EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 June 2020
EMA/376884/2020
Committee for Medicinal Products for Human Use (CHMP)

Extension of indication variation assessment report

Invented name: Remsima

International non-proprietary name: infliximab

Procedure No. EMEA/H/C/002576/II/0082

Marketing authorisation holder (MAH) Celltrion Healthcare Hungary Kft.

Note

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

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List of abbreviations

%DFT	Percent difference from theoretical value
%TE	Percent total error
6-MP	6-Mercaptopurine
ACE	Affinity Capture Elution
ACP	Assay (screening) cut point
ACR	American College of Rheumatology
ACR20	American College of Rheumatology 20% improvement criteria
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
AI	Auto-injector
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
Anti-CCP	Anti-cyclic citrullinated peptide
AR	Assessment report
ARR	Administration-related reaction
AS	Ankylosing spondylitis
ASAS	Assessment of spondyloarthritis international society score
AUC	Area under the concentration-time curve
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
$AUC_{22-30wk}$	Area under the curve from week 22 to week 30
AUC_{ss}	Area under the concentration-time curve at steady state
AUC_{ss8W}	Area under the concentration-time curve at steady state normalised to an 8-week interval
AUC_{τ}	Area under the concentration-time curve over the dosing interval
AZA	Azathioprine
BA	Bioavailability
BLQ	Below the limit of quantification
BMI	Body mass index
BP	Blood pressure
BSA	Bovine serum albumin
BSV	Between-subject variability
Cal	Calibrator
CCP	Confirmatory cut point
CD	Crohn's disease
CDAI	Crohn's disease activity index
CHF	Congestive heart failure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CIM	Concomitant immunosuppressive medication
CL	Total body clearance
CL/F	Apparent clearance after SC dosing
C_{max}	Maximum serum concentration
$C_{max,ss}$	Maximum serum concentration at steady state
C_{min}	Minimum serum concentration
CPK	Creatine phosphokinase
CPV	Cut point value
CRO	Contract research organisation
CRP	C-reactive protein
CS	Clinically significant
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CT-P13	Infliximab (Remsima)
C_{trough}	Trough concentration
$C_{trough,ss}$	Trough serum concentration at steady state
$C_{trough,week\ 22}$	Pre-dose level at Week 22
CV	Coefficient of variation
CV%	Percent coefficient of variation
DAS28	Disease activity score using 28 joint counts

DBP	Diastolic blood pressure
DMARD	Disease-modifying anti-rheumatic drugs
DNC_{max}	Dose normalised peak exposure
$DNC_{max,ss}$	Dose normalised peak exposure at steady state
DP	Drug product
DSMB	Data safety monitoring board
ECG	Electrocardiogram
ECHO	Echocardiography
ECL	Electrochemiluminescent
eCRF	Electronic case report form
ELISA	Enzyme-linked immunesorbent assay
EMA	European Medicines Agency
EOI	End of infusion
EOS	End of study
ESR	Erythrocyte sedimentation rate
EU	European Union
EULAR	European League Against Rheumatism
F	Female
F/T	Freeze-thaw
FC	Faecal calprotectin
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HBV	Hepatitis B virus
HIV	Human immunodeficiency virus
HPC	High positive control
HQC	High quality control
hr	Hour(s)
HV	Healthy volunteer
IBD	Inflammatory bowel disease
ICH	International Conference on Harmonisation
IgG1	Immunoglobulin G1
IGRA	**Interferon-γ** release assay
IOV	Inter-occasion variability
IQR	Interquartile range
IRR	Infusion related reaction
ISR	Injection site reaction
ITT	Intent-to-treat
IV	Intravenous(ly)
K_A	Absorption rate constant
kg	Kilogram(s)
LLOQ	Lower limit of quantitation
LOCF	Last observation carried forward
LPC	Low positive control
LQC	Low quality control
LS	Least squares
M	Male
mAb	Monoclonal antibody
Max	Maximum
MBS	Matrix blank spike control
MedDRA	Medical Dictionary for Regulatory Activities
µg	Microgram(s)
mg	Milligram(s)
Min	Minimum
mL	Millilitre(s)
MP	Mercaptopurine
MPC	Medium positive control
MQC	Medium quality control
MRD	Minimum required dilution
MRT	Mean Residence Time
MSD	Meso scale discovery
MTX	Methotrexate
N/A	Not applicable

Nab (or NAB)	Neutralising antibody
NC	Negative control
NCS	Not clinically significant
NYHA	New York Heart Association
PBS	Phosphate buffered saline
PC	Positive control
pcVPC	Prediction-corrected visual predictive check(s)
PD	Pharmacodynamic(s)
PDCO	Paediatric Committee
PFS	Pre-filled syringe
PGA	Physician's global assessment
PK	Pharmacokinetic(s)
PPD	Pharmaceutical Product Development
PPK	Population pharmacokinetic(s)
PS	Psoriasis
PsA	Psoriatic Arthritis
PT	Preferred term
PY	Patient-years
Q	Intercompartmental clearance
Q2W	Every 2 weeks
Q8W	Every 8 weeks
QC	Quality control
RA	Rheumatoid arthritis
RF	Rheumatoid factor
RLU	Relative light unit
RT	Room temperature
SA	Streptavidin
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SC	Subcutaneous(ly)
SD	Standard deviation
SDAI	Simplified disease activity index
SES-CD	Simplified endoscopic activity score for Crohn's disease
SIBDQ	Short inflammatory bowel disease questionnaire
SIR	Systemic injection reaction
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
ST-CT-P13	Sulfo-tag-labelled CT-P13
STEMI ST	Wave elevation myocardial infarction
$T_{1/2}$	Terminal half-life
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TM	Thawed matrix
T_{max}	Time to maximum serum concentration
TNF	Tumour necrosis factor
TNFα	Tumour necrosis factor alpha
sTNFα	Soluble tumour necrosis factor alpha
ST-TNFα	Sulfo-tag-labelled TNFα
UC	Ulcerative colitis
UF/DF	Ultrafiltration/Diafiltration
UK	United Kingdom
ULOQ	Upper limit of quantitation
US	United States
W	Week
V1	Central volume of distribution
V3	Peripheral volume of distribution
VAS	Visual analogue scale

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Celltrion Healthcare Hungary Kft. submitted to the European Medicines Agency on 14 January 2020 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication of the subcutaneous formulation of Remsima, to add treatment of adult patients with Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and psoriasis in line with the adult indications of the IV formulation; consequently, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC and relevant sections of the Package leaflet are updated. An updated RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics, Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

No paediatric indications are proposed for Remsima SC in this indication extension application.

Information relating to orphan market exclusivity

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

During the development of Remsima SC, the clinical development program was discussed with the Committee for Medicinal Products for Human Use (CHMP) through Scientific Advice (SA) meetings.

1 EMA - initial Scientific Advice (EMEA/H/SA/3220/1/2015/III; 28 Jan 2016)

2 EMA - Scientific advice Clarification letter (EMEA/H/SA/3220/1/2015/III; 21 Apr 2016)

3 EMA - Follow-up Scientific Advice (EMEA/H/SA/3220/1/FU/1/2016/II; 15 Sep 2016)

4 EMA - Scientific advice Clarification letter (EMEA/H/SA/3220/1/2015/III; 06 Dec 2016)

5 EMA - Follow-up Scientific Advice (EMEA/H/SA/3220/1/FU/2/2017/II; 14 Dec 2017)

6 EMA - Follow-up Scientific Advice (EMEA/H/SA/3220/2/FU/1/2017/I; 14 Dec 2017)

7 EMA - Follow-up Scientific Advice (EMEA/H/SA/3220/1/FU/3/2018/II; 26 Apr 2018)

1.2. Steps taken for the assessment of the product

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

Rapporteur: Outi Mäki-Ikola

Timetable	Actual dates
Submission date	14 January 2020
Start of procedure:	1 February 2020
CHMP Rapporteur Assessment Report	27 March 2020
PRAC Rapporteur Assessment Report	27 March 2020
PRAC members comments	6 April 2020
Updated PRAC Rapporteur Assessment Report	7 April 2020
PRAC Outcome	17 April 2020
CHMP members comments	20 Apri; 2020
Updated CHMP Rapporteur(s) (Joint) Assessment Report	23 April 2020
Request for supplementary information (RSI)	30 April 2020
CHMP Rapporteur Assessment Report	10 June 2020
PRAC Rapporteur Assessment Report	10 June 2020
PRAC members comments	15 June 2020
CHMP members comments	15 June 2020
Updated CHMP Rapporteur Assessment Report	17 June 2020
Updated PRAC Rapporteur Assessment Report	17 June 2020
Opinion	25 June 2020

2. Scientific discussion

2.1.1. Problem statement

As a biosimilar to Remicade IV, Remsima I V 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). Remsima SC has been approved for treatment of RA in the line extension EMEA/H/C/002576/X/0062.

With this indication extension variation the MAH seeks to add indications CD, UC, AS, PsA and Ps to the Remsima SC pharmaceutical form to be in line with the IV formulation.

While there are several other subcutaneously administered **TNFα-inhibitors** on the market, infliximab is available only in IV formulation for CD, UC, AS, PsA and Ps patients.

Compared to the approved IV Remsima, the line extension with a subcutaneous formulation principally introduced two major changes; 1) different pharmacokinetics and 2) flat dosing (after IV loading dosed according to mg/kg).

The development of this formulation focused on whether a subcutaneous formulation of infliximab may differ from IV infliximab in both efficacy and safety because of the different pharmacokinetic profile, with lower peak concentrations, higher C_{trough} values and a more even concentration time curve. In addition, differences in exposure and intrinsic immunogenicity of the subcutaneous administration route could alter the immunogenic response. The potential consequences of flat dosing were also of special interest, in particular for individuals that belong to the extremes with regards to body weight.

In the line extension application (EMEA/H/C/002576/X/0062), non-inferior efficacy and safety was shown for Remsima SC 120mg Q2W compared to Remsima IV 3mg/kg in RA patients. On Remsima SC dosing the mean AUC-values and C_{trough} levels were constantly and in long-term higher compared to Remsima IV. The number of patients (157) exposed to long term treatment with Remsima SC was limited and some uncertainty remained regarding the effect of higher C_{trough} levels of infliximab on the potential risk of some rare adverse events. Moreover, data on safety and immunogenicity among patients without the use of concomitant immunosuppressive medication (CIM) was lacking.

The main focus of this assessment is comparability of PK, with supporting evidence of non-inferior efficacy and safety between Remsima SC and Remsima IV across all proposed indications. The main concerns in relation to the new proposed indications (CD, UC, AS, PsA and Ps) is appropriate dosing and the possibility of higher immunogenicity in some target populations due to a lower rate of methotrexate (MTX) or other CIM in these populations.

2.1.2. About the product

The active substance of Remsima is infliximab, an immunosuppressant **TNFα-inhibitor** (L04AB02).

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 (EMEA/H/C/002576) as a biosimilar product to Remicade. Following a line extension application (EMEA/H/C/002576/X/0062), the subcutaneous formulation (Remsima SC) was approved for treatment of RA. Notably, the originator Remicade does not have a SC-formulation.

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

The dose of Remsima IV depends on the therapeutic indication: in RA patients the recommended dose is 3 mg/kg (up to a maximum maintenance dose of 7.5 mg/kg every 8 weeks or 3mg/kg every 4 weeks in case of inadequate response or loss of response) and in CD, UC, AS, PsA and Ps the dose is 5 mg/kg. Treatment is initiated with infusions at weeks 0, 2 and 6, followed by maintenance infusions every 8 weeks (Q8W) in RA, CD, UC, PsA and Ps or every 6-8 weeks in AS. In case of inadequate response or loss of response, the label includes an option to increase the dose in CD patients. No maximum dose is stated in the SmPC, but the studies referred to have used 10mg/kg Q8W.

The proposed dose for Remsima SC is 120 mg every 2 weeks (Q2W) for all patients in all indications, initiated as maintenance therapy 4 weeks after the last administration of two intravenous infusions of infliximab given 2 weeks apart.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The clinical development programme for Remsima SC (CT-P13 SC) includes two phase I -studies in healthy volunteers; CT-P13 1.5 and CT-P13 1.9, one phase I-study in IBD; CT-P13 1.6, and one phase I/III-study in RA; CT-P13 3.5. A total of 751 subjects (235 HVs, 363 RA, 79 CD and 74 UC patients) received at least 1 dose of CT-P13 SC 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 stated that there is no regulatory requirement to repeat the demonstration of biosimilarity against the reference product once the marketing authorization has been granted. 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 should be possible, given that SC dosing and regimen schedules for both the rheumatology and the IBD indications were identified.

It was further commented that the safety database 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.

The proposed extension to the indications in this variation application is supported by the results from the currently submitted Study CT-P13 1.6 in IBD patients and by the following information:

> The previously submitted results of pivotal Study CT-P13 3.5 Part 2, conducted in 343 patients with RA, which demonstrated:
>
> o Therapeutic non-inferiority in terms of the change from baseline in disease activity measured by disease activity score in 28 joints (DAS28) at Week 22 and comparable efficacy outcomes of Remsima SC to Remsima IV in American College of Rheumatology (ACR) responses, Health assessment questionnaire (HAQ), European League Against Rheumatism (EULAR) response criteria (erythrocyte sedimentation rate [ESR] or CRP) and study short-form health survey (SF-36).
>
> o Comparable safety profile, except for the increased incidence of localised ISRs in the SC group, including the incidence of treatment-emergent adverse events (TEAE), treatment-emergent serious adverse events (TESAE) and adverse events of special interest (AESI) between Remsima SC and Remsima IV. Patients in the Remsima IV arm switched from Remsima IV to SC treatment at Week 30 and the long-term safety profile of Remsima SC was assessed up to Week 54, which showed that no new or unexpected safety findings were observed after the switching.

     o   Comparable proportions of patients with positive anti-drug antibody (ADA) and neutralising antibody (NAb) response between the CT-P13 IV and CT-P13 SC arms

Additional information comes from the Population PK and PK-PD modelling (developed based on data obtained from CT-P13 SC studies conducted in RA and inflammatory bowel disease [IBD] patients [Studies CT-P13 3.5 and CT-P13 1.6]), from post-hoc analyses of efficacy and safety by region, age, race and body weight and from a literature review on the PK-efficacy/safety correlation in AS, PsA and Ps populations.

