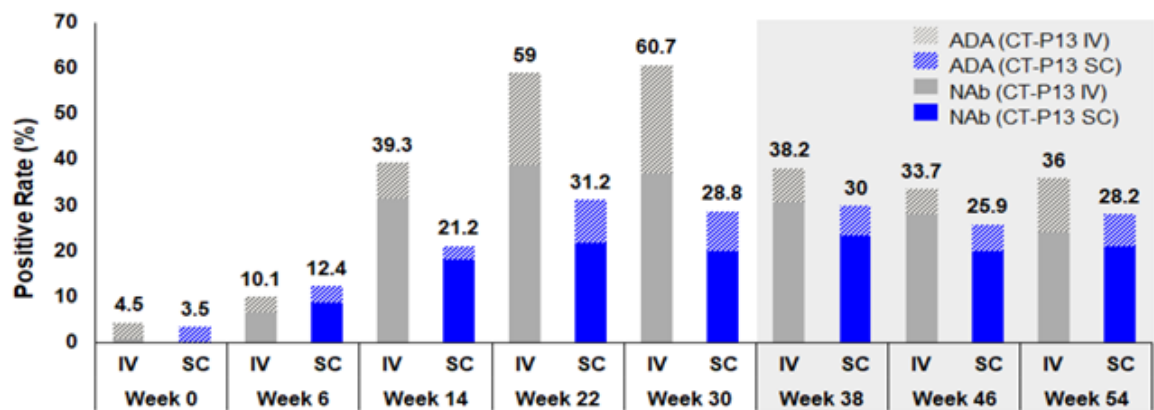
In study CT-P13 1.6 Part 1, a similar tendency was observed, with slightly lower ADA levels in SC groups compared to IV (18.2-37.5% vs 61.5%, respectively, at the end of study visit), with no clear differences between the timing of ADA-positivity, titers, or NAb frequencies.

In study CT-P13 3.5 part 1 (RA patients, multiple dose) there was a tendency for lower ADA frequency at the end of study in the groups that received Remsima SC compared to the group that received Remsima IV (50-81.8% vs. 84.6%), with no clear differences between the timing of ADA-positivity, titers, or Nab frequencies.

In the pivotal study (CT-P13 3.5 part 2; RA patients, multiple dose), the frequency of ADA-positivity post treatment up to week 54 was lower in the SC vs. IV group 49.4 vs. 72.0%, respectively). No clear differences between the timing of ADA-positivity, or Nab frequencies were observed. After switching to the SC formulation at Week 30 the proportion of patients who had positive ADA results in the CT-P13 IV arm reduced from 61.1% at week 30 to 36.6% at week 54. The MAH states that the detected difference in ADA levels among the same patients while on IV dosing compared to SC dosing is likely due to the higher C_{trough} levels after switching, which suggests that some low-titre ADAs in patients receiving CT-P13 SC have not been detected. This is probably due to drug interference of the assay; observed C_{trough} at Week 36 after switching was 8.79 µg/mL and 12.20 µg/mL in the CT-P13 IV and CT-P13 SC arms, respectively compared to Week 22 pre-switch levels of 1.03 µg/mL and 13.19 µg/mL, respectively.

In the IV arm 65 subjects (37.0%) were classified as NAb-positive at week 30 and 43 subjects (24.6%) at week 54. The MAH has provided an estimate of the number of patients with a possible false negative NAb result. Taking into consideration the drug tolerance level and drug serum concentration when the samples were taken, 15 (6.8%) patients had at least one potential false negative NAb sample due to a serum CT-P13 level over 10 µg/mL.

Figure 22 - ADA and NAb Positive Rates by Visit in Study CT-P13 3.5 Part 2 (Up to Week 54): Safety Population



Note: The grey-shaded area represents patients in the CT-P13 IV arm who were switched from CT-P13 IV to CT-P13 SC at Week 30 in Study CT-P13 3.5 Part 2.

Titres

In the pivotal study CT-P13 3.5 Part 2 the ADA titres seemed to be considerably higher in the SC group (

Table **42**). At week 30 the frequency of moderate and high titres (thought to be clinically significant) of ADAs seemed comparable between the two treatment arms, even though the frequency of low titres was lower in the SC arm. At the end of week 54 the titres were similar in both treatment arms even if the titres remained marginally lower in the patients initially treated with IV Remsima. Because of the very different drug levels influencing the ADA assay, comparing titre levels between the treatment arms is not completely reliable.

Table 42 - Summary of non-Transformed ADA and NAb Titer Results in Study CT-P13 3.5 Part 2

| Immunogenicity Test Visit Statistic | SC 120mg (N=168) | IV 3mg/kg (N=175) | Total (N=343) |
|---|---------------------|----------------------|------------------|
| ADA | | | |
| Week 22 | | | |
| n | 53 | 104 | 157 |
| Mean | 5.0 | 3.8 | 4.2 |
| SD | 2.69 | 1.88 | 2.25 |
| Minimum | 1 | 1 | 1 |
| Median | 5.0 | 4.0 | 4.0 |
| Maximum | 12 | 8 | 12 |
| Week 30 | | | |
| n | 49 | 107 | 156 |
| Mean | 5.0 | 4.3 | 4.5 |
| SD | 2.56 | 2.06 | 2.24 |
| Minimum | 1 | 1 | 1 |
| Median | 5.0 | 4.0 | 5.0 |
| Maximum | 11 | 10 | 11 |

| Immunogenicity Test Visit Statistic | SC 120mg (N=168) | IV 3mg/kg (N=175) | Total (N=343) |
|---|---------------------|----------------------|------------------|
| NAb | | | |
| Week 22 | | | |
| n | 37 | 69 | 106 |
| Mean | 3.1 | 2.1 | 2.5 |
| SD | 2.06 | 1.22 | 1.63 |
| Minimum | 1 | 1 | 1 |
| Median | 2.0 | 2.0 | 2.0 |
| Maximum | 8 | 6 | 8 |
| Week 30 | | | |
| n | 34 | 65 | 99 |
| Mean | 3.1 | 2.2 | 2.5 |
| SD | 2.03 | 1.17 | 1.58 |
| Minimum | 1 | 1 | 1 |
| Median | 3.0 | 2.0 | 2.0 |
| Maximum | 9 | 6 | 9 |

Effect of ADA on PK

Only assessment of the pivotal study is presented here. Results from studies CT-P13 1.6 Part 1 and CT-P13 3.5 Part 1 were in line with the results from the pivotal study.

In study CT-P13 3.5 Part 2 ADA presence in serum resulted in an overall decrease of drug exposure. The PK parameters tend to be lower in post-treatment ADA positive subgroup, and both IV 3 mg/kg and SC 120 mg arms show a similar trend Figure 23 and Table 43.

In Figure 23 a patient was classified as ADA positive if he/she had at least one ADA positive test result at any time. This classification is not optimal for determination of impact of ADA presence on drug concentration. Table 43 shows C_{trough} concentrations by visit-based ADA status.

Figure 23 - Box and Whisker Plot of PK Parameters (AUC_T , C_{max} and C_{trough}) by Post-treatment ADA Status at Weeks 22, 24, 26 and 28 in Study CT-P13 3.5 Part 2: PK Population

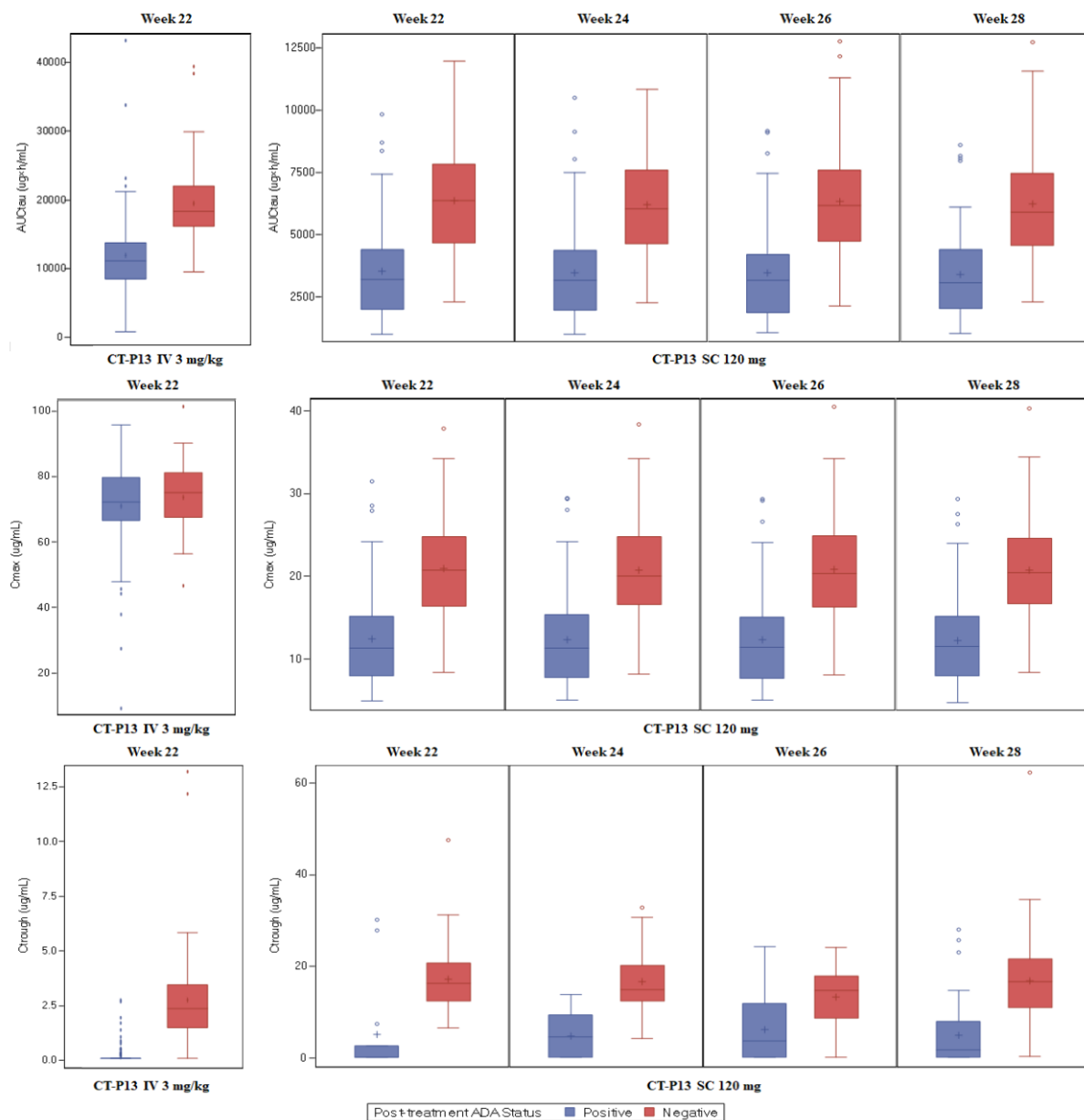


Table 43 - Pre-dose Concentrations by Visit-based ADA Status in Study CT-P13 3.5 Part 2: Pharmacokinetic Population

| Parameter Visit Statistic | | CT-P13 IV 3 mg/kg (N=174) | | CT-P13 SC 120 mg (N=166) | |
|---------------------------------|-------------|------------------------------|-------------------------|-----------------------------|-------------------------|
| | | Positive | Negative | Positive | Negative |
| Pre-dose concentration (µ g/mL) | | | | | |
| Week 6 | n | 18 | 152 | 21 | 142 |
| | Mean (± SD) | 2.1163 (± 3.72737) | 9.6333 (± 7.05668) | 1.9782 (± 4.14991) | 9.5588 (± 5.49621) |
| | 95% CI | (0.26270, 3.96986) | (8.50241, 10.7642) | (0.08922, 3.86725) | (8.64699, 10.47064) |
| Week 14 | n | 70 | 101 | 35 | 128 |
| | Mean (± SD) | 0.2964 (± 0.44268) | 3.0160 (± 2.22426) | 2.4211 (± 3.62302) | 14.9956 (± 7.01745) |
| | 95% CI | (0.19080, 0.40191) | (2.44272, 3.58938) | (1.21926, 3.62302) | (13.76821, 16.22298) |
| Week 22 | n | 98 | 65 | 51 | 109 |
| | Mean (± SD) | 2.8055 (± 13.41568) | 3.8400 (± 6.52074) | 3.3957 (± 4.07592) | 16.7116 (± 7.47154) |
| | 95% CI | (0.11584, 5.49518) | (2.22426, 5.45578) | (2.24935, 4.54210) | (15.29309, 18.13015) |
| Week 30 | n | 104 | 52 | 46 | 103 |
| | Mean (± SD) | 0.2308 (± 0.39479) | 2.6289 (± 2.9753) | 2.9753 (± 1.85888) | 16.3610 (± 8.67214) |
| | 95% CI | (0.15404, 0.30759) | (1.93462, 3.32315) | (1.85888, 4.09173) | (14.66615, 18.05591) |
| Week 38 | n | 68 | 83 | 51 | 106 |
| | Mean (± SD) | 1.5185 (± 2.80303) | 14.6447 (± 7.15986) | 3.0243 (± 5.23676) | 16.5088 (± 7.75673) |
| | 95% CI | (0.83999, 2.19695) | (13.08130, 16.20810) | (1.55143, 4.49716) | (15.01492, 18.00263) |
| Week 46 | n | 60 | 89 | 44 | 106 |
| | Mean (± SD) | 1.2902 (± 2.77101) | 15.8202 (± 8.09303) | 2.3708 (± 4.25218) | 14.9285 (± 6.96915) |
| | 95% CI | (0.57439, 2.00604) | (14.11541, 17.52504) | (1.07801, 3.66358) | (13.58628, 16.27063) |
| Week 54 | n | 64 | 83 | 48 | 98 |
| | Mean (± SD) | 2.2291 (± 3.56531) | 16.4067 (± 9.08748) | 2.3522 (± 3.82588) | 15.2001 (± 7.35665) |
| | 95% CI | (1.33855, 3.11973) | (14.42244, 18.39105) | (1.24131, 3.46315) | (13.72519, 16.67502) |

Note: The patients are categorised by ADA status at each visit. All analyses were conducted by excluding the data of patients from the significant GCP non-compliance site.

CI: Confidence interval, IV: Intravenous, n: The number of patients who had ADA status results at each visit, N: The number of patients in each treatment group, SC: Subcutaneous, SD: Standard deviation

Table 43 shows that mean C_{trough} drug concentrations remained around the level of 3 μ g/mL among ADA negative subjects in the IV treatment arm. Among ADA positive subjects treated with IV, C_{trough} concentrations were mostly well below 1 μ g/mL. In the SC treatment arm the presence of ADA in serum

also resulted in a clear decrease in drug levels but mean drug levels in ADA-positive patients treated with SC were still consistently above 1 µg/mL in both treatment arms.

To evaluate the impact of ADA titre on PK, pre-dose concentrations were assessed by visit-based ADA titre quartile. All patients who had 'Positive' ADA status result at each visit were included in this analysis and categorised into the 1st, 2nd, 3rd and 4th quartiles using the 25th, 50th, 75th percentiles of ADA titre result, respectively, at each visit in the Pharmacokinetic Population. The quartile division in ADA titre at each visit is summarised in Table 44.

The subgroup analysis showed that there was a trend for pre-dose concentration to decrease as ADA titre increases for both treatment arms (Table 45). In the IV arm ADA titres as low as ≤ 92 were accompanied by mean drug levels below 1 µg/mL, whereas in the SC group, drug levels remained on average above 1 µg/mL as long as ADA titres were < 736. At the highest titres the mean pre-dose drug concentrations were below the lower limit of quantitation (BLQ, < 0.1 µg/mL) for both treatment arms.

Table 44 - Quartile Division in ADA Titre

| Visit | 1 st Quartile | 2 nd Quartile | 3 rd Quartile | 4 th Quartile |
|---------|--------------------------|--------------------------|--------------------------|--------------------------|
| Week 6 | ADA titre ≤ 23 | 23 < ADA titre ≤ 46 | 46 < ADA titre ≤ 184 | ADA titre > 184 |
| Week 14 | ADA titre ≤ 46 | 46 < ADA titre ≤ 184 | 184 < ADA titre ≤ 368 | ADA titre > 368 |
| Week 22 | ADA titre ≤ 92 | 92 < ADA titre ≤ 184 | 184 < ADA titre ≤ 736 | ADA titre > 736 |
| Week 30 | ADA titre ≤ 92 | 92 < ADA titre ≤ 368 | 368 < ADA titre ≤ 736 | ADA titre > 736 |
| Week 38 | ADA titre ≤ 368 | 368 < ADA titre ≤ 736 | 736 < ADA titre ≤ 1472 | ADA titre > 1472 |
| Week 46 | ADA titre ≤ 368 | 368 < ADA titre ≤ 736 | 736 < ADA titre ≤ 2944 | ADA titre > 2944 |
| Week 54 | ADA titre ≤ 368 | 368 < ADA titre ≤ 736 | 736 < ADA titre ≤ 2944 | ADA titre > 2944 |

Note: Quartile division applies to the CT-P13 IV and CT-P13 SC arms at each visit.

Table 45 - Pre-dose Concentrations by Visit-based ADA Titre Quartile in Study CT-P13 3.5
Part 2: Pharmacokinetic Population

| Parameter Statistics | | CT-P13 IV 3 mg/kg (N=174) | | | | | CT-P13 SC 120 mg (N=166) | | | | |
|--------------------------------|----------------|------------------------------|--------------------------|------------------------------|------------------------------|------------------------------|-----------------------------|--------------------------|--------------------------|--------------------------|------------------------------|
| | | Negative | 1 st Quartile | 2 nd Quartile | 3 rd Quartile | 4 th Quartile | Negative | 1 st Quartile | 2 nd Quartile | 3 rd Quartile | 4 th Quartile |
| Pre-dose concentration (µg/mL) | | | | | | | | | | | |
| Week 6 | n | 152 | 9 | 2 | 4 | 3 | 142 | 9 | 1 | 5 | 6 |
| | Mean (± SD) | 9.6333 (± 7.05668) | 3.759 (± 4.7974) | 0.1000 (N/A) ¹ | 0.8625 (± 0.88047) | 0.204 (± 0.18013) | 9.5588 (± 5.49621) | 4.2052 (± 5.74868) | 1.4400 (N/A) | 0.2146 (± 0.25625) | 0.1972 (± 0.23801) |
| | 95% CI | (8.50241, 10.76420) | (0.0714, 7.4466) | N/A | (-0.53852, 2.26352) | (-0.24348, 0.65148) | (8.64699, 10.47064) | (-0.21361, 8.62405) | N/A | (-0.10358, 0.53278) | (-0.05261, 0.44694) |
| Week 14 | n | 101 | 29 | 24 | 7 | 10 | 128 | 7 | 7 | 5 | 16 |
| | Mean (± SD) | 3.0160 (± 2.90422) | 0.4708 (± 0.52205) | 0.1178 (± 0.06468) | 0.1720 (± 0.19049) | 0.3060 (± 0.65143) | 14.9956 (± 7.01745) | 6.9540 (± 4.78837) | 2.1420 (± 1.98252) | 0.6020 (± 1.12251) | 1.1286 (± 2.03915) |
| | 95% CI | (2.44272, 3.58938) | (0.27225, 0.66940) | (0.09048, 0.14510) | (-0.00418, 0.34818) | (-0.16000, 0.77200) | (13.76821, 16.22298) | (2.52550, 11.38250) | (0.30847, 3.97553) | (-0.79178, 1.99578) | (0.04204, 2.21521) |
| Week 22 | n | 65 | 40 | 17 | 33 | 8 | 109 | 14 | 7 | 17 | 13 |
| | Mean (± SD) | 3.8400 (± 6.52074) | 3.2727 (± 16.35856) | 0.1837 (± 0.20069) | 4.2458 (± 14.54344) | 0.1000 (N/A) ¹ | 16.7116 (± 7.47154) | 6.6664 (± 4.23399) | 4.5461 (± 3.94757) | 2.6864 (± 3.54603) | 0.1815 (± 0.29399) |
| | 95% CI | (2.22426, 5.45578) | (-1.95905, 8.50440) | (0.08052, 0.28689) | (-0.91112, 9.40264) | N/A | (15.29309, 18.13015) | (4.22180, 9.11106) | (0.89525, 8.19704) | (0.86321, 4.50961) | (0.00388, 0.35920) |
| Week 30 | n | 52 | 34 | 47 | 9 | 14 | 103 | 11 | 15 | 7 | 13 |
| | Mean (± SD) | 2.6289 (± 2.49374) | 0.4535 (± 0.62156) | 0.1338 (± 0.13044) | 0.1000 (N/A) ¹ | 0.1000 (N/A) ¹ | 16.3610 (± 8.67214) | 8.4700 (± 2.17071) | 2.3815 (± 2.65463) | 0.9530 (± 1.66985) | 0.1000 (N/A) ¹ |
| | 95% CI | (1.93462, 3.32315) | (0.23660, 0.67034) | (0.09547, 0.17206) | N/A | N/A | (14.66615, 18.05591) | (7.01169, 9.92831) | (0.91145, 3.85162) | (-0.59135, 2.49735) | N/A |

| Parameter Statistics | | CT-P13 IV 3 mg/kg (N=174) | | | | | CT-P13 SC 120 mg (N=166) | | | | |
|----------------------|----------------|------------------------------|--------------------------|--------------------------|--------------------------|------------------------------|-----------------------------|--------------------------|--------------------------|--------------------------|------------------------------|
| | | Negative | 1 st Quartile | 2 nd Quartile | 3 rd Quartile | 4 th Quartile | Negative | 1 st Quartile | 2 nd Quartile | 3 rd Quartile | 4 th Quartile |
| Week 38 | n | 83 | 26 | 15 | 10 | 17 | 106 | 20 | 13 | 6 | 12 |
| | Mean (± SD) | 14.6447 (± 7.15986) | 2.9890 (± 3.54105) | 1.0561 (± 2.47205) | 0.6620 (± 1.7772) | 0.1812 (± 0.3347) | 16.5088 (± 7.75673) | 6.2893 (± 6.53342) | 1.7311 (± 3.85508) | 0.7917 (± 1.69423) | 0.1000 (N/A) ¹ |
| | 95% CI | (13.08130, 16.20810) | (1.55874, 4.41926) | (-0.31284, 2.42511) | (-0.60933, 1.93333) | (0.00909, 0.35326) | (15.01492, 18.00263) | (3.23151, 9.34699) | (-0.59853, 4.06068) | (-0.98632, 2.56965) | N/A |
| Week 46 | n | 89 | 28 | 5 | 18 | 9 | 106 | 14 | 4 | 10 | 13 |
| | Mean (± SD) | 15.8202 (± 8.09303) | 2.5369 (± 3.69899) | 0.3470 (± 0.28973) | 0.2081 (± 0.29463) | 0.1000 (N/A) ¹ | 14.9285 (± 6.96915) | 5.4097 (± 5.84999) | 2.7338 (± 2.48181) | 0.6654 (± 1.73794) | 0.1000 (N/A) ¹ |
| | 95% CI | (14.11541, 17.52504) | (1.10254, 3.97118) | (-0.01275, 0.70675) | (0.06160, 0.35463) | N/A | (13.58628, 16.27063) | (2.03203, 8.78740) | (-1.21536, 6.68286) | (-0.57785, 1.90865) | N/A |
| Week 54 | n | 83 | 27 | 11 | 17 | 7 | 98 | 17 | 7 | 11 | 12 |
| | Mean (± SD) | 16.4067 (± 9.08748) | 3.4035 (± 2.90034) | 1.2506 (± 1.60862) | 0.2538 (± 0.48359) | 0.1000 (N/A) ¹ | 15.2001 (± 7.35665) | 4.9305 (± 5.00801) | 1.5457 (± 2.65483) | 1.5426 (± 2.31677) | 0.1000 (N/A) ¹ |
| | 95% CI | (14.42244, 18.39105) | (2.25615, 4.55082) | (0.16995, 2.33132) | (0.00512, 0.50240) | N/A | (13.72519, 16.67502) | (2.35559, 7.50535) | (-0.90960, 4.00102) | (-0.01379, 3.09906) | N/A |

Note: The patients who had 'Positive' ADA status result at each visit were included in this analysis and categorized using the 25th, 50th, 75th percentiles of ADA titre result at each visit in the Pharmacokinetic Population.

All analyses were conducted by excluding the data of patients from the

significant GCP non-compliance site (site 2840 in Russia).