2.1.4. General comments on compliance with GLP, GCP

Based on the provided data no need for triggered GLP or GCP inspections have been identified.

2.2. Non-clinical aspects

2.2.1. Ecotoxicity/environmental risk assessment

In line with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr2 and draft Rev. 1.), environmental risk assessment was submitted, with the justification of not submitting the ERA studies. The active substance is naturally occurring substance (protein), not posing a risk to the environment. The SC formulation does not contain such compounds that would lead to a significant increase of risk to the environment. In conclusion, the new indication is not leading to increase of the environmental risk for use of Remsima.

2.2.2. Conclusion on the non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

Considering that the active substance is a naturally occurring substance, the new indications of Remsima (infliximab) are not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

This indication extension variation is based on the whole clinical package presented in Table 1. The studies (except for CT-P13 1.6 Part 2 in IBD-patients) have been assessed within the line extension application (EMEA/H/C/002576/X/0062).

In summary, the benefit of Remsima SC has been demonstrated in RA-patients with concomitant methotrexate use. Clinical efficacy of Remsima SC as measured by DAS28 change/ACR 20 response was non inferior to Remsima IV. 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 Remsima SC 120mg Q2W, compared with Remsima IV 3mg/kg Q8W. Mean AUC levels over 8-week dosing are higher or slightly lower following the proposed SC dosing regimens, depending on the patient's body weight. These findings were supported by the small dose finding studies in RA and IBD patients.

The safety profiles for SC and IV were in general comparable. The only new unfavourable effect identified after SC dosing were injections site reactions. Also immunogenicity seemed comparable between SC and IV formulations.

There is still relatively limited safety data that would allow for a complete comparative safety assessment of Remsima SC with Remsima IV. However, the planned post-approval observational safety study to collect further safety data was considered acceptable.

This assessment report will focus on the previously unassessed Part 2 of Study CT-P13 1.6. Extrapolation of the combined results from the whole clinical package to indications not studied (ankylosing spondylitis, psoriatic arthritis and psoriasis) is discussed in relevant PK, Efficacy and Safety sections and also in the benefit-risk discussion.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH. 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.

Table 1 Tabular overview of clinical studies with CT-P13 SC

Protocol No.	Population	Design	Objective(s)	Study Treatment
Completed and Ongoing Clinical Studies				
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	An open-label, dose-escalating, single-dose, Phase I study to evaluate safety and PK of CT-P13 SC administration	Primary Objective: • To evaluate the safety of CT-P13 SC administration and CT-P13 IV administration Secondary Objective: • 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	An 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: • 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: • To evaluate additional PK variables, safety and immunogenicity over 12 weeks	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.

Protocol No.	Population	Design	Objective(s)	Study Treatment
CT-P13 3.5[1]	RA Part 1 Randomised: 48 • CT-P13 IV 3 mg/kg: 13 • CT-P13 SC 90 mg: 11 • CT-P13 SC 120 mg: 12 • CT-P13 SC 180 mg: 12 Part 2[2] Randomised: 343 • CT-P13 IV 3 mg/kg: 176 • CT-P13 SC 120 mg: 167	A randomised, parallel-group, Phase I/III study to evaluate efficacy, PK and safety of CT-P13 SC and CT-P13 IV	[Part 1] Primary Objective: • To find the optimal dose of CT-P13 SC over the first 30 weeks as determined by AUC_τ at steady state between Week 22 and Week 30 Secondary Objective: • To evaluate efficacy, PK, PD and safety of CT-P13 SC in comparison with CT-P13 IV up to Week 54 [Part 2] Primary Objective: • 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) Secondary Objective: • 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 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)	[Part 1] <Dose-loading phase> - Week 0 to 6 Two doses of CT-P13 IV 3 mg/kg at Weeks 0 and 2 for all patients <Maintenance phase> - Week 6 to 54 • 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 [Part 2] <Dose-loading phase> - Week 0 to 6 Two doses of CT-P13 IV 3 mg/kg at Weeks 0 and 2 for all patients <Maintenance phase> - Week 6 to 64 • Arm 1: Further 3 doses of CT-P13 IV were 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 was 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 were 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.
CT-P13 1.6	IBD Part 1 with CD Randomised: 44 • CT-P13 IV 5 mg/kg: 13 • CT-P13 SC 120 mg: 11 • CT-P13 SC 180 mg: 12 • CT-P13 SC 240 mg: 8 Part 2 with CD and UC Randomised: 131 (CD: 53, UC: 78)	An open-label, randomised, parallel- group, Phase I study to evaluate the PK, efficacy and safety of CT-P13 SC and CT-P13 IV	[Part 1] Primary Objective: • 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 Secondary Objective: • To evaluate efficacy, PK, PD and overall safety of CT-P13 SC in comparison with CT-P13 IV up to Week 54	[Part 1] <Dose-loading phase> - Week 0 to 6 Two doses of CT-P13 IV 5 mg/kg at Weeks 0 and 2 for all patients <Maintenance phase> - Week 6 to 54 • 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

Protocol No.	Population	Design	Objective(s)	Study Treatment
	• CT-P13 IV 5 mg/kg: 65 (CD: 25, UC: 40) • CT-P13 SC 120/ 240 mg: 66 (CD: 28, UC: 38)		[Part 2] Primary Objective: • To demonstrate that CT-P13 SC is non-inferior to CT-P13 IV in terms of PK, as determined by the $C_{trough,week\ 22}$ (pre-dose level at Week 22) Secondary Objective: • 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 Tertiary Objective: • To evaluate genotypes (optional) and amino acids as biomarkers • To evaluate patient overall satisfaction of CT-P13 IV and CT-P13 SC	every 2 weeks up to Week 54 [Part 2] <Dose-loading phase> - Week 0 to 6 Two doses of CT-P13 IV 5 mg/kg at Weeks 0 and 2 for all patients <Maintenance phase> - Week 6 to 54 • Arm 1: Further 3 doses of CT-P13 IV were administered at Week 6 and every 8 weeks thereafter up to Week 22 (Weeks 14 and 22). CT-P13 IV was then switched to CT-P13 SC at Week 30. Further doses of study treatment with CT-P13 SC every 2 weeks were 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 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).

1 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.

2 There were 5 patients excluded in all analysis populations due to the significant GCP non-compliance (Site 2840 in Russia).

AI: Auto-injector, 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, AUC_T: 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, Cmax: Maximum observed serum concentration, CRP: C-reactive protein, CSR: Clinical study report, Ctrough,week22: pre-dose level at Week 22, DAS28: Disease activity score using 28 joint counts, EOS: End-of-study, GCP: Good Clinical Practice, 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

2.3.2. Pharmacokinetics

Pharmacokinetics of Remsima SC were compared with Remsima IV in subjects with CD and UC in study CT-P13 1.6 Part 1 (dose finding) and Part 2 (dose confirming). PK of Remsima SC have also been investigated in subjects with RA (study CT-P13 3.5) and in healthy subjects (studies CT-P13 1.5 and CT-P13 1.9); these studies were assessed in procedure X/62.

Pharmacokinetics of Remsima SC were not investigated in subjects with AS, Ps and PsA, which is in accordance with the scientific advice given by the CHMP. Extrapolation to these therapeutic indications is discussed in Sections 2.4.3, 2.5.1 and section 5 of this AR.

Methods

Bioanalytical methods

For Study CT-P13 1.6 Part 1 and Part 2, a meso scale discovery (MSD) ECL method was used for the quantitation of CT-P13 in serum samples. The method has been originally validated during 2017.

For immunogenicity testing, the MAH has developed a new ADA method based on an ECL MSD platform with an affinity capture elution (ACE) step, which displays enhanced drug tolerance. Additionally, a new NAb ECL MSD immunoassay was developed with ACE step in order to improve drug tolerance and selectivity in the presence of lipaemia. For Studies CT-P13 1.6 Part 1 and 2 and CT-P13 3.5 Part 1 and Part 2, immunogenicity data are presented from both the original immunogenicity assay (ADA ELISA and NAb ECL bead methods) and the new immunogenicity assay (new ADA ECL ACE and NAb ECL ACE methods).

1. Determination of CT-P13 in human serum

1a. MSD ECL Method for the Quantitation of CT-P13 in Human Serum

For Study CT-P13 1.6 Part 1 and Part 2, an electrochemiluminescent (ECL) immunoassay utilizing MSD technology was applied to quantify CT-P13 in human serum. The method has been validated originally in September 2017 by PPD laboratories. Since then three Addendums 5-7 have been generated.

2. Determination of immunogenicity

As presented in the line extension (EMEA/H/C/002576/X/0062), ADA assessment was performed in Studies CT-P13 1.5, CT-P13 1.9, CT-P13 3.5 Part 1 and Part 2 and CT-P13 1.6 Part 1 using enzyme-linked immunosorbent assay (ELISA) method and NAb assessment based on ECL and ECL bead methods. However, taking into consideration of the potential for drug interference due to the relatively high drug serum concentrations in samples taken from patients receiving CT-P13 SC, the MAH has developed new ADA assay methods based on an ECL platform with an ACE step, which displays enhanced drug tolerance.

2a. Assessment of anti-CT-P13 antibodies by ADA ECL ACE method

A new ADA ECL ACE method is based on an ECL platform with an ACE step. Additional validation was performed to evaluate selectivity and drug tolerance, and to determine screening and confirmatory cut points in CD and UC human sera, and to evaluate drug tolerance in RA Human serum. The new method is described in the dossier in more detail. ADA ECL ACE has been validated at PPD.

A comparison of the original ADA ELISA and new ECL method with ACE step (new ADA ECL ACE method) both developed by PPD is provided in the dossier. Both the ADA ELISA and new ADA ECL ACE

methods employed a three-tiered approach consisting of (i) screening assay, (ii) specificity/confirmatory assay and (iii) titration and estimation of neutralising activity.

Comparing the sample analysis data from the original ADA ELISA method and the new ADA ECL ACE method in Studies CT-P13 1.6 Part 1 and Part 2 and CT-P13 3.5 Part 1 and Part 2, it was confirmed that most (> 87.8%) of the ADA positive samples in the original ADA ELISA method were also detected as ADA positive in the new ADA ECL ACE method (Table 2). Furthermore, many ADA negative samples in the original ADA ELISA method were determined to be ADA positive in the new ADA ECL ACE method.

Table 2 ADA Results Analysed with the Original ADA ELISA and the New ADA ECL ACE Methods

CT-P13 SC Clinical Studies		CT-P13 1.6 Part 1 (N=339)		CT-P13 1.6 Part 2 (N=633)		CT-P13 3.5 Part 1 (N=414)		CT-P13 3.5 Part 2 (N=2958)	
		ECL ACE Method							
		ADA (+)	ADA (-)	ADA (+)	ADA (-)	ADA (+)	ADA (-)	ADA (+)	ADA (-)
ELISA Method	ADA (+)	78	-	69	1	101	14	880	73
	ADA (-)	44	217	99	464	40	259	320	1685
PPA		100% (78/78)		98.6% (69/70)		87.8% (101/115)		92.3% (880/953)	
NPA		83.1% (217/261)		82.4% (464/563)		86.6% (260/299)		84.0% (1685/2005)	

PPA and NPA are calculated as follows:
PPA = (Number of samples confirmed positive with both of the original ADA ELISA method and the new ADA ECL ACE method)/(Number of samples confirmed positive with the original ADA ELISA method)*100.
NPA = (Number of samples confirmed negative with both of the original ADA ELISA method and the new ADA ECL ACE method)/(Number of samples confirmed negative with the original ADA ELISA method)*100.
ACE: Affinity capture elution, ADA: Anti-drug antibody, ECL: Electrochemiluminescent, ELISA: Enzyme-linked immunosorbent assay, PPA: Positive Percent Agreement, N: Total number of samples analysed with both of the original ADA ELISA method and the new ADA ECL ACE method, NPA: Negative Percent Agreement

The CHMP noted that the MAH has developed a new method for detection of ADA against infliximab in human serum samples. The rationale for the development of a new method is acceptable as better drug tolerance was sought due to high drug concentration in Remsima SC serum samples. In the new method, ADAs are detected using an ECL immunoassay that employs MSD platform.

<u>Method validation</u>

The new ADA ECL ACE method has been validated by PPD Laboratories during 2019. Full validation report is provided and validation acceptance criteria have been described in the method validation plan. Additionally, one addendum is provided to extend the method validation evaluation to CD, UC, and RA serums.

In general, the new ADA ECL ACE method has been appropriately validated. Negative and positive controls are appropriately described. Commercial human monoclonal anti-infliximab serves as a positive control. CoA of the positive control is provided including sufficient characterization information of the control antibody. Matrix-based negative control pools were prepared by pooling 30 individual drug-naïve sample lots with no detectable ADA.

3. Neutralising antibodies

For measuring NAb against CT-P13, originally a NAb ECL bead method was used for Studies CT-P13 1.6 Part 1 up to Week 54 and Part 2 up to Week 30 and CT-P13 3.5 Part 1 and Part 2 up to Week 54.

Of note, these validation and bioanalytical reports for the NAb ECL bead method for Studies CT-P13 1.6 Part 1 and CT-P13 3.5 Part 1 and Part 2 were included in the CT-P13 SC line extension (EMEA/H/C/002576/X/0062).

Subsequently, a new ECL immunoassay with ACE Step was used for Studies CT-P13 1.6 Part 1 and Part 2 and CT-P13 3.5 Part 1 and Part 2 in order to improve drug tolerance and selectivity under the influence of lipaemia. The validation and bioanalytical reports for the new NAb ECL ACE method are included in this submission.

Comparing the sample analysis data from the original NAb bead method and the new NAb ECL ACE method in Studies CT-P13 1.6 Part 1 and Part 2 and CT-P13 3.5 Part 1 and Part 2, it was confirmed that most (> 93.1%) of the NAb positive samples in the original NAb bead method were also detected as NAb positive in the new NAb ECL ACE method (Table 3). Furthermore, many NAb negative samples in the original NAb ECL bead method turned out to be NAb positive in the new NAb ECL ACE method. Therefore, the new NAb ECL ACE method was considered to provide reproducible and reliable data with minimised interference by residual drug in serum.