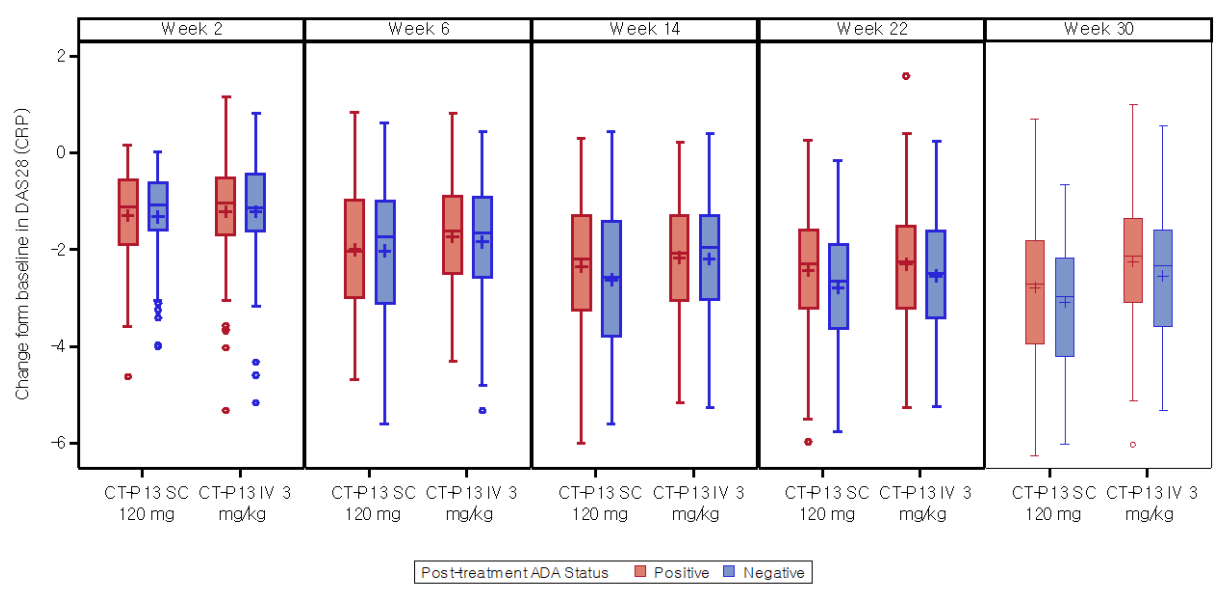
¹ All concentrations below limit of quantification (BLQ) after the first administration (Week 0, Dose 1) were set to Lower Limit of Quantification (LLOQ, 0.1 µg/mL).

CI: Confidence interval, IV: Intravenous, N/A: Not applicable, SC: Subcutaneous, SD: Standard deviation

Effect of ADA on efficacy and safety

There was a statistically and clinically non-significant tendency for weaker DAS28 and ACR improvement in ADA-positive RA patients compared to ADA-negative patients. This effect was similar between the SC and IV groups. (Figure 24 and Table 46).

Figure 24 - Box and Whisker Plot of Mean Change from Baseline in DAS28 (CRP) up to Week 30 by Post-treatment ADA Status in Study CT-P13 3.5 Part 2: Efficacy Population



At week 30, ADA positive patients in the SC arm had significantly higher response levels than ADA positive patients in the IV arm and numerically even slightly better response than ADA negative patients in the IV arm (Table 46). This is in line with the effects of ADA presence on drug concentrations shown above in Table 43.

Table 46 - Mean Change from Baseline of DAS28 (CRP) and Proportion of Patients Achieving ACR20 at Weeks 30 and 54 by Post-treatment ADA Status up to Week 54 in Study CT-P13 3.5 Part 2: Efficacy Population

| Parameter Visit Statistics | | CT-P13 IV 3 mg/kg (N=177) | | CT-P13 SC 120 mg (N=167) | |
|----------------------------------|------------------|------------------------------|---------------------|-----------------------------|----------------------|
| | | ADA Positive | ADA Negative | ADA Positive | ADA Negative |
| DAS28 (CRP) | | | | | |
| Week 30 | n | 112 | 49 | 74 | 85 |
| | Mean (\pm SD) | -2.25 (\pm 1.23) | -2.51 (\pm 1.37) | -2.84 (\pm 1.25) | -3.11 (\pm 1.35) |
| | 95% CI | (-2.48, -2.02) | (-2.91, -2.12) | (-3.12, -2.55) | (-3.40, -2.82) |
| Week 54 | n | 102 | 45 | 67 | 80 |
| | Mean (\pm SD) | -2.78 (\pm 1.29) | -3.24 (\pm 1.18) | -3.06 (\pm 1.33) | -3.381 (\pm 1.25) |
| | 95% CI | (-3.03, -2.53) | (-3.59, -2.88) | (-3.39, -2.74) | (-3.66, -3.10) |
| ACR20 | | | | | |
| Week 30 | n/N (%) | 92/126 (73.0) | 42/51 (82.4) | 65/78 (83.3) | 78/89 (87.6) |
| | 95% CI | (64.38, 80.53) | (69.13, 91.60) | (73.19, 90.82) | (78.96, 93.67) |
| Week 54 | n/N (%) | 83/126 (65.9) | 42/51 (82.4) | 59/78 (75.6) | 74/89 (83.1) |
| | 95% CI | (56.90, 74.08) | (69.13, 91.60) | (64.60, 84.65) | (73.73, 90.25) |

Note: All immunogenicity results (including End-of-Study and unscheduled) after study drug administration were included

Percentages for ACR20 were calculated using the number of patients in each subgroup as denominator. ACR20: American College of Rheumatology 20% improvement criteria, CI: confidence interval, CRP: C-Reactive Protein, SD: standard deviation.

Infections

With results from Study CT-P13 3.5 Part 2 up to Week 54, the impact of ADA positivity on the incidence of infection and different types of infections (pneumonia, latent tuberculosis [TB] and opportunistic infection) were assessed as presented in Table 47. There was no significant difference in the incidence of each infection between the post-treatment ADA subsets, with the exception of other opportunistic infections in the CT-P13 SC arm which showed a slightly higher incidence in the post-treatment ADA negative subset than ADA positive subset (4 [4.4%] patients and 0, respectively). However, all reported opportunistic infections were mild or moderate oral herpes, and the events were recovered within few days.

The percentages of latent tuberculosis were almost double in ADA positive arms (6.3% vs. 3.9% in the IV arm and 6.3% vs. 3.3% in the SC arm) but the treatment arms were similar compared to each other.

Overall, the incidence of infection and different types of infections are well balanced between post-treatment ADA positive and post-treatment ADA negative subsets in CT-P13 IV and CT-P13 SC arms.

Table 47 - Summary of Infection, Pneumonia, Latent Tuberculosis and Other Opportunistic Infections by Post-treatment ADA Status in Study CTP13 3.5 Part 2 up to Week 54: Safety Population

| System Organ Class Preferred Term | CT-P13 IV 3 mg/kg (N=178) | | CT-P13 SC 120 mg (N=170) | |
|-----------------------------------|---------------------------|---------------------|--------------------------|---------------------|
| | ADA Positive (n=127) | ADA Negative (n=51) | ADA Positive (n=80) | ADA Negative (n=90) |
| Infections | 37 (29.1%) | 17 (33.3%) | 23 (28.8%) | 25 (27.8%) |
| Pneumonia | 1 (0.8%) | 0 | 0 | 2 (2.2%) |
| Latent tuberculosis | 8 (6.3%) | 2 (3.9%) | 5 (6.3%) | 3 (3.3%) |
| Opportunistic infections | 1 (0.8%) | 2 (3.9%) | 0 | 4 (4.4%) |

No correlation between ADA titre and infection incidence rates overall could be observed in Study CT-P13 3.5 Part 2.

Safety related to drug-drug interactions and other interactions

Drug-drug interactions

No formal PK interaction studies have been performed with Remsima SC.

MAH has indicated that it is expected that the PK interactions of Remsima SC will be similar to Remsima IV. According to the Remicade EPAR (2005), in an interaction study with methotrexate (MTX), the plasma concentration of infliximab was slightly increased by MTX. With Remicade, lower frequencies of patients with antibodies to infliximab were also observed during MTX co-treatment.

Modelling of PK and safety parameters

To investigate the relationship between the safety profile of infliximab and exposure to infliximab, multiple logistic regression analyses for TEAE, TESA, infections and ARR were performed with

covariates, AUC, body weight, treatment arm and all possible interactions for Study CT-P13 3.5 Part 2. AUC_T was taken as the mean of the computed AUC values from Week 22 to Week 30.

Infusion-related reactions

The relationship between infliximab steady state exposure parameters (AUC_T (normalised to Q8W dosing frequency), C_{max}, C_{trough}) and reported AEs of special interest (infusion-related reactions (IRR) and infections) was explored. Individual exposure parameters were estimated using the population PK model.

In all patients, for both the IV and SC regimens, boxplots indicate no difference in steady state AUC_T and C_{trough} between the group of individuals who experienced IRR and those who did not.

In some patient groups subjects who experienced IRR tended to have lower infliximab exposure than those who did not, but the results should be interpreted with caution given the small number of patients. Boxplots of C_{max} vs. AEs were generally comparable to those for AUC_T vs. AEs.

Infections

The results concerning infections indicate that exposures between patients that experienced infection was comparable to that of patients without infections with the only exception being the CD SC group, which appears to present lower exposures for those patients that had infection. The number of CD SC patients that had any infection was, however, small (n=8), and only one CD SC patient had 'Related, Moderate/Severe' infection. Boxplots of C_{max} vs. AEs were generally comparable to those for AUC_T vs. AEs.

Discontinuation due to AEs

No subjects permanently discontinued from healthy volunteer studies due to AEs.

During the Maintenance Phase of Study CT-P13 3.5 Part 1, TEAEs leading to permanent discontinuation from study drug were reported for no patients in the IV 3 mg/kg cohort, 2 (18.2%) in the 90 mg SC cohort and 2 (16.7%) in the 120 mg SC cohort and 2 (16.7%) in the SC 180 mg cohort. For the SC group the most commonly reported TEAE leading to permanent discontinuation from study drug was ARR (1 patient (9.1%) in the SC 90 mg cohort and 2 patients (16.7%) in the SC 120 mg cohort). TEAEs leading to permanent discontinuation that were considered by the Investigator to be related to study drug were Grade 3 antiphospholipid syndrome and Grade 3 pulmonary TB, one patient each in the SC 180 mg cohort).

In Part 2 of the study, all 362 enrolled patients received CT-P13 IV in the Dose-loading Phase. Fourteen patients discontinued in the Dose-loading Phase; the most common primary reason for discontinuation was AE.

During the Maintenance Phase of Study CT-P13 3.5 Part 2 up to week 30, after randomisation, discontinuations due to an adverse event were more common in the IV group: only 1 (0.6%) patient in SC 120 mg treatment arm compared to 9 (5.1%) patients in IV 3 mg/kg treatment arm discontinued during the maintenance phase of the pivotal study. There seems to be a higher dropout rate in the IV group towards the later stages of the study. TEAEs leading to permanent discontinuation from study drug in the IV 3 mg/kg arm that were considered by the Investigator to be related to study drug were Grade 3 vertigo positional (2 patients), Grade 2 bronchitis (1 patient), Grade 2 latent TB (1 patient), Grade 2 ARR (3 patients) and Grade 3 ARR (1 patient). One patient in the SC 120 mg arm permanently discontinued from study drug due to the Grade 3, unrelated TESAE of duodenal ulcer haemorrhage; the patient recovered after receiving treatment for the event.

During the Maintenance Phase of the dose-finding study CT-P13 1.6 Part 1, at least 1 TEAE leading to permanent discontinuation from study drug was reported for 3 (23.1%) patients in the IV 5 mg/kg cohort, 1 (9.1%) patient in the SC 120 mg cohort, 2 (16.7%) patients in the SC 180 mg cohort and

1 (12.5%) patient in the SC 240 mg cohort . No TEAE by PT leading to permanent discontinuation from study drug was reported for > 1 patient overall.

The MAH provided data on extended follow-up in patients with RA. A total of 52 (14.9%) patients discontinued the maintenance phase up to end of study (up to Week 54 for Bulgaria, Korea, Poland, and Russia) (22 [13.0%] patients and 30 [16.8%] patients in the SC 120 mg and IV 3 mg/kg treatment arms, respectively). The proportion of patients who discontinued the maintenance phase up to end of study (up to Week 54 for Bulgaria, Korea, Poland, and Russia) was generally similar between two treatment arms.

Post marketing experience

Remsima SC has not yet been authorised for marketing in any country worldwide.

Remsima IV was developed as an infliximab biosimilar and was approved by the EMA in September 2013. The 5-year renewal application for marketing authorisation submitted to the EMA in November 2017 included post-marketing data up to a data lock point (DLP) of 10 August 2017 EMEA/H/C/002576/R/0047).

A total of 13,283 ADRs were reported during the renewal period (period from the initial approval date of Remsima to the DLP of the 5-year renewal application) from post-marketing data sources, including 5,759 serious ADRs. ADRs were most commonly reported for the SOC general disorders and administration site conditions (2455 ADRs) followed by the SOC skin and subcutaneous tissue disorders (1504 ADRs).

Further post-marketing exposure to Remsima IV is estimated at 370,108 patient-years up to 20 January 2018. There have been no safety-related significant changes made to the Remsima SmPC based on Remsima clinical data.

Human factor studies

The MAH provided the full human factor study (HFS) reports. The MAH conducted human factor studies to assess the safety and usability of the devices. Overall, the conducted HF studies provided evidence that the devices to be registered for delivery of Remsima SC are safe and usable in the intended environment.

2.8.1. Discussion on clinical safety

Summary of the clinical database

Intravenous infliximab has been widely used in clinical practice in EU since 1999 and its safety profile has been characterized by more than 15 years of clinical use. Remsima was initially developed for IV infusion and was approved in the EU in September 2013 (EMA/H/C/002576) as a biosimilar product to EU-approved Remicade. The estimated use of Remsima is 370,108 patient-years up to 20 January 2018.

Even though the safety profile of intravenous administration of infliximab is well established with long-term safety data, the safety profile of SC administration of infliximab is not known, as the SC formulation of infliximab has not been previously authorised.

The originally submitted safety dossier for this extension of indication for Remsima SC consisted of 4 randomised controlled clinical trials, two performed in healthy volunteers, one ongoing pivotal study in patients with Rheumatoid Arthritis (RA) and one ongoing study in Crohn's disease (CD)/colitis ulcerosa (CU).

The overall safety population consists of 693 subjects: 396 patients with RA, 44 patients with CD and 253 healthy subjects. Of these, 633 subjects (367 RA patients, 31 CD patients and 235 healthy subjects)

received at least 1 dose of Remsima SC, including 162 RA patients who switched to CT-P13 SC at Week 30 in Study CT-P13 3.5 Part 2.

The originally submitted 54 week safety data in RA was based on only 44 patients from the study CT-P13 3.5 Part 1, of whom 26 patients completed the one year treatment in this dose-finding part of the study (with SC doses 90 mg, 120 mg and 180 mg). In addition, 30-week safety data from about 160 RA patients, treated with the 120 mg SC dose was available from Part 2 of the study. Supportive safety data from patients with CD up to 54 weeks was available from only 22 patients from the dose-finding part of the study CT-P13 1.6 Part 1 (with SC doses 120 mg, 180 mg and 240 mg).

Based on the original submission, the amount of long-term safety and efficacy data was considered very limited. The need for more data was also underlined in previous CHMP Advice. During the review process, the MAH has provided data on extended follow-up in patients with RA from Study CT-P13 3.5. In total, out of 348 patients included in the study, 297 (85.3%) patients completed the maintenance phase up to week 54 (148 [42.5%] patients and 149 [42.8%] patients in the SC 120 mg and IV 3 mg/kg treatment arms, respectively). Further, according to data provided in the CSR, there were 171 (49.1%) patients who were continuing the study at Week 54, 86 patients in SC 120 mg and 85 patients in the original IV 3 mg/kg treatment arms, respectively). A total of 52 (14.9%) patients discontinued the maintenance phase up to end of study (22 [13.0%] patients and 30 [16.8%] patients in the SC 120 mg and IV 3 mg/kg treatment arms, respectively). In Part 2 of Study CT-P13 3.5 148 RA patients received 120 mg of CT-P13 SC for 54 weeks and 81 of these patients were treated for 64 weeks.

The long-term safety database in patients with RA has thus been extended, as requested. However, the numbers are still limited to identify potential rare and severe adverse events. More safety data will be obtained from the planned post-approval safety/ PV program as described in the RMP.

Summary of adverse events

In studies with healthy volunteers, the numbers of subjects with at least one TEAE appeared comparable for the SC arms and the IV arm although the comparison is hampered by the small number of subjects (especially in healthy volunteers with IV dosing). ISRs occurred only among healthy subjects that received the drug SC.

In original submission in the pivotal study in RA, 263 TEAEs were reported in 138 (39.7%) patients up to Week 30 of maintenance phase with a similar proportion of patients who experienced TEAEs between the 2 treatment arms. The most frequently reported TEAEs in all patients were injection site reaction (ISR) followed by viral upper respiratory tract infection. The majority of TEAEs were grade 1 or 2 in intensity. All of TEAEs classified as ISRs were grade 1 or 2 in intensity. Only few TESAEs were reported and the pattern was consistent with the known safety profile of infliximab IV administration. Overall, the analysis of the different types of AEs reported in the pivotal RA study did not reveal any unexpected findings.

The updated safety analyses confirm the earlier findings. In the safety analysis with data up to 54 weeks, no new safety concerns with regard to incidence and severity of TEAEs or TESAEs were observed. TEAEs and TESAEs were relatively evenly distributed between the SC and IV treatment arms, and their patterns were consistent with the known safety profile of infliximab with the exception of the local injection site reactions.

There were no clearly consistent differences between Remsima IV and SC treatment groups in TEAEs leading to discontinuations in the studies, nor between the Remsima AI and PFS treatment arms. However, with the updated safety data, the treatment-emergent AEs leading to permanent discontinuation of study drug during the treatment period were reported for 5 (2.9%) patients in SC 120 mg treatment arm and 14 (7.9%) patients in IV 3 mg/kg treatment arm. Treatment-emergent AEs classified as ARR during the treatment period were reported for 2 (1.2%) patients in SC 120 mg

treatment arm and 10 (5.7%) patients in IV 3 mg/kg treatment arm. This higher incidence of discontinuations in the IV arm may have minor influence on the overall results.

Overall, the safety profile of Remsima SC in the proposed dose range do not appear consistently worse than Remsima IV when analysing the number of patients that reported adverse events or the type of events recorded. There are no clear differences between the pattern of events in the SC arms compared to the pattern in the IV arms (or compared to the known safety-profile of the substance) with one notable exception: the proportion of patients that reported a TEAE classified as an ISR, often described as an erythema, was generally higher in the SC group.

Serious adverse events and deaths

In healthy volunteer studies there were no TESAEs that can possibly be considered related to the study drug, and there were no deaths.

During the maintenance phase of the dose-finding Study CT-P13 3.5 Part 1 in RA patients, TESAEs were reported for 1 (7.7%) patient in the IV 3 mg/kg cohort, 2 (18.2%) patients in the SC 90 mg cohort, no patients in the SC 120 mg cohort and 3 (25.0%) patients in the SC 180 mg cohort. No TESAEs of ARRs or ISRs were reported.

During the maintenance phase of the pivotal Study CT-P13 3.5 Part 2 with the updated safety data up to 54 weeks including the five patients from the site where major scientific misconduct was reported, there were 13 (7.3%) patients in the IV arm and 6 (3.5%) patients in the SC arm with at least one TESAEs. The TESAEs included 3 (1.8%) and 1 (0.6%) cases of infections for the SC and IV arms, respectively, 4 cardiac events (2.2%), all in the IV arm, and five deaths cases (see discussion below). The other TESAEs were mainly single cases each. The majority of TESAEs were grade 3 or lower in intensity.

During the maintenance phase of the dose-finding study CT-P13 1.6 Part 1 in patients with CD, at least 1 TESA was reported for 4 (30.8%) patients in the IV 5 mg/kg cohort, 2 (18.2%) patients in the SC 120 mg cohort, 1 (8.3%) patient in the SC 180 mg cohort and 3 (37.5%) patients in the SC 240 mg cohort. No TESAEs of ARRs or ISRs were reported. A total of 7 TEAEs leading to death have been reported in the Remsima SC studies in patients included in this application; 3 patients treated with IV only and 4 patients treated with SC. In study CT-P13 3.5 there were two cases of death in the Remsima IV group (sudden death and myocardial infarction) and three in those patients who received Remsima SC (hereditary haemochromatosis, myocardial infarction and cardiac arrest). There were three deaths that occurred on the Remsima administration day (myocardial infarction, cardiac arrest and sudden death). All the death cases were considered by the investigator not related to the study medication.

The MAH has presented data that there was no trend in regard to the pharmacokinetic parameters of serum drug levels and immunogenicity results in patient in the SC group (hereditary hemochromatosis) in who the C_{trough} concentrate was considered originally high. The MAH also summarized that the numbers of deaths were balanced between the treatment groups; 3/204 (1.47%) in Remsima IV and 4/399 (1.00%) in patients with at least one Remsima SC dose (these numbers include two death cases in CD patients). No autopsy was performed for any of the death cases and no more information concerning these patients can be retrieved. Based on analysis provided by the MAH, the incidence rate of death in Remsima SC clinical trials falls within the variation reported from historical studies.

In conclusion, with regards to serious adverse events and deaths, the safety profile of Remsima SC in the proposed dose range did not appear worse than Remsima IV. There were no serious events reported as ISRs or ARRs in the Remsima SC groups. Even though the MAH has now provided updated safety data, the numbers of patients with up to 1-year treatment are still limited and do not allow identification of all rare and serious AEs, which need to be followed-up in the planned post- marketing safety study as detailed in the RMP.

Adverse events of special interest

AEs of special interest included administration related reactions (ARR), infections (including opportunistic infections) and malignancies. In the original submission, no major differences were observed in the safety between Remsima IV and SC, except for infusion-related reactions (IRR) and injection site reactions (ISR) (all grade 1-2 in intensity). In the pivotal RA study with follow-up up to 30 weeks, ISRs were reported with higher proportion in the SC 120 mg treatment arm compared to the IV 3 mg/kg treatment arm (11 [6.5%] and 4 [2.2%], whereas the occurrence of systemic IRR, associated with the IV route was lower in the SC route group). ARRs were reported in 1 patient [0.6%] in the SC arm and in 8 [4.5%] patients in the IV arm during Part 2 of the RA study. Delayed hypersensitivity (ARRs that occurred after 24 hours from the study drug administration) was reported for 1 (0.6%) patient in SC arm only, with no signs of serum sickness. However, based on modelling of all safety data, the occurrence of IRR > 24 hours after SC administration was more common in the Remsima SC arm (4 patients including both Part 1 and 2). The potential reasons for higher numbers of IRR were not explained in the submitted data.

Further, across all clinical studies and data presented, the differences of AEs classified as ARR or IRR and hypersensitivity reactions were to some extent unclear, and more clarification was requested, along with the need to update the draft SmPC.

The MAH has now revised the terminology concerning IRR to make these distinctions clearer. Specifically, ARR was revised to infusion related reactions (IRR) and systemic injection reaction (SIR) for Remsima IV and Remsima SC arms, respectively, to distinguish systemic reactions as per the route of administration. ISR was revised to localised ISR to specify that these reactions occurred around the injection site only, and to differentiate from systemic reactions (IRR and SIR). IRR or SIR that occurred after 24 hours from study drug administration were maintained as "delayed hypersensitivity". All delayed hypersensitivity cases were examined to determine if these cases were serum sickness or not.

Based on these new classifications, the MAH has performed updated analysis with more mature data from Study CT-P13 3.5. TEAEs classified as IRR during the maintenance phase were reported for no patient in SC 120 mg treatment arm and 7 (4.0%) patients in IV 3 mg/kg treatment arm. Treatment-emergent AEs classified as SIR during the maintenance phase were reported for 2 (1.2%) patients in SC 120 mg treatment arm and 3 (1.7%) patients in IV 3 mg/kg treatment arm.

Treatment-emergent AEs classified as delayed hypersensitivity during the maintenance phase were reported for 4 (2.4%) patients in SC 120 mg treatment arm and no patient in IV 3 mg/kg treatment arm. Treatment-emergent AEs classified as localised ISR during the maintenance phase were reported for 30 (17.9%) patients in SC 120 mg treatment arm and 22 (12.6%) patients in IV 3 mg/kg treatment arm. This terminology is considered appropriate and this has now been applied also in the SmPC.

There were no obvious differences in the incidence of infections and the types of infections between the study arms. With the extended follow-up, the incidence of patients with infections during the maintenance phase was 49 (29.2%) in the SC arm and 60 (34.3%) in the IV arm. The majority of infections were of grade 1 or 2 in intensity. The most commonly reported infection was viral upper respiratory tract infection (10 patients in each group). The incidence of latent tuberculosis was 10 (5.7%) patients in the IV arm and 8 (4.8%) patients in the SC arm. No clear differences in opportunistic infections between the study arms (or other safety signals) were observed. Overall, the incidence of infections and different types of infections were comparable with the historical controls.