Table 3 NAb Results Analysed with the Original NAb bead Method and the New NAb ECL ACE Method

CT-P13 SC Clinical Studies		CT-P13 1.6 Part 1 (N=78)		CT-P13 1.6 Part 2 (N=69)		CT-P13 3.5 Part 1 (N=101)		CT-P13 3.5 Part 2 (N=823)	
		ECL ACE Method							
		NAb (+)	NAb (-)	NAb (+)	NAb (-)	NAb (+)	NAb (-)	NAb (+)	NAb (-)
Bead Method	NAb (+)	51	2	27	2	60	1	605	15
	NAb (-)	14	11	16	24	32	8	143	60
PPA		96.2% (51/53)		93.1% (27/29)		98.4% (60/61)		94.6% (605/620)	
NPA		44.0% (11/25)		60.0% (24/40)		20.0% (8/40)		29.6% (60/203)	

Note: PPA and NPA are calculated as follows:
PPA = (Number of samples confirmed positive with both of the original NAb bead method and the new NAb ECL ACE method)/(Number of samples confirmed positive with the original NAb bead method)*100.
NPA = (Number of samples confirmed negative with both of the original NAb bead method and the new NAb ECL ACE method)/(Number of samples confirmed negative with the original NAb bead method)*100.
ACE: Affinity capture elution, ECL: Electrochemiluminescent, PPA: Positive percent agreement, N: Total number of samples analysed with both of the original NAb bead method and the new NAb ACE method, NAb: Neutralising antibody, NPA: Negative percent agreement

The CHMP noted the following:

NAb ECL ACE method validation

New NAb ECL ACE method has been validated during 2019 by PPD Laboratories. Sufficient description of the method and method validation has been provided. Validation included evaluation of MRD, sensitivity, intra- and inter-assay precision, matrix interference, drug tolerance, and assay sensitivity. Assay validity in healthy and diseased matrices has been considered.

Furthermore, characteristics of the negative and positive controls are provided. Positive control pools were prepared by spiking positive control antibodies into the negative control pool. Human Anti-Infliximab MAb was used as positive control antibody. The negative control pool used for the previous ECL bead method was also used for ECL ACE method.

Non-parametric fixed cut point values (screening and titre cut points) were determined for CD/UC serum, whereas for RA serum a parametric approach was applied for determination of cut point values. According to cut point validation reports, floating SNR cut points were used for RA, as well as CD and UC serum samples.

Inter-assay precision data did not meet the acceptance criteria. According to MAH, precision did not meet the acceptance criteria due to highly variable NC RLU responses. Thus, SNRs were determined meeting the acceptance criteria for SNR precision. The MAH's effort to justify the variable inter-assay precision is acknowledged, however, not totally understood. Generally, CV of inter-assay precision should not exceed 20% and should preferably be <15%. Thus, with CV% values outside the acceptance criteria, the repeatability of the assay is questionable. The MAH was asked to clarify the root-cause for this high variability and discuss the impact of the high inter-run variability on the repeatability of the assay.

The MAH responded appropriately to the clarifications requested. The approach to employ SNR CV% is considered acceptable.

<u>Comparison of the original and new method</u>

The MAH has appropriately justified the rationale for the choice of the assay format. No full cross-validation between methods has been performed and no acceptance criteria for the method comparability has been set. However, in this particular case, direct comparison of the data between different clinical studies is not considered necessary, as such, and cross-validation of the methods is not necessary to pursue further.

A brief discussion on the comparability of new and old NAb method has been provided. The MAH considered basis on the selection of MRD, description of the negative and positive controls, justification on assay cut points, as well as discussion of drug tolerance limit in relation to residual drug levels in serum samples.

Sample analysis data of the original and the new NAb method were compared. The data from the original NAb bead method and the new NAb ECL ACE method in Studies CT-P13 1.6 Part 1 and Part 2 and CT-P13 3.5 Part 1 and Part 2 confirmed that over 93.1% of the NAb positive samples in the original NAb bead method were also detected as NAb positive in the new NAb ECL ACE method. Furthermore, great part of the samples confirmed negative with the original NAb bead method showed positive in the new NAb ECL ACE method.

According to MAH, the new NAb ECL ACE method have better sensitivity (no comparability results provided) and drug tolerance than the original NAb bead method. Additionally, according to MAH, the new method showed improved selectivity in lipaemic matrices during validation. The CHMP agreed with this analysis.

<u>Statistical analyses (study CT-P13 1.6 Part 2)</u>

The primary PK endpoint, observed serum infliximab pre-dose level at Week 22 ($C_{trough,week22}$), was analyzed using an analysis of covariance (ANCOVA) with treatment as fixed effect and current use of treatment with azathioprine (AZA) or 6-mercaptopurine (6-MP) or methotrexate (MTX) (used or not used), disease (CD or UC), clinical response at Week 6 (responder or non-responder by CDAI-70 for CD or partial Mayo score for UC), body weight at Week 6 (<80 kg or ≥80 kg) fitted as covariates in patients who received all doses (full) of study drug up to Week 22 (prior to Week 22) for the PK population. The $C_{trough,week22}$ was natural log transformed prior to analysis. Point estimates (geometric least square (LS) means and ratio of geometric LS means) were calculated by back transforming the LS means of the natural log transformed values of $C_{trough,week22}$ and difference in the LS means. Two-sided 90% CI of the ratio geometric LS means were also produced. Noninferiority of Remsima SC to

Remsima IV was concluded if the lower bound of two-sided 90% CI for the ratio of geometric LS means is higher than 80%.

<u>Population PK models</u>

The MAH recently performed population PK and PK/PD modeling and simulation to support the marketing authorisation application for Remsima SC in treatment of rheumatoid arthritis (RA). This population PK (PPK) model, hereafter referred to as <u>the 1st PPK model</u>, was assessed in application X/62. It was based on data from 7 clinical studies, including study CT-P13 3.5 Part 1 and Part 2 (RA patients) and study CT-P13 1.6 Part 1 (CD patients) where Remsima SC was compared with Remsima IV.

In brief, the 1st PPK model was a 2-compartment PK model with linear elimination from the central compartment. 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 (KA) 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 (V1 and V3, respectively) and clearance and intercompartmental clearance (CL and Q, respectively). Between-subject variability was estimated for CL and V1. 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.

The 1st PPK model was considered sufficient for the intended use, although it was likely that that parameterisation of the effects of ADA and NAB on clearance was not optimal. In addition, it was noted that the bioanalytical methods used for measurement of ADA and NAB were sensitive for drug interference.

Subsequently, the MAH developed <u>the 2nd PPK model</u>, which is described in the modelling report "*Population pharmacokinetic-pharmacodynamic modeling of CDAI and Mayo scores, safety, ESR and C-Reactive Protein in patients with active Crohn's disease and active ulcerative colitis – Part 2*". It was based on data from 8 clinical studies in patients and healthy volunteers, including study CT-P13 3.5 Part 1 and Part 2 (RA patients) and study CT-P13 1.6 Part 1 (CD patients) and Part 2 (CD and UC patients). The ADA and NAB data that were used in developing the 2nd PPK model were still obtained from the immunogenicity assays that were sensitive for drug interference, which diminishes the impact of the 2nd PPK model (and related PK/PD models) on the current variation application.

Finally, the MAH developed <u>the 3rd PPK model</u>, which is the most important PPK analysis for the current application.

The 3rd PPK model

An abbreviated summary report "*Population Pharmacokinetic-Pharmacodynamic Modeling and Simulation using Immunogenicity Titer on CT-P13 PK, CDAI and Mayo Scores in Patients with Active Crohn's Disease and Active Ulcerative Colitis*", was submitted by the MAH.

The 3rd PPK model was based on data from study CT-P13 3.5 Part 1 and Part 2 (RA patients) and study CT-P13 1.6 Part 1 (CD patients) and Part 2 (CD and UC patients). ADA and NAB samples for these studies were re-analysed using the improved immunogenicity assays that were less sensitive for drug interference. Immunogenicity data from single-dose studies in healthy subjects and from older studies comparing Remsima IV with Remicade IV were not reanalysed; therefore, data from these studies were omitted.

The objectives of the 3rd population PK analysis were to:

- Evaluate the impact of ADA titer and NAB status on infliximab clearance and update the PPK model by incorporating the relationship between ADA titers/NAB status and infliximab clearance into the model as needed.

- Conduct simulations to predict steady state exposure ($AUC_{8w,ss}$, $C_{max,ss}$, and $C_{trough,ss}$) of infliximab in subjects with different body weights and different ADA titers/NAB status following two maintenance dosing regimens (120 mg SC Q2W, 5 mg/kg IV Q8W)

The updated PPK model was subsequently used for efficacy PK/PD analyses in patients with CD and UC; see section "PK/PD modelling" in this AR.

Datasets: The *existing dataset* for the previous PK and PK/PD analyses (The 2nd population PK/PD analysis) was used as the starting point for developing new dataset in this population PK and PK/PD analysis. The existing dataset contained information on PK, patient characteristics and other covariates of interest, and clinical efficacy and safety from 8 studies (IV studies [CT-P13 1.1, CT-P13 1.4, CT-P13 3.1, and CT-P13 3.4] and SC/IV studies [CT-P13 1.5, CT-P13 3.5, CT-P13 1.6, and CT-P13 1.9]). The *new dataset* for the current analysis was created by keeping only the records for subjects from Study CT-P13 1.6 (Part 1 and Part 2) and 3.5 (Part 1 and Part 2) and appending the dataset with newly available ADA titer values and NAB status data to replace the previous immunogenicity data. If all scheduled ADA/NAB observations for the individual were missing, that individual was excluded. Last observation carried forward (LOCF) was applied to impute missing and incomplete ADA titer after a non-missing record. NAB status was treated as "once positive, remain positive."

PK, PD and immunogenicity data up to Week 30 was included for Study CP-P13 1.6 Part 2 while PK, PD and immunogenicity data for Study CT-P13 3.5 Part 1 and Part 2 and Study CT-P13 1.6 Part 1 were up to end of study (Week 54). BLQ observations (10.1% and 10.2% of all observations for IV and SC dosing, respectively) were excluded. A total of 6864 infliximab concentration observations obtained from 571 subjects were available for analysis.

Model development: The *2nd PPK model* was employed as the starting point. It was a 2-compartment IV infusion model with linear first-order elimination from the central compartment, and an additional depot compartment with a first-order SC absorption rate constant term linked to the central compartment. Both clearance (CL and Q) and volume of distribution parameters (V1 and V3) were allometrically scaled with estimated allometric exponents as a part of the structural model. The effect of immunogenicity on the PK of infliximab was characterized via a covariate relationship between ADA status (positive vs. negative) and clearance. It was assumed that once a patient demonstrated a positive ADA response, they remained positive (once positive, remain positive) through the rest of the study. Independent random effects to describe the unexplained between subject variability (BSV) in clearance and the central compartment volume of distribution (assuming a log-normal distribution across the population) and a normally distributed additive residual error of the log-transformed concentration data (equivalent to a proportional residual error model on the untransformed scale) were integrated into the model.

The 3rd PPK model relating ADA titer value and NAB status with infliximab clearance was developed step-by-step as follows. First, the ADA status parameter in the previous (2nd) population PK model was removed. Inter-occasion variability (IOV) on clearance corresponding to different ADA sampling interval was introduced (run 304; see Table 7 and 8) to examine the relationship of clearance and ADA titer and NAB status at each ADA sampling intervals. The PK data of studies CT-P13 1.6 and CT-P13 3.5 were fitted to the model to obtain the individual clearance estimates associated with the different ADA titer values and NAB status.

Table 4 Summary of population PK model runs

| Run Number	Reference Model	Model Description	OFV	**ΔOFV**
Run300	n/a	PK model without ADA and NAB data only from study 1.6 and 3.5	-1625.01	n/a
Run301	Run300	Same as Run300 PK model with newly generated dataset including ADA titer and new NAB data	-1625.01	0
Run304	Run301	Base PK model with Inter-occasional variability	-5508.78	- 3883.8
Run305	Run301	Include ADA titer on CL using a power function	-2611.48	-986.5
Run305b	Run301	Include ADA titer on CL using a linear function	-2383.95	-758.9
Run308	Run305	Include NAB	-2788.60	-177.1
Minimisation and covariance steps were successful for each run.				

Table 5 Summary of additional population PK model runs.

Run Number	Reference Model	Model Description	OFV	Δ OFV	Note
Run 308	N/A	PK model with ADA titer for NAb positive (PK model from 3rd PK-PD Modelling)	-2788.6	N/A	
Run 339	Run 308	Include effect of NAb on CL (CHMP requested model)	-2795.7	-7.14	Model over-parameterized: (Condition Number: 6078.03)
Run 345	Run 308	Include off-diagonal OMEGA block between CL and V1	-2820.3	-31.7	Moderate correlation CL-V1: Cov (CL, V1) = 0.0729
Run 347	Run 308	Combined residual error model	-	-	No successful convergence
Run 340	Run 339	Include off-diagonal OMEGA block between CL and V1 (CHMP requested model)	-2827.1	-31.4	Model over-parameterized (Condition Number: 6568.42) Moderate correlation CL-V1: Cov (CL, V1) = 0.0723
Run 341	Run 339	Combined residual error model (CHMP requested model)	-	-	No successful convergence

Second, the individual clearance estimates were plotted against the corresponding ADA titer and NAB status to explore the relationship between ADA titer/NAB status and clearance. ADA titer was treated as a continuous variable. As shown in Figure 1 without considering the NAB status, estimated infliximab clearance increased with the ADA titer values. Infliximab clearance for positive NAB was higher than clearance for negative NAB or N/A (no measurable ADA response). In the observed data, proportion of NAB- patients with high ADA titer value from 27 to 243 was significantly lower than proportion of NAB- patients with low ADA titer value from 1 to 9 (2.50 % vs. 49.17 %, respectively). Therefore, the NAB status effect was considered to have a pivotal role in determining the effect of ADA on PK, especially for the ADA titer range of 1 to 9.

Figure 1 Impact of ADA titer and NAB status on estimated clearance of infliximab.
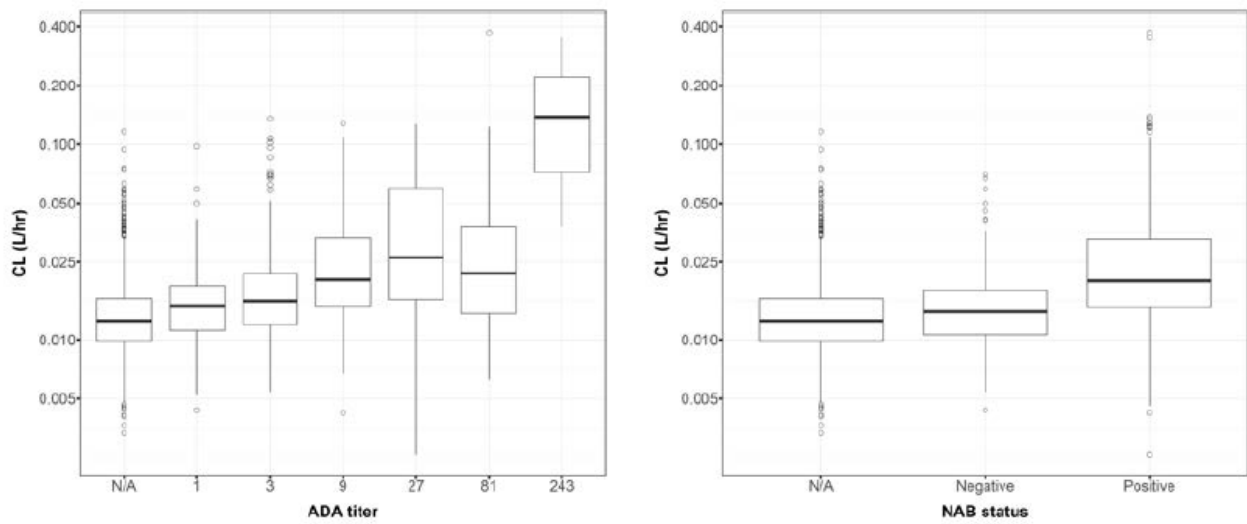
Third, the relationship between ADA titer/NAB status and clearance was evaluated in the population PK model. A summary of model runs is presented in Table 4. The ADA titer-dependent increase in infliximab clearance was described using a power model (run305) and a linear model (run305b). The power model resulted lower OFV and was chosen to describe the impact of ADA titer on infliximab clearance. A NAB flag was subsequently introduced into the clearance model to turn on the effect of ADA titer on infliximab clearance at positive NAB and turn off at negative NAB (run308). Run308 resulted in a further decrease in OFV of 177.1 and was declared as the final population PK model. The final population PK model is presented in Figure 2.

Additional models were also tested as per request of the CHMP but no meaningful improvement of the fit was observed. Run308 remained the final population PK model.

Figure 2 The final population PK model equations and model diagram (run308)

$$\frac{dA(0)}{dt} = -KA \cdot A(0)$$

$$\frac{dA(1)}{dt} = Infusion(t) + KA \cdot A(0) - \frac{Q}{V1}$$
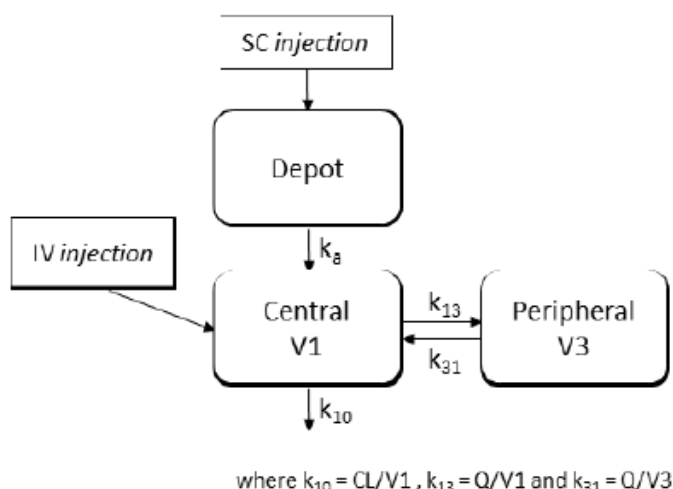$$\cdot A(1) + \frac{Q}{V3} \cdot A(2)$$
$$- \frac{CL}{V1} \cdot A(1)$$

$$\frac{dA(2)}{dt} = \frac{Q}{V1} \cdot A(1) - \frac{Q}{V3} \cdot A(2)$$

$$CL = \theta_{CL} \cdot \left(\frac{WGTBL}{70}\right)^{\theta_{CL,exp}} \cdot ADA\ titer^{(\theta_{CL,ADA} \cdot NAB\_FLAG)} \cdot e^{\eta CL}$$

$$V1 = \theta_{V1} \cdot \left(\frac{WGTBL}{70}\right)^{\theta_{V,exp}} \cdot e^{\eta V1}$$

$$V3 = \theta_{V3} \cdot \left(\frac{WGTBL}{70}\right)^{\theta_{V,exp}}$$

$$Q = \theta_{Q} \cdot \left(\frac{WGTBL}{70}\right)^{\theta_{CL,exp}}$$

where $k_{10} = CL/V1$, $k_{13} = Q/V1$ and $k_{31} = Q/V3$

Abbreviations: **A(0)**: Amount of drug in the SC depot compartment; **F**: Absolute bioavailability of the SC dose; **A(1)**: Amount of drug in the central compartment; **A(2)**: Amount of drug in the peripheral compartment; **Ka**: absorption rate constant; **V1**: Central volume of distribution; **V3**: Peripheral volume of distribution; **Q**: Intercompartmental clearance; **WGTBL**: body weight at baseline; $\boldsymbol{\theta_{CL,exp}}$: Allometric scaling constant applied to clearance parameters; $\boldsymbol{\theta_{V,exp}}$: Allometric scaling constant applied to volume parameters; $\boldsymbol{\theta_{CL,ADA}}$: Exponent of proportional effect of ADA titer on CL when NAB status is positive; **NAB_FLAG**: binary (1/0) variable which assumes the value of 1 only when NAB status is positive; **t**: time; $\boldsymbol{\eta x}$: Inter-individual random effects for the x parameter.

Model parameter estimates of the final population PK model are presented in Table 6. When NAB status is negative, the typical clearance of infliximab was 0.0148 L/h. When NAB status is positive, the clearance increases with the ADA titer values.

Table 6 Parameter estimates of the final population PK model (Run308)

Parameter	Final Parameter Estimate		
	Typical Value	**RSE (%)**	**Shrinkage (%)**
F	0.721	1.3	n/a
K_A (h^{-1})	0.0152	3.3	n/a
CL_{NAB-} (L/h)	0.0148	2.7	n/a
Exponent of proportional effect of ADA titre	0.224	0.9	n/a

Parameter	Final Parameter Estimate		
	Typical Value	RSE (%)	Shrinkage (%)
on CL when NAB is negative			
Q (L/h)	0.0364	16.1	n/a
V1(L)	3.4	4.8	n/a
V3 (L)	2.08	6.7	n/a
Allometric exponent on CL & Q	0.695	12.3	n/a
Allometric exponent on V1 & V3	0.913	7.8	n/a
BSV CL (CV%)	43.6	5.7	3.8
BSV V1 (CV%)	39.8	8.1	35.6
Proportional residual error (CV%)	42.1	0.3	n/a

CV % of proportional error is calculated as 100 * THETA, error is estimated as a THETA; CV % of exponential ETAs are calculated as 100 * sqrt(exp(OMEGA)-1)

Abbreviations: RSE = Relative Standard Error; n/a = not applicable; F = Bioavailability SC administration; KA = Absorption rate constant; CL_{NAB-} = clearance in NAB-; ADA titre = exponent of proportional effect of ADA titre on CL; Q = Intercompartmental CL; V1 = Central volume of distribution: V3 = Peripheral volume of distribution; BSV = Between-subject variability; CV = coefficient of variation

Diagnostic plots and pcVPC plots at steady state (Weeks 22 to 30) for the final population PK model are presented in Figures below. The MAH concluded that the model generally described the observed data adequately and that the pcVPC overall confirmed that the final population PK model generally captured the central tendency of the observed data, with an acceptable characterization of the variability generally observed for both routes of administration.

Figure 3 Goodness of fit plots for final population PK model (run308)
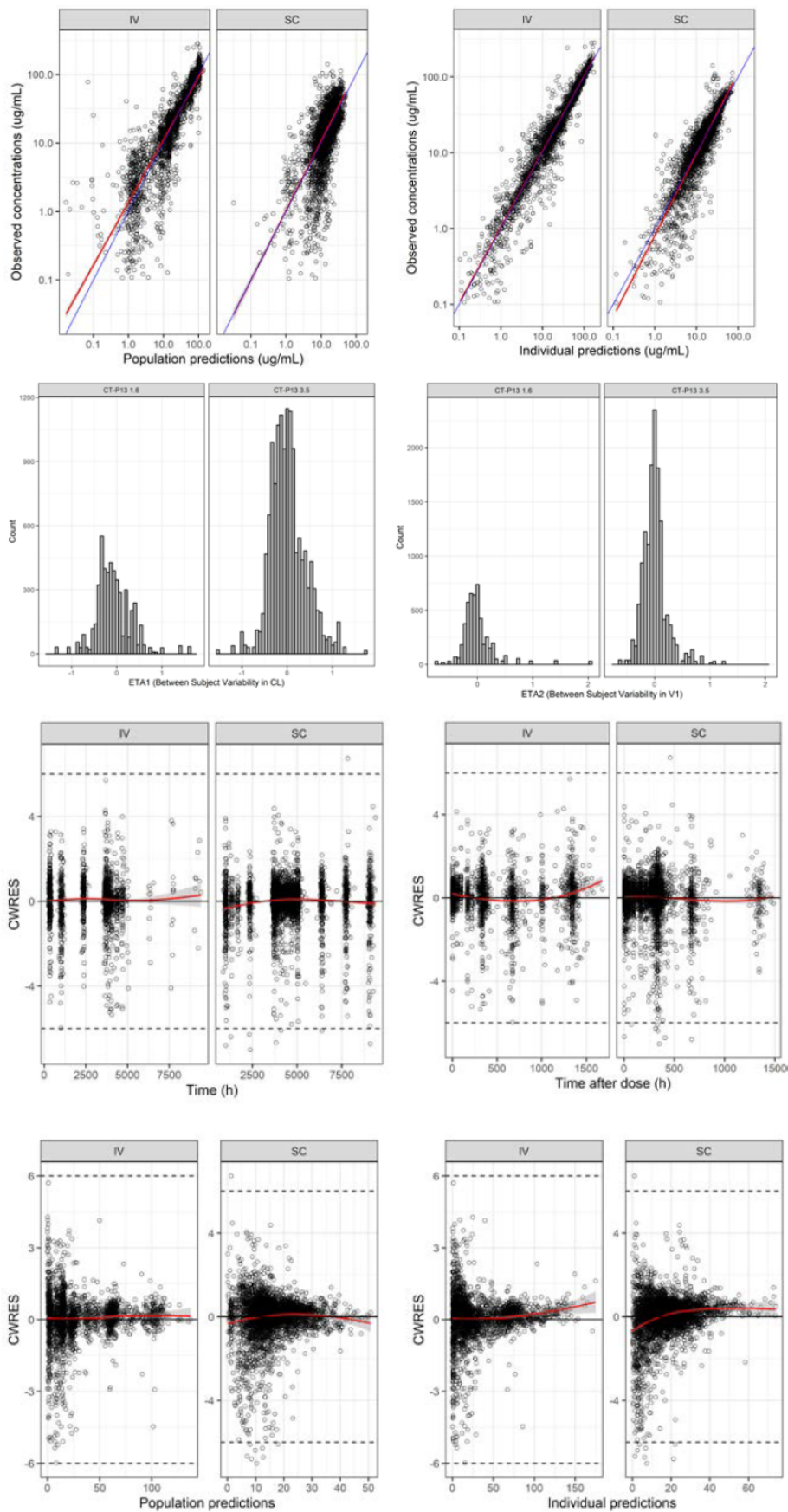
Figure 4 pcVPC for the final population PK model: steady state (Week 22–30) exposure, stratified by route of administration (run308)
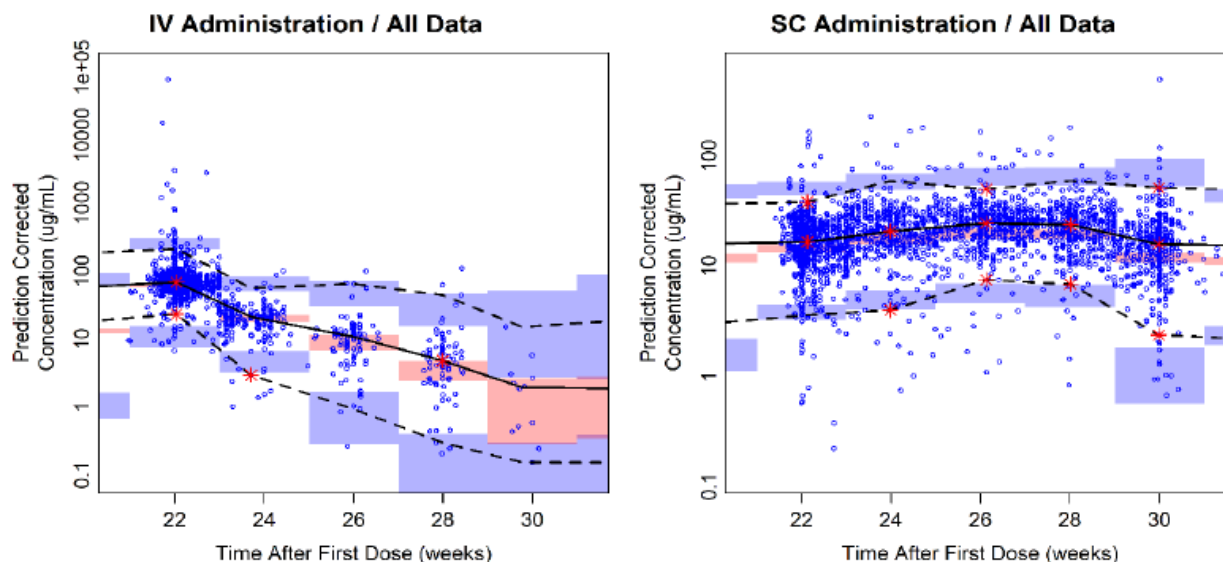
Blue symbols: Prediction corrected observed infliximab concentrations. **Black solid line**: The median prediction corrected observed infliximab concentrations. **Black dashed lines**: The 5th and 95th percentiles of the prediction corrected observed infliximab concentrations. **Orange shaded area**: The 95 % CI of the median of the prediction corrected model predicted data. **Blue shaded area**: The 95 % CI of the 5th and 95th percentiles of the prediction corrected model predicted data. **Red star symbol**: the median of the prediction corrected observed infliximab concentrations is not in the 95% CI of the prediction corrected model predicted infliximab concentrations.