Only one case of malignancy (ovarian cancer) was reported in the Remsima SC arm (considered related). As per request, the MAH has provided additional data on serum concentration level of infliximab and the confirmed cardiac events and all potential cardiac events (including cardiac deaths and sudden deaths). Based on data presented, there was no indication of increased pre-dose serum concentration, nor

increased AUC and C_{trough} levels in those patients with cardiac events compared to overall patients at the same sampling week.

Laboratory values

In healthy volunteer study CT-P13 1.9 there were relatively high numbers of CPK increases: 20 subjects (9.3%) overall; 6.4% subjects in the AI arm and 12.3% subjects in the PFS arm, of which 15 were Grade 3 or 4 CPK increases. The MAH has now clarified that the events of blood CPK increases in Study CT-P13 1.9 for healthy volunteers are considered unrelated to SC infliximab and likely be caused by increased physical activity, and this has also been confirmed by the Investigator. In addition, the MAH has confirmed that in studies where patients were administered with multiple doses of Remsima SC, the incidence rate of TEAE of blood CPK increased was very low and the rate of Grade 3 and 4 TEAE of blood CPK increased was less than 1%.

In the original submission there were more Grade 3 or 4 liver enzyme elevations in the SC arm compared to IV arm. With the updated safety data, laboratory results showed numerically more Grade 3 or 4 liver enzyme elevation, which were reported for 2 (1.1%) patients (2 events) and 4 (2.4%) patients (6 events) in the CT-P13 IV and SC arms, respectively. However, the incidence of liver enzyme elevations was balanced between the 2 treatment arms, taking into account the events which occurred during the Dose-Loading Phase (Week 0 to Week 6): 4 (2.2%) and 4 (2.4%) patients. In total, the increases in liver enzymes were observed in a small number of patients and were transient in nature and none of these cases fulfilled laboratory and clinical criteria for drug-induced liver injury (DILI).

Otherwise no major findings, nor differences between the study arms were seen in laboratory values. However, limited database does not allow conclusions concerning laboratory values.

Correlation between PK and AEs

Based on historical studies and on post hoc analyses conducted in IV and SC studies, increased infliximab serum concentrations did not appear to increase safety risks. However, the numbers of SC patients are small and therefore no conclusions can be made.

Exploratory graphical analyses indicated that subjects who experienced infusion related reactions (IRR) and infections did not have higher exposure to infliximab. Patients that had moderate to severe IRR tended to have lower exposure to infliximab, but this finding should be interpreted with caution because of small number of patients (n=2 to 4).

Immunogenicity

As stated by the MAH, in healthy volunteers, the proportion of subjects with positive results for ADA was higher in the CT-P13 SC cohorts compared to the CT-P13 IV cohort in Study CT-P13 1.5. On the contrary, in the patient studies (Studies CT-P13 3.5 and CT-P13 1.6), the ADA results showed a trend to lower proportions of patients with positive ADA response in the CT-P13 SC cohorts compared to the IV cohort. Generally, regardless of treatment-arm, the proportion of ADA-positive individuals appeared lower in patients than in healthy subjects, but this phenomenon was most pronounced in the SC arms.

In the pivotal clinical trial in RA patients, the frequency of ADA-positivity was lower in the SC vs. IV group (49.4 vs. 72.0% up to Week 54). After switching to the SC formulation at Week 30 the proportion of patients who had positive ADA results in the CT-P13 IV arm reduced to 36.6% at week 54. However, it is possible that some low-titre ADAs in patients receiving CT-P13 SC have not been detected. Because of very different drug concentrations in the IV and SC groups the sensitivity to detect ADAs was different and therefore the treatment arms are not comparable in the lower range of ADA titres.

Most ADAs were neutralizing and there seemed to be no major difference between the groups regarding proportion of Nabs per ADA (69.4% vs. 60.7% for SC and IV respectively at week 30).

The MAH has provided an estimate of the amount of patients with a possible false negative NAb result. Taking into consideration the drug tolerance level and drug serum concentration when the samples were taken, 15 (6.8%) patients had at least one potential false negative NAb sample due to a serum CT-P13 level over 10 µg/mL. Considering that 65 subjects (37.0%) in the IV arm were classified as NAb-positive at week 30 and 43 subjects (24.6%) at week 54, it seems that the drop in Nab frequency cannot be solely attributed to potentially false negative samples. Therefore, it seems that at least some conversion from seropositive to seronegative occurred after switching from IV to SC. In addition, the NAb frequency was constantly slightly lower in the SC arm, also after switching. Therefore, even if some of the NABs went undetected due to higher drug concentrations and low sensitivity to detect low titres of NABs, the formation of NABs was not greater with the SC formulation.

ADA presence in serum resulted in an overall decrease of drug exposure, as expected, with a similar trend in both arms. Mean C_{trough} drug concentrations remained around the level of 3 µg/mL among ADA negative subjects in the IV treatment arm up to Week 30. Among ADA positive subjects treated with IV, C_{trough} concentrations were mostly well below 1 µg/mL. In the SC treatment arm the presence of ADA in serum also resulted in a substantial decrease in drug levels but mean drug levels in ADA-positive patients treated with SC were still consistently above 1 µg/mL. Taking into account that a serum level of 1 µg/mL is considered the threshold for efficacy, these results indicate that patients treated with Remsima SC at the proposed posology could have a better probability of maintaining therapeutic serum drug levels than those treated with IV Remsima, even if they develop ADAs.

At week 30 the frequency of moderate and high titres (thought to be clinically significant) of ADAs seemed comparable between the two treatment arms, even though the frequency of low titres was lower in the SC arm (possibly due to under detection). At the end of week 54 the titres were similar in both treatment arms even if the titres remained marginally lower in the patients initially treated with IV Remsima. Because of the very different drug levels influencing the ADA assay, comparing titre levels between the treatment arms is not completely reliable.

It is not completely clear what level of ADA titre leads to a clinically significant drop in drug concentration. A substantial drop in mean drug concentrations was seen in both treatment arms already at the lowest ADA titres. In the IV arm ADA titres as low as ≤ 92 were accompanied by mean drug levels below 1 µg/mL, whereas in the SC group, drug levels remained on average above 1 µg/mL as long as ADA titres were < 736 . This finding shows that defining a cut-point for where ADA titre becomes clinically significant is not feasible.

With regards to the effect of ADA on patient safety, particularly for TEAE, TSEAE and infections, no consistent correlations were observed between the ADA formation and the occurrence of the adverse events across all clinical studies. The percentages of latent tuberculosis were almost double in ADA positive arms. The difference between ADA positive and ADA negative subjects in both treatment arms was similar in this respect. The numbers are too limited to allow conclusions and the occurrence of latent tuberculosis in relation to ADA positivity remains unclear. However, this issue will not be pursued further as more safety data particularly concerning latent tuberculosis may be obtained from ongoing clinical studies and proposed post-approval SC programme.

The immunogenicity of Remsima SC applied through either an autoinjector or prefilled syringe is not expected to influence the immunogenicity of the product, and this was supported by the data from study CT-P13 1.9.

The population to be treated with Remsima SC will be partly different from the population treated with Remsima IV. It will consist of patients who have switched from the Remsima IV and patients that have been treated with other anti-TNF α products administered subcutaneously. Remsima is very immunogenic and the immune response to infliximab is likely to be partly similar (anti-TNF-binding site) and partly different as compared to other anti-TNF products that do not contain murine sequences. The differences

may include different types of antibodies and antibody-antigen complexes. Such differences may lead to hypersensitivity reactions, including acute and delayed hypersensitivity reaction.

In the 54-week data from Study CT-P13 3.5 switching from IV to SC did not give rise to an increased ADA positivity. On the contrary, the proportion of ADA positive patients was reduced after switching from IV to SC. However, this result can partly be explained by lower sensitivity to detect ADAs in patients with higher drug concentrations. Likewise, switching from IV to SC did not affect the efficacy. If anything, the subjects gained better efficacy after switching from IV to SC. There were no new safety concerns after switching. Overall, the results from CT-P13 3.5 Part 2 suggest that switching from CT-P13 IV to CT-P13 SC does not have an impact on safety. Data on switching from IV infliximab or other subcutaneously administered anti-TNF products to CT-P13 SC will be collected in the observational safety study in RA patients planned to assess AEs associated with the use of CT-P13 SC (Study CT-P13 4.8).

In conclusion, the current data provide evidence for a comparable immunogenicity profile between Remisma dosing through subcutaneous route compared to IV route. There is some uncertainty regarding the bioanalytical assays to detect ADAs. However, even if there is a possibility of undetected ADAs in the SC arm, the number of ADAs should not be higher in the SC arm than in the IV arm. Moreover, the results of non-inferior efficacy and safety are convincing. Therefore, the issue of undetected low titres will not be pursued further.

2.8.2. Conclusions on clinical safety

In general, the safety profile of intravenous infliximab is well established. However, safety data for SC infliximab is still relatively limited.

In the main RA-study, the SC route of administration was associated with reduced occurrence of systemic infusion-related reactions (IRR), which have been associated with the IV route, whilst the injection site reactions (ISR) were more common in the SC group. MAH has clarified the classification of the systemic and local infusion and injection site reactions. The occurrence of an administration related reactions is not an unexpected event and implications for the Benefit/Risk balance of this known risk given the change in treatment setting (self-administration at home) should be considered. The MAH has included appropriate warnings in the SmPC and Patient Information on this. The MAH has also confirmed that no specific premedication for SC injection is required in accordance with SC treatment of other comparable products. In addition, updated information concerning adverse events (particularly those related to injection reactions) and self-administration at home, as well as handling of the missed dose has been reflected in the product information.

Otherwise the safety profile seemed broadly similar between the IV and SC formulations (TEAEs, TSEAEs, laboratory data). There was no increase in the incidence of infection risk in general, and opportunistic infections in particular. Modelling analyses showed no association between Remisma SC PK profile and incidence of infections. The database is, however, too limited to allow analysis concerning more rare adverse events and occurrence of malignancies. The MAH therefore proposed additional pharmacovigilance activities with regards to "Long term treatment" with SC infliximab (Study CT-P13 4.8), as detailed in the RMP.

Generally, regardless of treatment-arm, the proportion of ADA-positive individuals appeared lower in patients than in healthy subjects. The reason for this is not entirely clear and it can be questioned whether the use of immunosuppressants can play a role. In the pivotal RA-study the frequency of ADA-positivity at week 30 was lower in the SC group compared to IV group. After switching to the SC formulation at Week 30 the proportion of patients who had positive ADA was similar between treatment arms up to week 54. ADA presence in serum resulted in an overall decrease of drug exposure. There was a statistically and clinically non-significant tendency for weaker DAS28 improvement in ADA-positive

RA patients compared to ADA-negative patients in both SC and IV groups. With regards to the effect of ADA on patient safety, no consistent correlations were observed between ADA and the occurrence of the adverse events across all studies. However, the amount of latent tuberculosis was higher among ADA positive subjects, but the treatment arms were similar to each other.

The clinical safety and immunogenicity data from study CT-P13 1.9 and the usability part of study CT-P13 3.5 part 2 did not indicate any increased risks for the AI compared to the PFS.

The PK data showed that infliximab C_{trough} concentrations were constantly higher (>10-fold) after SC dosing when compared to the IV route. However, no increased safety concerns related to higher drug concentrations were detected in the provided clinical data.

Even with the extended follow-up, the safety database can be considered limited and robust post-approval safety follow-up programme including patients with SC dosing is needed and additional studies have been proposed in the RMP.