Absorption

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 parallel-group study CT-P13 1.5 (see ARs of process X/62). Median T_{max} was at approximately 170 h (range 72 to 314 h) in each SC cohort. The mean bioavailability was 60.56% (90% CI 51.93% - 70.63%) for overall Remsima SC cohorts.

The estimated typical bioavailability for Remsima SC was 57.6%, 57.5% and 72.1% in the 1st, the 2nd and the 3rd population PK model, respectively.

Distribution

The parameter estimates from the population PK model and previous noncompartmental analyses indicate that infliximab is largely constrained to systemic circulation, with a volume of distribution of approximately 5 to 6 litres.

Elimination

No new data on routes of excretion and metabolism were submitted and none are required. It is expected that elimination mechanisms of subcutaneously and intravenously administered infliximab are similar.

Dose proportionality and time dependencies

Pharmacokinetics of Remsima IV is linear over the approved dose range.

Results of three parallel-group studies (CT-P13 1.5; CT-P13 3.5 Part 1; CT-P13 1.6 Part 1) indicated that following SC injection, exposure increased approximately in proportion with dose over the dose range 90 mg to 240 mg. See ARs of process X/62 for detailed assessment.

Pharmacokinetics in target population

<u>Observed exposure</u>

Study CT-P13 1.6 Part 1

<u>Design</u>: Study CT-P13 1.6 Part 1 was an open-label, randomized, multicenter, parallel-group study. The primary objective for Part 1 was to find the optimal dose of Remsima SC in patients with active CD. The secondary objective for Part 1 was to evaluate efficacy, PK, PD and overall safety of Remsima SC in comparison with Remsima IV. Only descriptive statistics of the data were provided, in accordance with the statistical analysis plan.

The overview of study design is illustrated in Figure 5. During the dose-loading phase, all enrolled patients initially received Remsima IV infusion (5 mg/kg) 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 on week 6 into 4 study cohorts: Remsima IV 5 mg/kg Q8W (n=13); Remsima SC 120 mg Q2W (n=11); Remsima SC 180 mg Q2W (n=12); Remsima 240 mg SC Q2W (n=8).

Figure 5 Overview of Study CT-P13 1.6 Part 1.
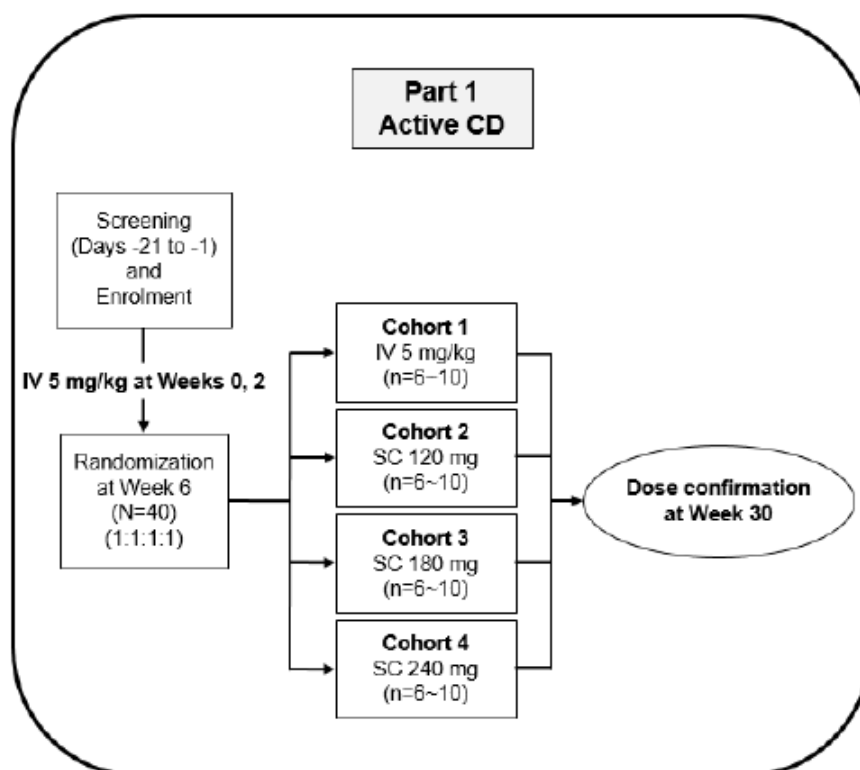
Abbreviations: CD, Crohn's disease; IV, intravenous; SC, subcutaneous.

Frequent PK samples were collected at steady state between Week 22 to Week 30. Individual serum concentration data over actual time data will be used to calculate PK parameters of infliximab were calculated by standard non-compartmental methods using individual concentration data and actual time after dose.

<u>Results</u>: The PK population consisted of 41 patients. One randomised patient was excluded from the PK population in the SC 240 mg cohort due to major protocol deviation (wrong dose administered at week 6), and 2 additional patients were excluded from the PK population in the IV 5 mg/kg and SC 240 mg cohort because they did not have any concentration data after Week 6 administration.

Overall, demographic characteristics were generally well balanced among the 4 cohorts. The median (min, max) baseline weight was 68.60 (44.6, 95.0), 71.0 (47.0, 87.9), 71.0 (43.0, 105.0) and 70.25 (43.0, 105.0) kg in the IV 5 mg/kg, SC 120 mg, SC 180 mg and SC 240 mg cohorts, respectively.

Mean (± SD) serum concentrations of infliximab versus time by cohort during the PK monitoring period (from Week 22 to Week 30) are presented in Figure 6. Descriptive statistics of the observed C_{trough} and steady state AUC normalised to 8-week interval (AUC_{ss8W}) are shown in Tables below.

Figure 6 Mean (±SD) Serum Concentration of Infliximab versus Time by Cohort (Study CT-P13 1.6 Part 1; Weeks 22 to 30)
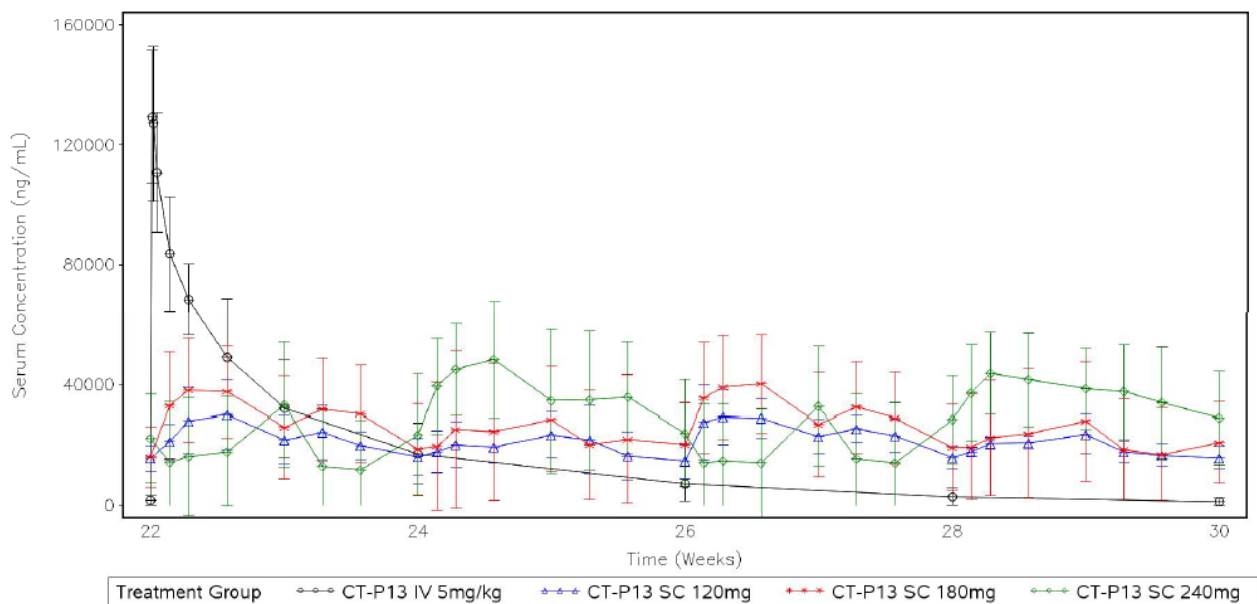
Table 7 Pre-dose infliximab levels (C_{trough}) (Study CT-P13 1.6 Part 1)

		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} (hr*µg/mL)	Week 22	n	11	10	11	6
		Mean	20977.08 ± 8590.04	28250.82 ± 9272.13	34278.64 ± 23104.83	41157.14 ± 27161.50
		CV%	40.95	32.82	67.40	66.00

AUC_{ss8W}: Area under the concentration-time curve normalised to an 8-week interval, calculated over actual dosing interval, CV%: Percent coefficient of variation

Study CT-P13 1.6 Part 2

See section 2.4.2 (Clinical efficacy / Main studies) for details of study CT-P13 1.6 Part 2. The PK population (n=127) consisted of the all-randomized population who received at least 1 full dose of study drug at Week 6 or thereafter and who had at least 1 PK concentration result after Week 6 treatment.

The primary endpoint of Study CT-P13 1.6 Part 2 was the observed serum infliximab pre-dose level at Week 22 ($C_{trough,week22}$). Population PK analysis was employed to estimate the other PK parameters (e.g. predicted trough and maximum serum concentrations ($C_{trough,ss}$ and $C_{max,ss}$, respectively) and AUC normalized to an 8-week interval ($AUC_{8W,ss}$)).

PK parameters

Pre-dose PK samples were collected at weeks 0, 2, 6, 14, 22, 30, 38, 46 and 54. Additional PK samples were collected at steady state between weeks 22 and 30 (Table 9).

Table 9 Steady State PK Sampling Time Points (study CT-P13 1.6 Part 2)

Visit (Day)	Arm 1 (Remsima IV)	Arm 2 (Remsima SC)			
		Group A[3]	Group B[3]	Group C[3]	Group D[3]
Week 22 (Day 154)	• Pre-dose[1], after EOI (+15 min), 1 h (±15 min) after EOI, 8 h (±15 min), 24 h (±15 min), 48±2 h, and 168±6 h after SOI	• Pre-dose[2], 24±2, 48±2, 72±2, 96±4, 120±4, 144±4, 168±6, 216±4, and 264±4 h after injection	• Pre-dose[2]	• Pre-dose[2]	• Pre-dose[2]
Week 24 (Day 168)	• 14 days (±12 h) after SOI at Week 22	• Pre-dose[2]	• Pre-dose[2], 24±2, 48±2, 72±2, 96±4, 120±4, 144±4, 168±6, 216±4, and 264±4 h after injection	• N/A	• N/A
Week 26 (Day 182)	• 28±1 days after SOI at Week 22	• N/A	• Pre-dose[2]	• Pre-dose[2], 24±2, 48±2, 72±2, 96±4, 120±4, 144±4, 168±6, 216±4, and 264±4 h after injection	• N/A
Week 28 (Day 196)	• 42±1 days after SOI at Week 22	• N/A	• N/A	• Pre-dose[2]	• Pre-dose[2], 24±2, 48±2, 72±2, 96±4, 120±4, 144±4, 168±6, 216±4, and 264±4 h after injection
Week 30 (Day 210)	• Pre-dose[1]	• Pre-dose[2]	• Pre-dose[2]	• Pre-dose[2]	• Pre-dose[2]

Abbreviations: **EOI**, end of the infusion; **h**, hours; **min**, minutes; **N/A**, not applicable; **SOI**, start of the infusion.
1.   Prior to the beginning of study treatment administration on dosing day (or 56 days after previous dosing day only if patient had not received study treatment on each relevant dosing day).
2.   Prior to the beginning of study treatment administration on dosing day (or 14 days after previous dosing day only if patient had not received study treatment on each relevant dosing day).
3.   Patients in the SC arm were randomly assigned at Week 14 in a 1:1:1:1 ratio into one of 4 PK sampling groups.

Observed infliximab levels

Serum infliximab concentrations versus time from Week 22 to Week 30 are presented in Figure 7. Descriptive statistics for the observed pre-dose concentrations are summarised in Table 10. After randomization at week 6, the mean pre-dose serum concentration levels were consistently higher in the SC 120/240 mg treatment arm compared to the IV 5 mg/kg treatment arm; note that subjects randomised to Remsima IV were switched to Remsima SC at week 30.

The geometric LS means of observed $C_{trough,week22}$ were 20.9844 and 1.8181 µg/mL in the SC 120/240 mg and IV 5 mg/kg treatment arms, respectively. The lower bound 90% CI for the ratio of the geometric LS means was 786.37%, which was greater than 80%, indicating noninferiority of Remsima SC 120/240 mg compared to Remsima IV 5 mg/kg .

Figure 7 Observed Mean (SD) Serum infliximab Concentrations by treatment arm from Week 22 to week 30 in Study CT-P13 1.6 Part 2
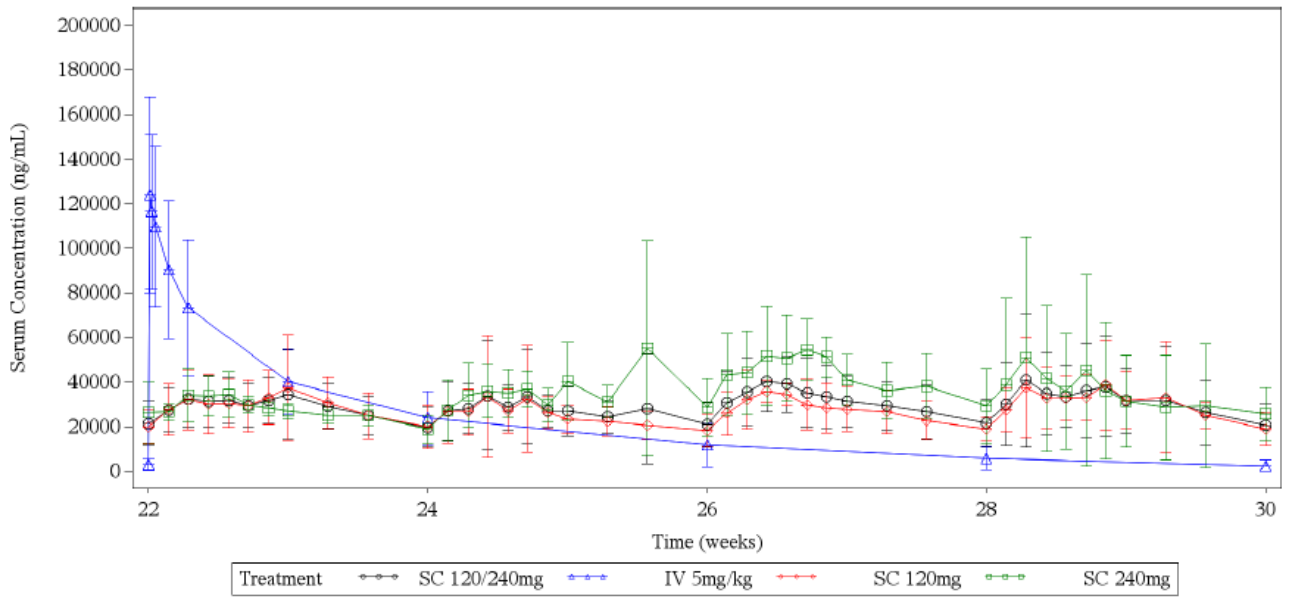
Table 10 Observed infliximab pre-dose concentration (Study CT-P13 1.6 Part 2)

		Remsima IV 5 mg/kg (N=64)	Remsima SC 120/240 mg		
			Remsima SC Combined (N=63)	Remsima SC 120 mg (N=45)	Remsima SC 240 mg (N=18)
Observed pre-dose concentration (µg/mL)					
Week 0	n	64	62	45	17
	Mean ± SD	0.01 ± 0.09	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
	CV%	800.0	N/A	N/A	N/A
Week 2	n	64	63	45	18
	Mean ± SD	21.86 ± 7.37	23.54 ± 8.44	23.89 ± 7.01	22.66 ± 11.45
	CV%	33.7	35.8	29.4	50.5
Week 6	n	64	63	45	18
	Mean ± SD	14.07 ± 7.74	15.47 ± 9.16	16.12 ± 7.99	13.85 ± 11.70
	CV%	55.0	59.2	49.6	84.5
Week 14	n	64	63	45	18
	Mean ± SD	3.79 ± 3.00	20.97 ± 9.22	19.67 ± 7.18	24.21 ± 12.68
	CV%	79.1	44.0	36.5	52.4
Week 22	n	57	59	44	15
	Mean ± SD	2.93 ± 2.61	21.45 ± 9.86	19.83 ± 7.75	26.19 ± 13.65
	CV%	89.0	46.0	39.1	52.1
Week 30	n	48	50	36	14
	Mean ± SD	2.43 ± 2.49	20.73 ± 9.26	18.85 ± 7.39	25.58 ± 11.87
	CV%	102.8	44.7	39.2	46.4
Week 38	n	53	59	44	15
	Mean ± SD	18.60 ± 11.41*	22.20 ± 10.00	22.26 ± 10.40	22.00 ± 8.96
	CV%	61.4	45.0	46.7	40.7
Week 46	n	50	57	43	14
	Mean ± SD	19.64 ± 10.49*	22.42 ± 11.68	22.00 ± 12.62	23.70 ± 8.44
	CV%	53.4	52.1	57.4	35.6
Week 54	n	49	53	39	14
	Mean ± SD	20.58 ± 12.45*	22.79 ± 13.17	23.03 ± 13.64	22.14 ± 12.21
	CV%	60.5	57.8	59.2	55.2

*Subjects randomized to Remsima IV at Week 6 were switched to Remsima SC 120/240 mg at Week 30

Table 11 Analysis of Covariance of observed infliximab $C_{trough,week22}$

Arm	n	Geometric LS mean (µg/mL)	Ratio (%) of Geometric LS Means	90% CI of the Ratio (%)
CT-P13 IV 5 mg/kg	57	1.8181	1154.17	786.37 – 1694.00
CT-P13 SC 120/240 mg	59	20.9844		

<u>Predicted exposure</u>

Infliximab exposure parameters at steady state following 120 mg Q2W SC and 5 mg/kg Q8W IV dosing regimens were simulated using the final 3rd PPK model (run308). Virtual patients with different body weights ranging from 50 kg to 150 kg were simulated assuming uniform distribution (1000 subjects per 10 kg weight band). For this virtual patient population, NAB status was assumed either negative or positive with ADA titer values of 1, 3, 9, 27, 81, or 243.

Two separate simulations were performed. The simulation in NAB- patients, where immunogenicity had no impact on CL, was performed to investigate the effect of body weight on infliximab exposure. The simulation in NAB+ patients, where immunogenicity had impact on CL, was performed to investigate the effect of ADA titer on infliximab exposure. As the PPK model used continuous ADA titer values, it was difficult to investigate each impact of immunogenicity or body weight on PK when the ADA titer values are simultaneously incorporated into each of the weight strata. Therefore, the body weight was stratified (<80 kg or ≥80 kg).

Predicted infliximab $C_{trough,ss}$ and AUC over 8 weeks ($AUC_{8w,ss}$) in NAB- patients following 120 mg Q2W SC and 5 mg/kg Q8W IV dosing regimens are presented below. The geometric mean ratio of exposure (SC/IV) was calculated for all patients and by each 10-kg body weight strata. The $C_{trough,ss}$ of infliximab SC was 2.63~10.62-fold higher than the $C_{trough,ss}$ of infliximab IV. As expected, the difference decreased in patients with high body weights. The $AUC_{8w,ss}$ of infliximab SC was 0.48~1.3-fold of $AUC_{8w,ss}$ infliximab IV. The $C_{max,ss}$ of infliximab SC was about 5~10- fold lower than $C_{max,ss}$ of infliximab IV, as expected.

Figure 8 Predicted infliximab $C_{trough,ss}$ at steady state following 120 mg Q2W SC and 5 mg/kg Q8W IV in NAB- patients stratified by weight.
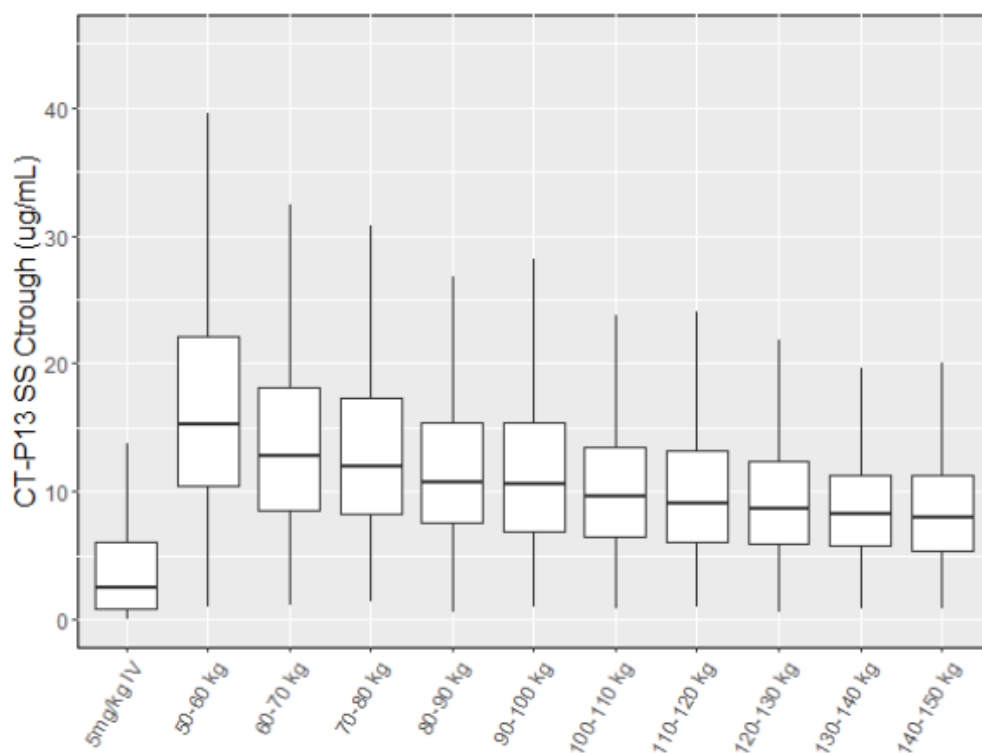
Figure 9 Predicted infliximab $AUC_{8w,ss}$ at steady state following 120 mg Q2W SC and 5 mg/kg Q8W IV in NAB- patients stratified by weight.
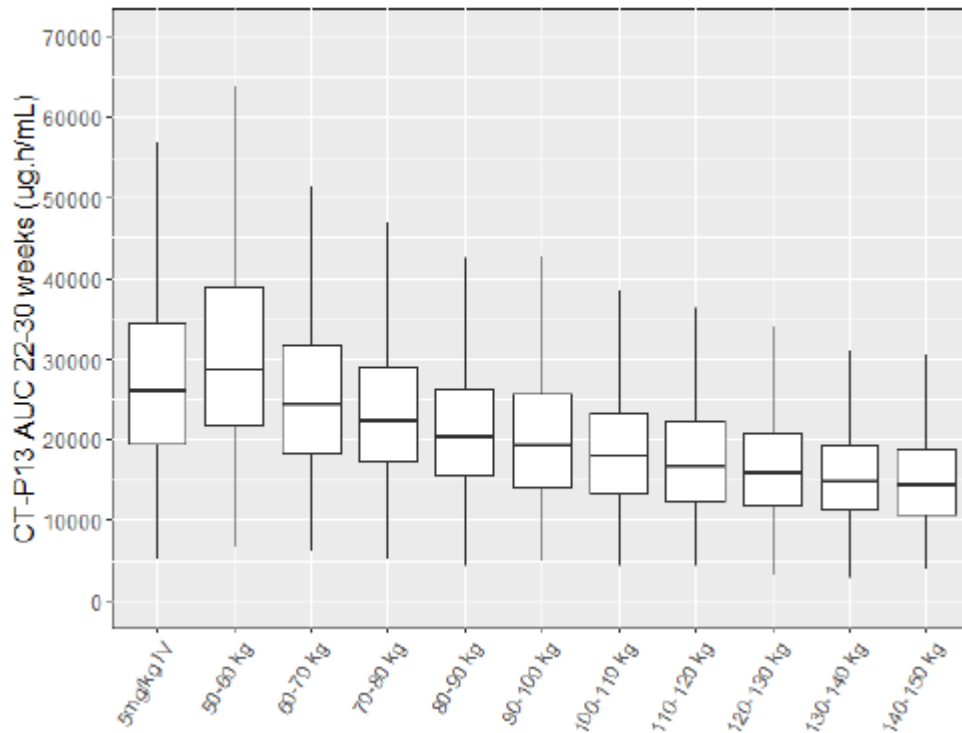
The predicted infliximab $C_{trough,ss}$ following 120 mg Q2W SC and 5 mg/kg Q8W IV dosing regimens in patients with the highest ADA titer values (81 or 243) is presented in Figure 10. The exposures decreased with increasing ADA titer.

The combined impact of body weight and NAB+ associated ADA titer value on infliximab exposure was explored. Infliximab steady state exposures following 120 mg Q2W SC dosing regimen in NAB+ patients with different body weights and ADA titer values (test population) were compared with the exposures in patients with a body weight of 80 kg and negative ADA status following 5 mg/kg Q8W IV infusion (reference population). The body weight in the test population ranged from 50 kg to 150 kg in this analysis and was stratified by <80 kg or ≥80 kg. Figure 11 and Figure 12 display the forest plots of $C_{trough,ss}$ and $AUC_{8w,ss}$, respectively, showing the exposure in test population relative to the reference population. A similar trend was observed in changes in infliximab exposure as ADA titer increases regardless of body weight stratum.

Figure 10 Predicted infliximab $C_{trough,ss}$ following 120 mg Q2W SC and 5 mg/kg Q8W IV in patients with high ADA titer stratified by weight
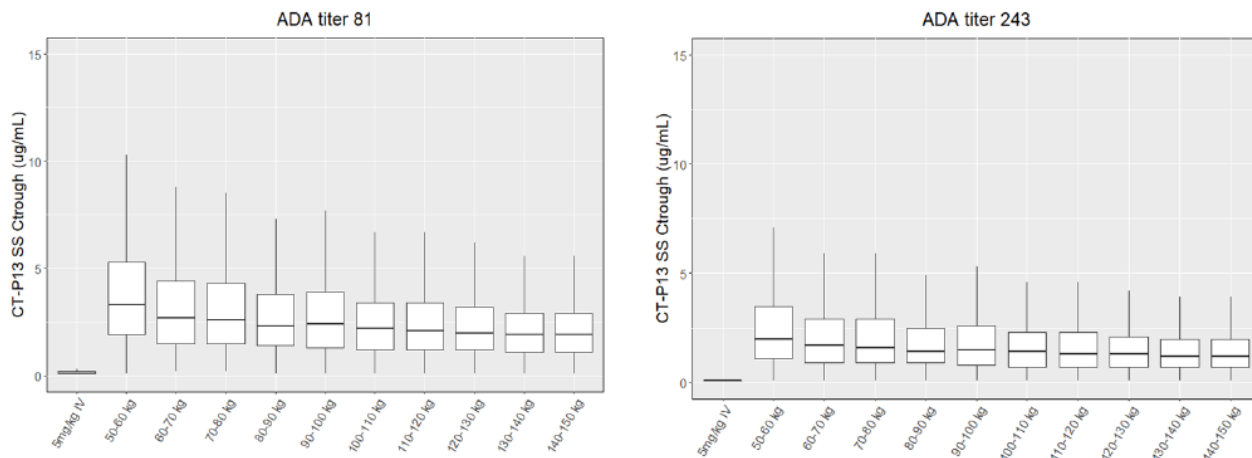
Figure 11 Forest plot of predicted $C_{trough,ss}$ following 120 mg Q2W SC dosing regimen in NAB+ patients stratified by ADA titer and weight.

Figure 12 Forest plot of predicted $AUC_{8w,ss}$ following 120 mg Q2W SC dosing regimen in NAB+ patients stratified by ADA titer and weight.

2.3.3. 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 tumour necrosis factor alpha (TNF-α) preventing TNF from binding to its receptor and inducing associated cellular functions.

Primary and secondary pharmacology

Remsima SC contains the same active ingredient infliximab as Remsima IV. New studies were not conducted to investigate the primary and secondary pharmacology of infliximab.