2.9. Risk Management Plan

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| Important identified risk: Serious infections including sepsis | <p>Routine risk minimisation measures:</p> <p><i>SmPC section 4.2 where advice is given that Remsima/Inflectra treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of conditions for which Remsima/Inflectra is indicated.</i></p> <p><i>SmPC section 4.2 where advice is given that patients treated with Remsima/Inflectra should be given the package leaflet and the patient reminder card.</i></p> <p><i>SmPC section 4.4 where a warning is given that patients must be monitored closely for infections including TB before, during and after treatment with infliximab.</i></p> <p><i>SmPC section 4.4 where warning is given that the suppression of TNF-α may mask symptoms of infection such as fever.</i></p> <p><i>Severe infections such as sepsis is listed as a contraindication in SmPC section 4.3.</i></p> <p><i>Serious infections including sepsis is listed as special warnings and precautions for use in SmPC section 4.4.</i></p> <p><i>Serious infections including sepsis is listed as an adverse reaction in SmPC section 4.8.</i></p> <p><i>PL section 2 where a warning is given that, tell your doctor if you have an infection or if you have ever lived in or travelled to an area where infections called histoplasmosis, coccidioidomycosis, or blastomycosis are</i></p> | <p>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</p> <p>None.</p> <p>Additional pharmacovigilance activities:</p> <p>CT-P13 4.2</p> <p>CT-P13 4.3</p> <p>CT-P13 4.4</p> <p>BSRBR-RA (Sponsor: Celltrion Inc.)</p> <p>RABBIT (Sponsor: Celltrion Inc.)</p> <p>BSRBR-RA (Sponsor: Pfizer Inc.)</p> <p>RABBIT (Sponsor: Pfizer Inc.)</p> <p>ZOB INF 1402/CONNECT-IBD</p> <p>ZOB INF 1505/PERSIST</p> <p>CT-P13 SC 1.6</p> <p>CT-P13 SC 4.8</p> |

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|--|--|---|
| | <p><i>common before you are given Remsima/Inflectra.</i></p> <p><i>Serious infection is listed as contraindication and warning and precautions in PL section 2.</i></p> <p><i>Legal status: Medicinal product subject to restricted medical prescription.</i></p> <p>Additional risk minimisation measures:</p> <p><i>Patient reminder card.</i></p> | |
| <p>Important identified risk:</p> <p>BCG breakthrough infection and agranulocytosis in infants within utero exposure to infliximab</p> | <p>Routine risk minimisation measures:</p> <p><i>SmPC section 4.2 where advice is given that patients treated with Remsima/Inflectra should be given the package leaflet and the patient reminder card.</i></p> <p><i>SmPC section 4.4 where a warning is given that infants exposed in utero to infliximab, fatal outcome due to disseminated Bacillus Calmette-Guérin (BCG) infection has been reported following administration of BCG vaccine after birth.</i></p> <p><i>SmPC section 4.6 where guidance is given that administration of live vaccines (e.g. BCG vaccine) to infants exposed to infliximab in utero is not recommended for at least 6 months after birth and cases of agranulocytosis have also been reported.</i></p> <p><i>Agranulocytosis is listed as an adverse reaction in SmPC section 4.8.</i></p> <p><i>PL section 2 where a warning is given that, talk to your doctor if you have recently received or are scheduled to receive treatment with a therapeutic infectious agent (such as BCG instillation used for the treatment of cancer).</i></p> <p><i>Legal status: Medicinal product subject to restricted medical prescription.</i></p> <p>Additional risk minimisation measures:</p> <p><i>Patient reminder card.</i></p> | <p>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</p> <p><i>None.</i></p> <p>Additional pharmacovigilance activities:</p> <p><i>None.</i></p> |
| <p>Important identified risk:</p> <p>Demyelinating disorders</p> | <p>Routine risk minimisation measures:</p> <p><i>SmPC section 4.4 where a warning is given that use of TNF-blocking agents, including infliximab, has been associated with cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis, and peripheral demyelinating disorders, including Guillain-Barré syndrome.</i></p> <p><i>SmPC section 4.4 where guidance is given that the in patients with</i></p> | <p>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</p> <p><i>None.</i></p> <p>Additional pharmacovigilance activities:</p> <p><i>CT-P13 4.2</i></p> <p><i>CT-P13 4.3</i></p> <p><i>CT-P13 4.4</i></p> |

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|--|---|--|
| | <p><i>pre-existing or recent onset of demyelinating disorders, the benefits and risks of anti-TNF treatment should be carefully considered before initiation of infliximab therapy. Discontinuation of infliximab should be considered if these disorders develop.</i></p> <p><i>Demyelinating disorders is listed as an adverse reaction in SmPC section 4.8.</i></p> <p><i>Legal status: Medicinal product subject to restricted medical prescription.</i></p> <p>Additional risk minimisation measures:</p> <p><i>None.</i></p> | <p><i>BSRBR-RA (Sponsor: Celltrion Inc.)</i></p> <p><i>BSRBR-RA (Sponsor: Pfizer Inc.)</i></p> <p><i>RABBIT (Sponsor: Celltrion Inc.)</i></p> <p><i>RABBIT (Sponsor: Pfizer Inc.)</i></p> <p><i>ZOB INF 1402/ CONNECT-IBD</i></p> <p><i>ZOB INF 1505/PERSIST</i></p> |
| <p>Important identified risk:</p> <p>Malignancy</p> | <p>Routine risk minimisation measures:</p> <p><i>SmPC section 4.4 where warning is given that there is an increased background risk for lymphoma and leukaemia in RA patients with long-standing, highly active, inflammatory disease, which complicates risk estimation.</i></p> <p><i>Malignancy is listed in SmPC section 4.8.</i></p> <p><i>PL section 2 where a warning is given that, patients taking Remsima/Inflectra may have an increased risk of developing lymphoma or another cancer. Tell your doctor if you have or have ever had lymphoma (a type of blood cancer) or any other cancer before you are given Remsima/Inflectra.</i></p> <p><i>Cancer in children and adults is listed in PL section 4.</i></p> <p><i>Legal status: Medicinal product subject to restricted medical prescription.</i></p> <p>Additional risk minimisation measures:</p> <p><i>None.</i></p> | <p>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</p> <p><i>None.</i></p> <p>Additional pharmacovigilance activities:</p> <p><i>CT-P13 4.2</i></p> <p><i>CT-P13 4.3</i></p> <p><i>CT-P13 4.4</i></p> <p><i>BSRBR-RA (Sponsor: Celltrion Inc.)</i></p> <p><i>BSRBR-RA (Sponsor: Pfizer Inc.)</i></p> <p><i>RABBIT (Sponsor: Celltrion Inc.)</i></p> <p><i>RABBIT (Sponsor: Pfizer Inc.)</i></p> <p><i>ZOB INF 1402/ CONNECT-IBD</i></p> <p><i>ZOB INF 1505/PERSIST</i></p> <p><i>CT-P13 SC 1.6</i></p> <p><i>CT-P13 SC 4.8</i></p> |
| <p>Important potential risk:</p> <p>Colon carcinoma/dysplasia (in paediatric ulcerative colitis)</p> | <p>Routine risk minimisation measures (not applicable for SC):</p> <p><i>SmPC section 4.4 where a warning is given that all patients with UC who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing UC or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course.</i></p> <p><i>SmPC section 4.4 where guidance is given that this evaluation should include colonoscopy and biopsies per local</i></p> | <p>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</p> <p><i>None.</i></p> <p>Additional pharmacovigilance activities:</p> <p><i>CT-P13 4.3</i></p> <p><i>ZOB INF 1402/ CONNECT-IBD</i></p> <p><i>ZOB INF 1505/PERSIST</i></p> |

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|--|--|
| | <p><i>recommendations. Current data do not indicate that Remsima/Inflectra treatment influences the risk for developing dysplasia or colon cancer.</i></p> <p><i>Abnormal tissue swelling or growth is listed in PL section 4.</i></p> <p><i>Legal status: Medicinal product subject to restricted medical prescription.</i></p> <p>Additional risk minimisation measures:</p> <p><i>None.</i></p> | |
| <p>Missing Information:</p> <p>Long term treatment with SC infliximab (SC only)</p> | <p>Routine risk minimisation measures:</p> <p><i>Legal status: Medicinal product subject to restricted medical prescription.</i></p> <p>Additional risk minimisation measures:</p> <p><i>None.</i></p> | <p>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</p> <p><i>None.</i></p> <p>Additional pharmacovigilance activities:</p> <p><i>CT-P13 SC 4.8</i></p> |

Conclusion

The CHMP and PRAC considered that the risk management plan version 9.4 is acceptable.

2.10. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.11. Product information

2.11.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

This is a line extension application to introduce a subcutaneous formulation of Remsima IV, which is a biosimilar of EU approved Remicade.

The following indication for Remsima SC is sought:

Rheumatoid arthritis

Remsima, in combination with methotrexate, is indicated for the reduction of signs and symptoms as well as the improvement in physical function in:

- adult patients with active disease when the response to disease-modifying antirheumatic drugs (DMARDs), including methotrexate, has been inadequate.
- adult patients with severe, active and progressive disease not previously treated with methotrexate or other DMARDs.

In these patient populations, a reduction in the rate of the progression of joint damage, as measured by X-ray, has been demonstrated (see section 5.1).

The MAH has withdrawn the initial application for indications ankylosing spondylitis, psoriatic arthritis and psoriasis and is not seeking for the IBD indications, not for adults nor children, in this submission.

3.1.2. Available therapies and unmet medical need

There are several medicinal products containing infliximab for intravenous infusion on the market. However, no subcutaneously administered infliximab is available so far. Several other TNF α inhibitors are available in SC formulation with similar indications as Remicade. Thus, this application does not address an unmet need.

The availability of a SC formulation of infliximab would increase the treatment options available to patients, facilitate administration and add convenience. Potential benefits of SC administration include optimisation of medical resources.

3.1.3. Main clinical studies

Study CT-P13 3.5:

This was a multi-dose, randomised, controlled, parallel group, 54-week study to evaluate PK, efficacy and safety of CT-P13 SC in RA patients.

Part 1 was conducted to, based on PK-data determine the optimal dose of CT-P13 SC in 48 RA patients, whereas Part 2 is performing to establish therapeutic non-inferiority (based on clinical efficacy) of CT-P13 SC compared with CT-P13 IV in 343 RA patients.

Part 1 of study CT-P13 3.5 was considered as the RA dose finding study. It was an open-label study that compared CT-P13 SC (in 3 different dose levels; 90, 120 and 180 mg at week 6 and then every 2 weeks) and CT-P13 IV (3 mg/kg at week 6 and then every 8 weeks) when co-administered with MTX in patients with active RA who were not adequately responding to MTX. The study included a dose-loading phase during which all enrolled patients initially were to receive a 2-hour CT-P13 IV infusion at Weeks 0 and 2.

Part 2 of CT-P13 3.5 was considered as the pivotal clinical study in RA. The primary objective of CT-P13 3.5, Part 2 was to demonstrate that CT-P13 SC (120 mg at week 6 and then every 2 weeks) is non-inferior to CTP13 IV (3 mg/kg at week 6 and then every 8 weeks) at Week 22, in terms of efficacy, as determined by clinical response according to change from baseline in disease activity as measured by Disease Activity Score using DAS28 (CRP). This pivotal trial comprised 167 patients in the Remsima SC 120mg treatment arm and 176 patients in the Remsima IV 3mg/kg treatment arm. All enrolled patients initially received Remsima IV 3mg/kg infusion at Weeks 0 and 2.

3.2. Favourable effects

The efficacy of Remsima IV has been established during initial marketing authorisation assessment. The primary purpose of this application is to show non-inferiority of Remsima SC to Remsima IV in terms of efficacy without additional safety concerns. In terms of PK the objective of the proposed Remsima SC dosing regimen in treatment of RA was to maintain the steady state $C_{trough} > 1 \mu\text{g/mL}$ and to align AUC over 8 weeks as closely as possible to that achieved following 3 mg/kg IV administration.

In patients with active RA and concomitantly treated with methotrexate the following favourable effects were seen:

The proportion of patients that achieved the target $C_{trough} (> 1 \mu\text{g/mL})$ in Remsima SC cohort was 81.8% (126/154), while only 28.5% (45/158) in the IV population reached the target.

The mean change from baseline in DAS28 (CRP) at Week 22 was 2.21 and 1.94 in SC 120 mg and IV 3 mg/kg treatment arms, respectively. This response is comparable to previous findings in RA patients treated with Remsima IV. The decline in DAS28(CRP) scores continued after week 6 up until week 54 and was similar between treatment arms.

The estimate of treatment difference was 0.27 with corresponding lower limit of the two-sided 95% CI of 0.02, which was greater than the pre-specified non-inferiority margin of -0.6 indicating non-inferiority of SC 120 mg compared to IV 3 mg/kg.

By week 30 92.7% in the SC 120mg arm and 83.3% in the IV 3mg/kg arm had achieved a good or moderate clinical response according to EULAR response criteria (based on DAS28 [CRP]).

The results of all secondary outcome endpoints were in line with the primary outcome and supported the observation of equal, if not even better efficacy of Remsima SC compared to Remsima IV up to week 54.

There were no apparent differences in efficacy among subject according to region, age, race, body weight, CRP at screening or DAS28 score at baseline. Thus, the clinical efficacy results are considered robust over all the analyzed subgroups.

Of note, among patients who developed ADAs, clinical response was significantly better in the SC arm than among ADA positive patients in the IV arm. This is probably explained by the fact that most ADA positive patients who were treated with IV Remsima had very low drug concentrations, while the drug concentrations remained on average above the threshold of $1 \mu\text{g/mL}$ even among ADA-positive subjects when treated with SC.