2.3.4. PK/PD modelling

Exposure-response (ER) models for efficacy and safety were developed using predicted individual post-hoc PK parameter estimates from the 2nd population PK model. Subsequently, the 3rd PPK model was developed (see section 2.3.2 Pharmacokinetics / Methods / Population PK models) and the ER efficacy analyses for CDAI and partial Mayo scores were re-evaluated using the predicted PK parameter estimates obtained with the 3rd PPK model. ER safety analyses were not re-run.

The 2nd population PK/PD analysis

Modelling report "*Population pharmacokinetic-pharmacodynamic modeling of CDAI and Mayo scores, safety, ESR and C-Reactive Protein in patients with active Crohn's disease and active ulcerative colitis – Part 2*".

Population PK/PD Analysis for CDAI Score in Patients with active Crohn's disease

The population PK/PD modelling of CDAI score in CD patients was performed using the 2nd population PK model, along with the CDAI scores obtained from Studies CT-P13 3.4 (IV infliximab only, n=220) and CT-P13 1.6 Parts 1 and 2 (IV and SC infliximab, n=97). Patients were included in the analysis if they entered the active treatment phase of their trial, had at least one adequately documented infliximab administration and one adequately documented assessment of CDAI score. The analyses were performed in NONMEM employing first-order conditional estimation with η-ε interaction for all runs.

A total of 1236 quantifiable CDAI scores from 317 subjects were available for the model development, of which 19 negative observations were excluded as anomalous observations (the anticipated lower bound of potential CDAI scores is 0). An exploratory graphical data analysis of CDAI response versus time indicated a general trend towards reduction of the CDAI score during the induction phase from baseline (Week 0) to Week 6, after which the effect appeared to be maintained or further improved during the maintenance phase. Visual inspection did not indicate strong relationship between any of the covariates of interest and the reduction in CDAI scores following exposure to infliximab.

Individual patient simulated plasma concentrations were obtained from the individual patient post-hoc PK parameter estimates derived from the final population PK model. The CDAI response was initially (Run100) characterized by an indirect response model wherein an inhibitory probit transformed I_{max} model was used to describe the suppressive effect of infliximab on the zero-order rate constant of CDAI score production (k_{in}), while the baseline CDAI score was defined as the ratio of k_{in} to the first order rate constant of the amelioration of CDAI score (k_{out}). Between-subject variability (BSV) was included in baseline CDAI and I_{max}. Residual variability was implemented with additive residual error structure.

Further evaluation explored inclusion of additional BSV in k_{out} and IC_{50} parameters. In both cases, the resulting goodness of fit plots indicated that inclusion of the additional parameters did not result in an improvement of the model performance. As a result, the additional parameters were deemed redundant and were not retained. Correlation between the BSV in baseline CDAI score and I_{max} (Run101) improved the fit and the off-diagonal element was retained in the model. Run101 was selected as the final base model and was carried forward to the covariate modeling.

Baseline CDAI score, disease duration, baseline albumin, age, gender, race (white vs non-white), and azathioprine co-medication (AZA) were investigated in covariate analyses. No covariate was deemed to provide meaningful improvement and the base model (Run101) was declared the final model.

The final PK/PD model for CDAI obtained was an indirect-response model, parameterized with a probit transformed inhibitory I_{max} model to describe the suppressive effect of infliximab on the zero-order rate constant of CDAI score production (k_{in}), and baseline CDAI response (R0) defined as the ratio of k_{in}^0 to the first order rate of the amelioration of CDAI response (k_{out}). A schematic and the parameter estimates of the final model are presented below. Results of the bootstrap analysis demonstrated minimal bias (<1% difference between parameter estimates in the final model and bootstrap parameters). However, the relative standard error for IC_{50} was very high (156%) in bootstrap indicating that the parameter was poorly estimated.

Figure 13 Population PK/PD Model of CDAI Score: Equations and Model Diagram (Run101)

$$\frac{dR}{dt} = \left(k_{in}^0 * I(t)\right) - (k_{out} * R)$$

$$I(t) = 1 - \frac{I_{max} * C_p}{IC_{50} + C_p}$$

$$I_{max,i} = F\left(\theta_{Imax} + h_i\right)$$
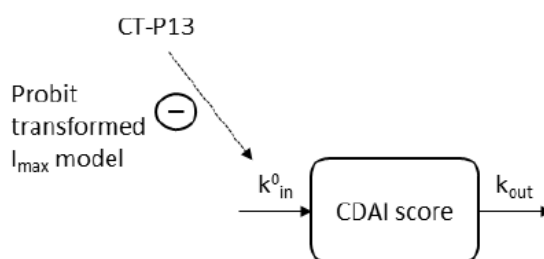
Abbreviations: k_{in}: apparent zero-order rate constant for production of the response; k_{out}: first-order rate constant for the amelioration of response; I_{max}: maximum fractional ability of the drug to affect baseline CDAI score; IC_{50}: drug concentration that produces 50% of maximum inhibition; $I_{max,i}$: I_{max} value in the ith individual; Φ: cumulative distribution function of the normal distribution, θ_{Imax}: typical value of I_{max}; η_i: deviation of individual i from the typical value of I_{max}.

Table 12 Parameter Estimates of the final Population PK/PD Model of CDAI Score (Run101)

Parameter	Final parameter estimate		Bootstrap results		
	Typical value [a]	RSE (%)	Estimate [a]	95% CI [c]	% RSE [b]
Baseline CDAI Score	5.69	0.19	5.69	[5.67 ; 5.71]	0.18
k_{out} (/day)	-6.49	1.8	-6.50	[-6.73 ; -6.15]	1.9
I_{max}	0.189	29	0.198	[0.088 ; 0.369]	29
IC_{50} (µg/mL)	-2.36	30	-2.33	[-15.7 ; -0.67]	156
Additive Residual Error (SD)	3.93	1	3.93	[3.84 ; 4.03]	1.1
Unexplained BSV in Baseline CDAI	0.0159	25	0.0161	[0.008 ; 0.025]	24
Correlation in Unexplained BSV (Baseline CDAI and I_{max})	-0.0327	25	-0.0331	[-0.049 ; -0.0139]	24
Unexplained BSV in I_{max}	0.344	15	0.348	[0.253 ; 0.512]	15

[a] Raw untransformed parameters

[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.

Abbreviations: CV: Coefficient of Variation; RSE: Relative Standard Error; n/a: not applicable; k_{out}: first-order rate constant for the amelioration of response; I_{max}: maximum fractional ability of the drug to affect baseline CDAI score; IC_{50}: drug concentration that produces 50% of maximum inhibition; BSV: Between Subject Variability.

Visual inspection of the goodness of fit plots indicated that the model (Run101) generally described the observed data well. In the pcVPC plots, the median, 5th and 95th percentiles of the prediction corrected observed data were generally contained within the 95 % confidence intervals of the corresponding simulations, indicating adequate performance of the model.

Population PK/PD analysis of partial Mayo scores for patients with active ulcerative colitis

A total of 455 quantifiable partial Mayo scores from 78 subjects from study CT-P13 1.6 Part 2 until week 30 were available for the PK/PD model development.

Initial base model development considered the partial Mayo score as an ordered categorical endpoint with values ranging from 0 to 8. However, the tested categorical models were not able to properly characterize the observed data. This was attributed to the absence of placebo data, the dosing schedule (i.e. loading phase up to week 6) and the limited number of observations in comparison with the number of model parameters (a categorical model has more parameters than a continuous model). As a result, model development switched to the continuous approach and a base model similar to the one employed to characterize the CDAI score in CD patients was pursued.

The initial continuous model (Run001) employed the final model from the previous analysis on the CDAI score with the aim of estimating only fixed effects and residual error. Subsequently, BSV on I_{max}, baseline partial Mayo score and k_{out} were explored. All resulted in a statistically significant improvement of the model performance and were, as such, retained. The last attempt consisted in improving the characterization of the baseline partial Mayo score by changing its distribution from log-normal to normal (consistent with the observed data; Run008) and implementing a logit transformation of the baseline partial Mayo score parameter to constrain it to range between the anticipated values of 0 to 8 (Run010). Scatterplots of the Bayesian post-hoc individual ETA estimates (k_{out}, baseline partial Mayo score and I_{max}) from Run010 indicated no relevant correlation between any pair of parameters and the goodness of fit and pcVPC plots indicated adequate characterisation of the observed data. As a result, Run010 remained unchanged and was selected as the base model. Model structure and parameter estimates are displayed in Figure 14 and Table 13, respectively. The bootstrap analysis (1000 replicates, 61% of which converged successfully, with the remaining runs terminating due to rounding errors) indicated that IC_{50} and the additive residual error were poorly estimated.

Figure 14 Final Population PK/PD model for partial Mayo score: Equations and model diagram.

$$\frac{dR}{dt} = \left(k_{in}^0 * I(t) \right) - \left(k_{out} * R \right)$$

$$I(t) = 1 - \frac{I_{max} * C_p}{IC_{50} + C_p}$$

$$I_{max,i} = F \left(\theta_{Imax} + h_i \right)$$

$$k_{in}^0 = logit(Base + h) * k_{out}$$

k_{in}: apparent zero-order rate constant for production of the response; k_{out}: first-order rate constant for loss of the response; I_{max}: maximum fractional ability of the drug to affect baseline partial score; IC_{50}: drug concentration that produces 50% of maximum inhibition; $I_{max,i}$: I_{max} value in the ith individual; Φ: cumulative distribution function of the normal distribution, θ_{Imax}: typical value of I_{max}; η_i: deviation of individual i from the typical value of I_{max}, logit: logit transformation of baseline partial Mayo score to constrain baseline between 0 and 8.
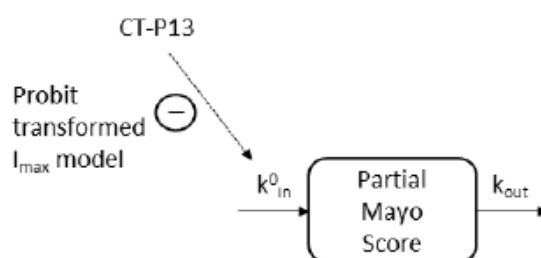
Table 13 Population PK/PD model for partial Mayo score: Parameter estimates (Run010).

Parameter	Final parameter estimate		Bootstrap results		
	Typical [a]	RSE (%)	Estimate [a]	95% CI [c]	% RSE [b]
Baseline Partial MAYO Score	0.901	7.1	0.9	[0.72 ; 1.1]	11
k_{out} (/day)	-6.13	2.7	-6.16	[-6.6 ; -5.6]	4.3
I_{max}	0.713	3.5	0.755	[0.46 ; 1.2]	23
IC_{50} (µg/mL)	-2.82	2.3	-4.62	[-16 ; -0.23]	570
Additive Residual Error (SD)	0.0461	25	0.043	[-0.11 ; 0.2]	190
Unexplained BSV in Baseline Partial Mayo	0.392 [a]	25	0.391 [a]	[0.19 ; 0.63]	29
Unexplained BSV in k_{out}	1.89 [a]	25	1.88 [a]	[0.89 ; 3.2]	31
Unexplained BSV in I_{max}	0.583 [a]	31	0.626 [a]	[0.23 ; 1.3]	49

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 partial Mayo response, BMAYO = baseline partial Mayo score, K_{out} = first-order rate constant for loss of the response, RSE = relative standard error
Note: Bootstrap datasets obtained by replicated with replacement from cel-pkpd-s16p12-34-20190722.csv
[a] Raw untransformed parameters
[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.

A stepwise covariate approach was implemented to test the potential effect of pre-specified covariates (age, gender, concomitant azathioprine medication, disease duration, and baseline albumin level) on model parameters I_{max}, K_{out} and baseline partial Mayo score. Additionally, effect of baseline partial Mayo score on I_{max} was tested. None of them provided a statistically significant drop in the objective function value. Hence, the final base model (Run010) was selected as the final model.

Safety Exposure-Response Analyses

A graphical exploratory analysis was performed to evaluate the exposure-response relationship for infections and infusion/injection-related reactions (IRR). No formal model-based analyses were performed. The safety analysis population comprised a total of 1611 patients from CD, UC, RA and AS Studies CT-P13 1.1, 1.6, 3.1, 3.4 and 3.5, with a total of 591 infection events (150 being related to treatment, mild and moderate severity) and 143 IRRs (73 of which were related to treatment, mild and moderate severity).

Boxplots of IRR and infections versus infliximab serum exposure (stratified by dosing route) showed no apparent difference in average steady-state AUC, C_{max} or C_{trough} in patients that experienced the event compared to those that did not, either in pooled analysis or in subgroups stratified by disease.

3rd PK/PD model

Population PK/PD Model of CDAI Scores

A total of 591 quantifiable CDAI scores from 97 subjects in Study CT-P13 1.6 were available for the population PK/PD model of CDAI scores. The previously developed base model (Figure 13) was retained and re-run with individual infliximab plasma concentrations predicted using the 3rd population PK model (Run204). Parameter estimates of the model are presented in Table 14.

Table 14 Population PK/PD model for CDAI score: Parameter estimates (Run204).

Parameter	Untransformed Parameter Value	RSE (%)	Shrinkage (%)	Parameter Value (Original Scale)

Parameter	Untransformed Parameter Value	RSE (%)	Shrinkage (%)	Parameter Value (Original Scale)
Baseline CDAI Score	5.67	0.41	n/a	290
k_{out} (/day)	-6.62	3.5	n/a	0.00134
I_{max}	0.185	24	n/a	0.574
IC_{50} (ug/mL)	-2.95	27	n/a	0.0521
Additive Residual Error (SD)	3.96	1.2	n/a	52.5
Unexplained BSV in Baseline CDAI (CV%)	17.8	33	20	n/a
Correlation in Unexplained BSV (Baseline and Imax)	-0.158	110	n/a	n/a
Unexplained BSV in I_{max} (CV%)	71.5	9	18	n/a

All RSEs are related to the untransformed parameters; CV % of exponential ETAs are calculated as 100 * sqrt(exp(OMEGA)-1).
Abbreviations: BSV=between-subject variability; RSE = Relative Standard Error; n/a = not applicable; k_{out}= first-order rate constant for loss of the response; I_{max}=Maximum fractional ability of the drug to affect baseline CDAI scores; IC_{50}=drug concentration that produces 50% of maximum inhibition; SD=standard deviation.