3.3. Uncertainties and limitations about favourable effects

The main factor that might affect persistence of response in a different manner for the two routes of administration is immunogenicity and the formation of NABs. The efficacy results from study CT-P13 3.5 Part 2 showed good persistence of response throughout the whole 54-week treatment period in both treatment arms. Therefore, the possible differences in Nab formation do not affect the conclusion regarding non-inferiority in efficacy.

3.4. Unfavourable effects

Unfavourable effects for infliximab

In general, unfavourable effects associated with the use of TNF-blockers that have been reported for infliximab (Remsima SmPC), also apply for Remsima SC with the exception of acute infusion reactions (as no infusion is given). However, the risk of administration related reactions (including hypersensitivity) exist.

The most serious ADRs with infliximab include the following: SC hepatitis B virus (HBV) reactivation, congestive heart failure (CHF), serious infections (including sepsis, opportunistic infections and tuberculosis [TB]), serious infusion reactions, serum sickness (delayed hypersensitivity [i.e., delayed type hypersensitivity/type IV hypersensitivity] reactions), haematologic reactions, systemic lupus erythematosus/lupuslike syndrome, demyelinating disorders, hepatobiliary events, malignancies including lymphoma, hepatosplenic T-cell lymphoma (HSTCL), leukaemia, Merkel cell carcinoma, melanoma, paediatric malignancy, sarcoidosis/sarcoid-like reaction.

Unfavourable effects for SC infliximab

Overall, the safety profile of Remsima SC in RA patients was similar to the safety profile of the intravenous formulation, except for ISR and ARR. No clear additional unfavourable effects, except ISR, could be identified.

According to safety results in the pivotal RA Study CT-P13 the proportion of patients who experienced at least 1 TEAE during the maintenance phase was slightly higher in the IV arm compared to the SC arm (92 [54.1%] patients and 113 [63.5%] patients in SC and IV respectively). The most frequently reported TEAEs in the SC arm were localised ISR (28 [16.5%] patients) followed by viral upper respiratory tract infection (10 [5.9%] patients). The most frequently reported TEAEs during the maintenance phase for patients in the IV arm were localised ISR (22 [12.4%] patients) followed by viral upper respiratory tract infection (10 [5.6%] patients).

With safety data up to 54 weeks there were 13 (7.3%) patients in the IV arm and 6 (3.5%) patients in the SC arm with at least one TESAEs. The TESAEs included 3 (1.8%) and 1 (0.6%) cases of infections for the SC and IV arms, respectively, and five deaths cases. The other TESAEs were mainly single cases each. The majority of TESAEs were grade 3 or lower in intensity.

The incidence and severity of infections with Remsima SC and IV administration were comparable and in line with Remsima SmPC. With the safety data up to 54 weeks, the incidence of patients with infections was 48 (28.2%) in the SC arm and 54 (30.3%) in the IV arm. The majority of infections were of grade 1 or 2 in intensity. The most commonly reported infection was viral upper respiratory tract infection. No clear differences in opportunistic infections between the study arms were observed. Overall, the incidence of infections and different types of infections were comparable with the historical controls.

Concerning infusion and injection reactions the MAH has revised the terminology based on the new classification, TEAEs classified as IRR during the treatment period were reported for 2 (1.2%) patients in SC arm and 10 (5.6%) patients in IV arm. Treatment-emergent AEs classified as ISR during the treatment period were reported for 2 (1.2%) patients in SC arm and 3 (1.7%) patients in IV arm.

Treatment-emergent AEs classified as delayed hypersensitivity during the treatment period were reported for 3 (1.8%) patients in SC arm and 1 (0.6%) patient in IV 3 arm. Treatment-emergent AEs classified as localised ISR during the treatment period were reported for 28 (16.5%) patients in SC 120 mg treatment arm and 22 (12.4%) patients in IV 3 mg/kg treatment arm.

In the SmPC, the safety data is reported as incidence per 100 patient years, excluding patients from the non-compliant site. The incidence of systemic injection reactions (e.g. rash, pruritus, flushing and

oedema) was 1.2 per 100 patient-years in the Remsima subcutaneous group (from Week 6) and 2.1 per 100 patient-years in the Remsima intravenous group who switched to Remsima subcutaneous administration (from Week 30).

In the pivotal clinical trial in RA patients, the frequency of ADA-positivity at week 30 was lower in the SC vs. IV group (38.2 vs. 69.7% at week 30). Most ADAs were neutralizing and there seemed to be no difference between the groups regarding proportion of NABs/ADAs (66.9% vs. 75.4% for SC and IV respectively). After switching to the SC formulation at Week 30 the proportion of patients who had positive ADA results in the Remsima IV arm reduced to 38.2% by week 54. However, it is possible that some low-titre ADAs in patients receiving Remsima SC have not been detected. Hence, it cannot be concluded that Remsima SC is less immunogenic than Remsima IV. However, there is no indication of higher immunogenicity.

The treatment-emergent AEs leading to permanent discontinuation of study drug during the treatment period were reported for 5 (2.9%) patients in SC 120 mg treatment arm and 14 (7.9%) patients in IV 3 mg/kg treatment arm.

A total of 5 deaths were reported during the treatment period up to Week 54, 3 among patients who were receiving Remsima SC and 2 among patients in the IV arm. The causes of death in the SC arm were hereditary haemochromatosis, myocardial infarction and cardiac arrest. All the death cases were considered by the investigator not related to the study medication.

There were no findings from the other clinical studies in the application that would imply a worse safety profile for Remsima SC (in the proposed dose) compared to Remsima IV (in the approved dose) regarding treatment of RA patients. The frequency of ADA, were both in the IV and the SC arms in the clinical patient studies, including the pivotal RA study, higher than numbers that have been previously reported for infliximab and presented in the SmPC but not higher among the patients treated with SC compared to IV. The MAH conducted analysis of the relationship between ADA-status and clinical outcome in Study CT-P13 3.5 Part 2 up to week 54 and concluded that ADA-status only marginally affected clinical response. ADA presence in serum resulted in an overall decrease of drug exposure. It was also noted that patients positive for ADA had a higher prevalence of latent tuberculosis, but the treatment arms did not differ from each other in this respect.

In conclusion, with regards to serious adverse events and deaths, the safety profile of Remsima SC in the proposed dose range did not appear worse than Remsima IV.

3.5. Uncertainties and limitations about unfavourable effects

In general, the safety profile of infliximab IV is well established. However, the sample size and duration of SC infliximab treatment in the pivotal study in RA patients are still limited. According to data provided by the MAH, 196 patients overall (174 RA and 22 CD patients) have been treated with CT-P13 SC for 54 weeks, 166 of these patients (157 RA and 9 CD patients) with the proposed posology of 120 mg Q2W. In addition, 81 of the RA patients in study CT-P13 3.5 Part 2 continued the treatment for 64 weeks.

A total of 52 (14.9%) patients discontinued the maintenance phase up to end of study (22 [13.0%] patients and 30 [16.8%] patients in the SC 120 mg and IV 3 mg/kg treatment arms, respectively). The long-term safety database in patients with RA has thus been extended. However, the numbers are still limited to identify potential rare and severe adverse events. More post-approval safety data is thus required.

On Remsima SC dosing the mean AUC-values and C_{trough} levels were constantly and in long-term higher compared to Remsima IV. The effects of this higher long-term exposure to infliximab on patient safety (e.g. infections, autoimmune diseases and malignancies) are unknown. Concerning malignancies, several

years of follow-up would be required. However, in the 54-week data, no increased safety concerns related to higher drug concentrations were detected.

Some methodological weaknesses preclude complete assessment of the immunogenicity data. Because of very different drug concentrations in the IV and SC groups the sensitivity to detect ADAs was different and therefore the treatment arms are not comparable in the lower range of ADA titres. In the IV arm ADA titres as low as ≤ 92 were accompanied by mean drug levels below 1 $\mu\text{g/mL}$, whereas in the SC group, drug levels remained on average above 1 $\mu\text{g/mL}$ as long as ADA titres were < 736 . This finding shows that defining a cut-point for where ADA titre becomes clinically significant is not feasible. However, it seems that ADA titres at levels below the detection limit would not have a clinical impact on efficacy in patients treated with Remsima SC because the drug concentrations remain high despite a substantial drop in concentration due to antibody formation.

Moreover, even if there is a possibility of undetected ADAs in the SC arm, the number of ADAs should not be higher in the SC arm than in the IV arm. In addition, no new concern regarding ADA related safety issues have emerged in SC treated patients. Therefore, the issue of undetected low titres will not be pursued further.

It is obvious that the population to be treated with Remsima SC will be partly different from the population treated with Remsima IV. It will consist of patients switched from the Remsima IV and patients that have been treated with other anti-TNF- α products administered subcutaneously. Remsima is very immunogenic and the immune response to infliximab is likely to be partly similar (anti-TNF-binding site) and partly different as compared to other anti-TNF products that do not contain murine sequences. The differences may include different types of antibodies and antibody-antigen complexes. Such differences may lead to hypersensitivity reactions, including acute and delayed hypersensitivity reaction. In the 54-week data from Study CT-P13 3.5 switching from IV to SC did not give rise to an increased ADA positivity. Likewise, switching from IV to SC did not affect the efficacy. There were no new safety concerns after switching. Further data on switching from IV infliximab or other subcutaneously administered anti-TNF products to CT-P13 SC will be collected in the observational safety study in RA patients planned to assess AEs associated with the use of CT-P13 SC (Study CT-P13 4.8 as detailed in the RMP).

Further, cases of jaundice and non-infectious hepatitis, some with features of autoimmune hepatitis, have been observed in the post-marketing experience of infliximab, including cases of liver failure resulting in liver transplantation or death (Remsima SmPC). In Study CT-P13 3.5, even though the numbers are small, there were numerically more Grade 3 or 4 liver enzyme elevations in the SC arm.

To summarize, for the sought RA indication, the uncertainties with regards to the unfavourable effects pertain mainly to the fact that there is still relatively limited safety data that would allow for a complete comparative safety assessment with Remsima IV. Additional pharmacovigilance activities with regards to Long term treatment with SC infliximab (CT-P13 3.8 and CT-P13 4.8) have been proposed in the RMP.

3.6. Effects Table

Table 48 - Effects Table for Remsima SC 120mg in the treatment of rheumatoid arthritis

| Effect | Description | Unit | SC 120mg | IV 3mg/kg | Uncertainties/ Strength of evidence | References |
|--------------------|-------------|------|----------|-----------|---|------------|
| Favourable Effects | | | | | | |

| Effect | Description | Unit | SC 120mg | IV 3mg/kg | Uncertainties/ Strength of evidence | References |
|---|--|-------|--------------|--------------|---|--------------------------|
| DAS28(CRP) | Change from baseline, LS mean (SE) at week 22 | score | 2.21 (0.221) | 1.94 (0.209) | The difference between groups is not clinically significant. The majority of the effect was achieved already during IV loading phase. | Study CT-P13 3.5 Part 2 |
| ACR20 | Number of subjects achieving ACR20 by week 22 | N (%) | 139 (84.2%) | 137 (78.7%) | | Study CT-P13 3.5 Part 2 |
| Unfavourable Effects up to week 30 | | | | | | |
| Infections | Infections | N (%) | 34 (20%) | 32 (18%) | | Study CT-P13 3.5 Part 2 |
| ISR | Acute reaction related to SC dosing | N (%) | 11 (6.5%) | 4 (2.2%)* | In the IV group, 3 ISR were related to SC placebo and 1 after switching from IV to SC | Study CT-P13 3.5 Part 2 |
| ARR | Reactions related to administration of infliximab | N (%) | 1 (0.6%) | 8 (4.5%) | | Study CT-P13 3.5. Part 2 |
| ADA | ADA-positive patients up to week 30 | N (%) | 65 (38.2) | 124 (69.7) | | Study CT-P13 3.5. Part 2 |
| Unfavourable Effects up to week 64 (both treatment arms on SC 120mg from week 30) | | | | | | |
| Infections | Infections | N (%) | 49 (29.2%) | 60 (34.3%) | | Study CT-P13 3.5 Part 2 |
| ISR | Acute reaction related to SC dosing | N (%) | 30 (12.6%) | 22 (12.6%) | | Study CT-P13 3.5 Part 2 |

Abbreviations: ISR: injection site reactions, ACR20: American College of Rheumatology 20% improvement criteria, ARR: Administration related reactions (including infusion-related reactions, acute and delayed hypersensitivity reactions). DAS28: Disease Activity Score using 28 joint counts, CRP: C-reactive protein, LS: least squares, SE: standard error, ADA: anti-drug antibodies.

3.7. Benefit-risk assessment and discussion

Rheumatoid arthritis is a chronic and potentially disabling systemic inflammatory disease. An established treatment option for these patients is IV infliximab. In addition, several other anti-TNF-alfa-inhibitors are already available as SC formulations. Therefore, the SC infliximab is not fulfilling any unmet medical need as such.

However, a SC formulation of infliximab has significant practical advantages over the current IV formulation. IV administration of infliximab takes place in hospitals and outpatient clinics. The use of the IV formulation causes both administrative costs for hospitals and inconvenience to patients to be treated with infliximab that could be avoided by a formulation intended for SC administration. Self-administration of SC infliximab allows greater flexibility and ability for home use, which may affect quality of life of patients. The fixed dose approach in RA-patients is simple and practical and may diminish the risk of medication errors. Further, from the medical point of view, one benefit of the SC route of administration is that it does not require an IV access after the initial IV loading dose, which is especially important for patients with poor venous access. The shorter administration time is also a benefit for patients.

3.7.1. Importance of favourable and unfavourable effects

Importance of favourable effects

The efficacy and safety of Remsima IV have been established, as it is a biosimilar to Remicade. Since no formal bioequivalence can be established between Remsima SC and Remsima IV, non-inferior efficacy and safety of Remsima SC must be shown to ensure a positive benefit-risk balance.

Only one double blind RCT performed in the intended target population was submitted. The number of patients was small, 167 RA patients-initiated treatment with Remsima SC. The follow up duration of 54 weeks is acceptable for evaluation of persistence of treatment response and immunogenicity.

The primary efficacy endpoint in the pivotal RA study was defined as the change from baseline in disease activity measured by DAS28 (CRP) at Week 22, which is a clinically relevant endpoint.

Patients in both treatment arms reached clinically significant response in the DAS28(CRP) score by week 6 and the response persisted throughout the reported period of 54 weeks. The magnitude of response in patients treated with Remsima SC (mean change from baseline of -3.2 points in DAS28(CRP) at week 54) is classified as good according to EULAR response criteria. The results of all secondary outcome endpoints were in line with the primary outcome and supported the observation of non-inferior, if not even better efficacy of Remsima SC compared to Remsima IV up to week 30 and a good persistence of response after switching from IV to SC. The results were in line with historical data and were also supported by improvement in quality of life, which supports the notion of robustness.

However, it must be noted that the treatment arms were identical until week 6 and the main part of the response was already achieved by week 6. Also, the difference between treatment arms was already seen at week 6 and hence cannot be taken as an indication of superiority of the SC formulation. Moreover, the difference between treatment arms after 22 weeks of treatment (0.27 points in DAS 28 (CRP)) in favour of Remsima SC is not considered clinically significant, but superiority does not need to be shown.

The pivotal study (study CT-P13 3.5 Part 2) is in effect more suitable to show the efficacy of maintenance treatment and the results should be interpreted with focus on the change from week 6, rather than change from baseline. In essence, the data only supports the use of Remsima SC after an initial loading dose with the IV Remsima.

The high initial concentration of infliximab achieved only with IV administration might be crucial to the induction of response. Whether the same response may be achieved with the subcutaneous formulation, without initial loading with IV infliximab, is not known. This fact is adequately reflected in the SmPC since Remsima SC is only proposed to be initiated after a loading dose comprising two intravenous infusions of infliximab.

Region, age, race, body weight and CRP at screening had no apparent effect on efficacy. Thus, the clinical efficacy results are considered robust over all the analyzed subgroups.

At Week 22 the mean difference in mean change from week 6 of DAS28 (CRP) was equal for the two study arms (or better in the SC arm) in almost all subgroups. The only subgroup where the IV treated patients had significantly better efficacy results than the SC treated patients was the non-Caucasian subgroup. This subgroup had similar efficacy in both study arms when assessed as change from baseline. Moreover, the difference between races seems to reflect a delayed response in the IV arm rather than a lesser response in the SC arm. Therefore, based on these results no caution related to race is warranted.

The usability of both AI and PSF devices are acceptable in terms of patient satisfaction and rate of successfully and appropriately completed self-administration. In conclusion, Remsima SC was shown to be non-inferior to Remsima IV in terms of efficacy over a 30-week period. The response persisted over the whole 54-week treatment and was robust over different subgroups. Since the SC formulation was consistently shown to give rise to slightly better results than the IV formulation, there is no reason to question the non-inferiority despite the fact that the sensitivity of the study to demonstrate non-inferiority was not optimal.

Importance of unfavourable effects

Overall, it can be agreed with the MAH that the selected SC treatment resulted in only marginal differences in clinical safety across the weight bands in the RA-study Study CT-P13 3.5 Part 2. Thus for the RA-indication, there are no signals from the clinical data that the proposed posology would be inaccurate in that regard.

In general, the safety profile of infliximab IV is well established. However, after SC administration especially the long-term safety data is limited. Based on limited safety database, the safety profile for Remsima SC and IV were in general comparable, and only few SAEs were reported. There were no unexpected unfavourable effects, but several uncertainties exist.

The only new unfavourable effect identified after SC dosing were injections site reactions, which are common for SC dosing in general. However, ISRs in the SC arm in the pivotal study were all mild or moderate in severity and all manageable. However, ARR is not an unexpected event and implications for the BR balance of this known risk given the change in treatment setting (self-administration at home) has been considered and appropriate warnings have been included in the product information, educational material and will be followed up in the RMP.

A total of 5 deaths; 3 patients treated with SC and 2 patients treated with IV only, were reported during the treatment period up to Week 54 in the pivotal RA study. The causes of deaths for the patients treated with SC were hereditary haemochromatosis, myocardial infarction and cardiac arrest. The contribution of the administration of the study medication in some of the death cases cannot be fully excluded, but all the death cases were considered by the investigator not related to the study medication. In the whole SC database (including non-RA indications) seven cases of death occurred on the study drug administrations. However, no autopsy was performed, and no further data is available. Any deaths events will be carefully followed-up in the post-marketing safety study.

Even though there were no additional clear safety findings, there were several uncertainties, which were not fully clarified with extended safety database.

Particularly the adverse events concerning infections (including opportunistic infections) and the effects of higher exposure of infliximab after SC administration e.g., on malignant tumours, needs to be established in long-term, and therefore additional pharmacovigilance activities with regards to Long term treatment with SC infliximab (CT-P13 3.8 and CT-P13 4.8) have been proposed in the RMP.

Immunogenicity

This is a totally new SC formulation of a very immunogenic product (with 30% murine variable region amino acid sequence), administered via a highly immunogenic route (SC). The composition of the SC

product is largely similar to the IV product already on market and should not be inherently more immunogenic. The administration route and the considerable difference in PK profiles might have in theory altered the immunogenic response. However, the current data provide preliminary evidence for a comparable immunogenicity profile between Remsima dosing through subcutaneous route compared to IV route and no new concern regarding ADA related safety issues have emerged in SC treated patients.

The MAH conducted analysis of the relationship between ADA-status and clinical outcome in Study CT-P13 3.5 Part 2 up to week 54 and concluded that ADA-status only marginally affected clinical response and did not affect the rates of infections or hypersensitivity reactions.

The frequency of ADA was higher both in the IV arm and in the SC arm than frequencies that have been previously reported for infliximab and presented in the SmPC but not higher among the patients treated with SC Remsima compared to IV Remsima.

3.7.2. Balance of benefits and risks

The efficacy and safety profile of infliximab IV is well established. The clearly higher drug concentrations during SC administration did not seem to translate into a higher risk for infections or other adverse events, although the number of patients and duration of follow-up is still limited.

The total number of RA patients exposed for one year to CT-P13 SC in the proposed posology has been clarified (n=148 in study CT-P13 3.5 Part 2 and an additional 9 in study CT-P13 3.5 Part 1). The number of patients is limited but can be considered acceptable. Remsima is a biosimilar and there are plenty of data on exposure to the originator Remicade IV and to Remsima IV.

Some uncertainty remains regarding the effect of higher C_{trough} levels of infliximab on the potential risk of some rare adverse events (e.g. cardiac AEs); long-term safety will be further studied in a post-approval PV programme (including a non-interventional study in patients with RA).

The 2.2 point improvement in DAS28(CRP) score achieved with Remsima SC at week 22 and maintained over a period of 54 weeks is clinically relevant and the difference between SC and IV Remsima is neither clinically nor statistically significant. The benefit of the product has been demonstrated in RA-patients with concomitant methotrexate use.

The safety profiles for SC and IV were in general comparable. The only new unfavourable effect identified after SC dosing were injections site reactions which were observed in 17.9% of patients in the SC arm and were all mild or moderate in severity and all manageable, which is reflected in the product information. Also, immunogenicity seemed comparable between SC and IV formulations (if anything, immunogenicity was lower in SC group).

Based on these considerations, the benefit/risk balance is positive.

3.7.3. Additional considerations on the benefit-risk balance

Indication

Even if Remsima SC is only used as “maintenance therapy” (after IV-loading dose), the wording of therapeutic indications, as detailed in the SmPC, was agreed to remain equal to those of IV-Remsima (and IV Remicade), as the Remsima SC line extension is largely based on extrapolation on data from IV Remsima and especially on data from originator IV Remicade.

The IV formulation of infliximab is indicated for patients with active RA when the response to DMARDs, including methotrexate, has been inadequate, and also for RA-patients with severe, active and progressive disease not previously treated with methotrexate or other DMARDs. The non-inferior efficacy

of SC infliximab as compared to IV infliximab was demonstrated in second line setting, more specifically in the MTX-inadequate responders.

It is plausible to expect that the two formulations that are comparable in this setting would also be comparable in the setting of RA-patients with severe, active and progressive disease not previously treated with DMARDs. Hence, the data can be extrapolated to this other RA population. The similar anti-inflammatory effects in this setting can also be extrapolated to retardation of joint damage that is mentioned in the proposed therapeutic RA-indication. Notwithstanding, according to current regulatory practices, endpoints should not be included in the indication, as in the currently proposed RA indication ("reduction in the rate of the progression of joint damage, as measured by X-ray"); however, as discussed, it is preferable to keep the indications aligned between IV and SC Remsima, as well as with reference medicinal product Remicade, and hence this wording is acceptable.

In addition, it is agreed that using "infliximab" within the sentence "Remsima, following an initial dose of two intravenous infusions of infliximab..." in the indication statement is acceptable. This is albeit it refers to changing from all different IV infliximab-products to Remsima SC, while the evidence is only from switching (after the loading dose) from Remsima IV to Remsima SC. However, as Remsima is a biosimilar medicinal product to Remicade, and there is sufficient evidence already from switching from at least from Remicade IV to Remsima IV, it is assumed that all of the biosimilar infliximab-products and Remicade are similar here and hence there is no need to specify that the switch could only occur from Remsima IV to Remsima SC (and not from other IV infliximab products).

3.8. Conclusions

The overall B/R of Remsima SC for the treatment of rheumatoid arthritis is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality and safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, Remsima in the new subcutaneous pharmaceutical forms is favourable in the following indication:

Rheumatoid arthritis

Remsima, in combination with methotrexate, is indicated for the reduction of signs and symptoms as well as the improvement in physical function in:

- *adult patients with active disease when the response to disease-modifying antirheumatic drugs (DMARDs), including methotrexate, has been inadequate.*
- *adult patients with severe, active and progressive disease not previously treated with methotrexate or other DMARDs.*

In these patient populations, a reduction in the rate of the progression of joint damage, as measured by X-ray, has been demonstrated (see section 5.1).

The CHMP therefore recommends the extension(s) of the marketing authorisation for Remsima subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regards to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

The educational programme consists of a patient reminder card to be held by the patient. The card is aimed at both serving as a reminder to record the dates and outcomes of specific tests and to facilitate the patient sharing of special information with healthcare professionals(s) (HCPs) treating the patient about on-going treatment with the product.

The patient reminder card shall contain the following key messages:

- A reminder to patients to show the patient reminder card to all treating HCPs, including in conditions of emergency, and a message for HCPs that the patient is using Remsima
- A statement that the brand name and batch number should be recorded
- Provision to record the type, date, and result of TB screenings
- That treatment with Remsima may increase the risks of serious infections/sepsis, opportunistic infections, tuberculosis, hepatitis B reactivation, and BCG breakthrough in infants with *in utero* exposure to infliximab, and when to seek attention from a HCP
- Contact details of the prescriber