Exploratory graphical analysis of covariates effects (gender, race, age, concomitant medication (Azathioprine), disease duration, baseline CDAI score, and baseline albumin) on the post-hoc Bayesian parameter estimates did not suggest strong correlation between covariates and model parameters. Hence, the base model run 204 was declared as the final population PK/PD model for CDAI.

Visual inspection of the goodness of fit plots indicated that the model generally described the observed data well, although a small deviation from the expectation was noted in the CWRES versus Time Since First Dose plot. The pcVPC plots, stratified by route of administration, are presented in Figure 15. The median, 5th and 95th percentiles of the prediction corrected observed data were generally contained within the 95% confidence intervals of the corresponding simulations, indicating adequate performance of the model.

Figure 15 Visual Predictive Check of the final Population PK/PD Model of CDAI Score (Run204).

Prediction corrected observed CDAI scores are represented by **black symbols**. The median prediction corrected observed CDAI scores are represented by a **black solid line**. The 5th and 95th percentiles of the prediction corrected observed CDAI scores are represented by **dashed blacklines**. The **grey shaded area** represents the 95 % CI of the median of the prediction corrected model predicted data. The **blue shaded area** represents the 95 % CI of the 5th and 95th percentiles of the prediction corrected model predicted data. The pcVPC was obtained from the final model, including the residual error, resulting in the negative scores returned by the simulation.

Population PK/PD Model of partial Mayo Scores

A total of 455 quantifiable partial Mayo scores from 78 subjects in Study CT-P13 1.6 Part 2 was available for the development of a population PD model of partial Mayo scores. The previously developed base model Figure 14) was retained and re-run with individual infliximab plasma concentrations predicted using the 3rd population PK model (Run020). Parameter estimates of the model are presented in Table 15.

Table 15 . Population PK/PD model for partial Mayo score: Parameter estimates (Run020).

Parameter	Untransformed Parameter Value	RSE (%)	Shrinkage (%)	Parameter Value (Original Scale)
Baseline Partial Mayo Score	0.901	12	n/a	5.69
k_{out} (/day)	-6.1	3.4	n/a	0.0536
I_{max}	0.689	19	n/a	0.755
IC50 (ug/mL)	-4.48	35	n/a	0.0113
Additive Residual Error (SD)	0.0464	61	n/a	1.05
Unexplained BSV in Baseline Partial Mayo (CV%)	68.6	42	31	n/a
Unexplained BSV in k_{out} (CV%)	244	30	25	n/a
Unexplained BSV in I_{max} (CV%)	87.8	29	24	n/a
All RSEs are related to the untransformed parameters; CV % of exponential ETAs are calculated as 100 * sqrt(exp(OMEGA)-1). Abbreviations: BSV=between-subject variability; RSE = Relative Standard Error; n/a = not applicable; k_{out}= first-order rate constant for loss of the response; I_{max}=Maximum fractional ability of the drug to affect baseline partial mayo scores; IC_{50}=drug concentration that produces 50% of maximum inhibition; SD=standard deviation.				

Exploratory graphical analysis of covariates (gender, age, concomitant medication (AZA), disease duration, baseline partial Mayo scores, and baseline albumin) did not exhibit any noticeable correlation with PD model parameters. Hence, Run020 without covariates was declared as the final population PK/PD model for partial Mayo scores. The pcVPC plots (Figure 16) indicated adequate characterisation of the observed data.

Figure 16 Population PK/PD model for partial Mayo score: Prediction Corrected Visual Predictive Check (Run020).

Prediction Corrected VPCs | run020vpcx
Number of simulations: 1000, confidence interval: 95%

Prediction corrected observed partial Mayo scores are represented by **black symbols**. The median prediction corrected observed partial Mayo scores are represented by a **black solid line**. The 5th and 95th percentiles of the prediction corrected observed partial Mayo scores are represented by **dashed blacklines**. The **grey shaded area** represents the 95% CI of the median of the prediction corrected model predicted data. The **blue shaded area** represents the 95% CI of the 5th and 95th percentiles of the prediction corrected model predicted data. The pcVPC was obtained from the final model, including the residual error, resulting in the negative scores returned by the simulation.

PK/PD simulations

Two sets of simulations were performed for patients with CD and UC to investigate the effects of body weight and immunogenicity on efficacy. The simulations based on the NAB- patients were performed to investigate the effect of body weight alone by categorizing the body weight from 50 kg to 150 kg into 10-kg weight strata. The simulations based on the NAB+ patients, where immunogenicity had impact on CL, were performed to investigate the effect of ADA titer; body weight was stratified by <80 kg or ≥80 kg. Results of simulations with the 3rd PK/PD model are presented below.

Simulations of CDAI Scores: Figure 17 presents the SC (test) to IV (reference) geometric mean ratio (GMR) of the steady state CDAI scores stratified by 10-kg body weight strata. In all body weight strata, the GMRs were close to 1.0, suggesting no significant difference in efficacy between SC and IV treated NAB- patients with CD. Lower CDAI score indicates better clinical response, hence GMR < 1 suggests better response for the SC dosing regimen.

Figure 17 Forest plot of CDAI scores following 120 mg Q2W SC dosing regimen compared with 5 mg/kg Q8W IV regimen stratified by weight in NAB- patients.

Figure 18 presents the GMR of the steady state CDAI scores between NAB+ patients following 120 mg Q2W SC dosing regimen (test) and patients with a standard body weight of 80 kg and ADA- status following 5 mg/kg Q8W IV infusion (reference). The test population had body weight distribution ranged from 50 kg to 150 kg, positive NAB status, and ADA titer values of 1, 3, 9, 27, 81, or 243. In all ADA titer and weight strata, the GMRs were close to 1.0, suggesting no significant impact of ADA titer and body weight on efficacy following 120 mg Q2W SC dosing regimen in the simulated patient population with CD.

Figure 18 Forest plot of CDAI scores following 120 mg Q2W SC dosing regimen in NAB+ patients stratified by ADA titer and weight.

Simulations of partial Mayo scores: Figure 19 presents the SC (test) to IV (reference) GMR of the steady state partial Mayo scores stratified by 10-kg body weight strata. In all body weight strata, the GMRs were close to 1.0, suggesting no significant difference in efficacy between SC and IV treated NAB- patients with UC. Lower Mayo score indicates better clinical response, hence GMR < 1 suggests better response for the SC dosing regimen.

Figure 19 Forest plot of partial Mayo scores following 120 mg Q2W SC dosing regimen in NAB- patients stratified by weight
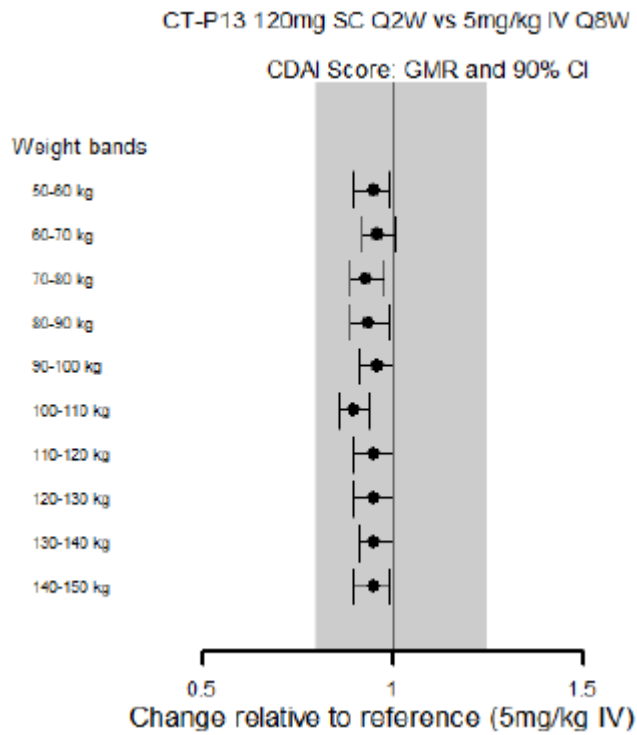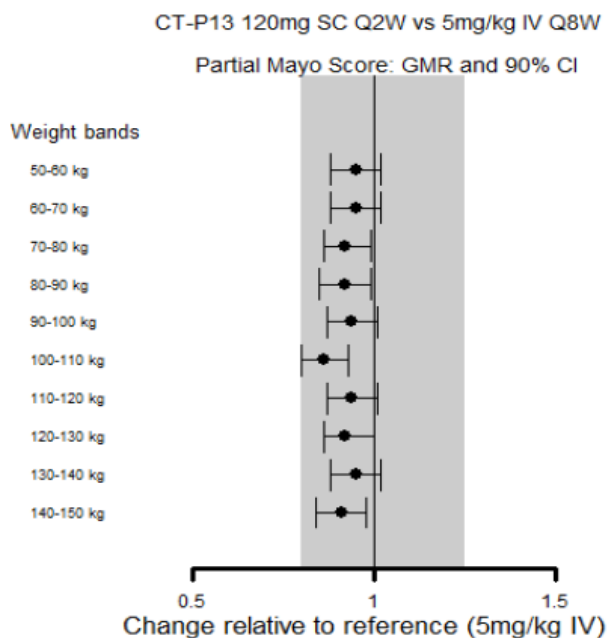

The MAH also presented the GMR of the steady state partial Mayo scores between NAB+ patients following 120 mg Q2W SC dosing regimen (test) and patients with a standard body weight of 80 kg and ADA- status following 5 mg/kg Q8W IV infusion (reference). The test population had body weight distribution ranged from 50 kg to 150 kg, positive NAB status, and ADA titer values of 1, 3, 9, 27, 81, or 243. In all ADA titer and weight strata, the GMRs were close to 1.0, suggesting no significant impact of ADA titer and body weight on efficacy following 120 mg Q2W SC dosing regimen in the simulated patient population with UC.

2.3.5. Discussion on clinical pharmacology

Bioanalytics

The MAH has presented a method validation data on a meso scale discovery (MSD) ECL method that was used for the quantitation of CT-P13 in serum samples. The validation of MSS-ECL method to quantify the amount of CT-P13 in human serum has been previously accepted during line extension procedure (EMEA/H/C/2576/X/62). In this submission three addendums were provided to study analyte stability in frozen state and further evaluate dilutional parallelism of the method in different matrices. Adequate data was provided to demonstrate method validity. The MAH has provided adequate clarification on reanalyzed samples. An additional dilution was used for the reanalysis of samples for which the initial result was outside of the calibration curve. This is acceptable. Hence, it is agreed by CHMP that the assay used for study CT-P13 1.6 Part 2 samples is accurate.

In addition, new MSD platform based methods were introduced for immunogenicity testing. The new ADA ECL ACE and new NAb ECL ACE methods used for ADA and NAb detection were adequately validated. A floating cut point approach was employed and the inter-assay precision %CV were calculated from normalized values (SNR). The MAH's approach is considered acceptable. The %CV of SNR for both methods were below 20%, and the assays are repeatibile.

Pharmacokinetics

The MAH presents pharmacokinetic, safety and efficacy data for Remsima SC in patients with active CD or active UC in support of the current variation application. Recently, within the application X/62, data for Remsima SC in patients with RA and in healthy subjects were presented.

Study CT-P13 1.6 was designed to find the optimal dose of Remsima SC and to demonstrate steady state C_{trough} non-inferiority of Remsima SC to Remsima IV in patients with active CD or active UC. C_{trough} was chosen as the exposure parameter of interest based on published scientific literature. Population PK (PPK) analyses were conducted to evaluate the impact of immunogenicity on clearance of and exposure to infliximab. AUC and C_{max} values are largely obtained using simulations with the PPK model. However, dense PK samples at steady state were collected in study CT-P13 1.6 Part 1, which allowed calculation of AUC using noncompartmental analyses (NCA).

In study CT-P13 1.6 Part 2, the observed mean infliximab C_{trough} at week 22 following Remsima SC 120 mg (in subjects <80 kg; n=44) and 240 mg (in subjects ≥80 kg; n=15) Q2W were approximately 6.8 fold and 8.9 fold higher, respectively, than following Remsima IV 5 mg/kg Q8W posology. The proposed posology is 120 mg SC Q2W for all patients with CD or UC; therefore, C_{trough} in subjects with body weight ≥80 kg will be lower than that observed in study CT-P13 1.6 Part 2 but still several folds higher than with the approved Remsima IV posology. Likewise, simulations using the PPK model indicated that infliximab $C_{trough,ss}$ of infliximab 120 mg SC Q2W was 2.63~10.62-fold higher than the $C_{trough,ss}$ of infliximab 5 mg/kg IV Q8W over weight from 50 kg to 150 kg, the difference decreasing with high body weights.

The mean infliximab AUC over 8 weeks at steady state ($AUC_{8W,ss}$) calculated using NCA in study CT-P13 1.6 Part 1 was 28251 h*μg/mL for dosing regimen 120 mg SC Q2W (n=10, mean weight 68.2 kg), approximately 1.35-fold higher compared with dosing regimen 5 mg/kg IV Q8W (n=11, mean weight 68.5 kg). For comparison, $AUC_{8W,ss}$ in RA patients treated with 120 mg SC Q2W in study CT-P13 3.5 Part 1 was 20927 h*μg/mL (n=162, mean weight 73.1 kg). Simulations using the PPK model indicated that the $AUC_{8w,ss}$ of infliximab 120 mg SC Q2W was 0.48~1.3-fold of $AUC_{8w,ss}$ infliximab 5 mg/kg IV Q8W in subjects without anti-infliximab antibodies.

PK/PD analyses

PK/PD analyses for efficacy were conducted using clinically observed response as efficacy endpoints. The analyses suggested body weight and positive ADA/NAB response to have negligible impact on efficacy in CD and UC patients following the SC dosing 120 mg Q2W. However, the efficacy endpoints used in PK/PD analyses were from open-label studies without placebo group. Furthermore, all subjects were treated with IV infliximab for the first 6 weeks and a large part of the clinical response was achieved before randomization to IV or SC arm. These limitations are reflected in poor precision of some model parameters, e.g. IC_{50} values. Because the PK/PD analyses for efficacy are not considered to be essential for the overall benefit/risk assessment, these issues are not pursued by CHMP.

Exploratory graphical PK/PD analyses for safety did not suggest strong associations between exposure and IRR and infections. The results should be interpreted cautiously due to limited number of events in patients treated with the SC formulation.

2.3.6. Conclusions on clinical pharmacology

The population PK model sufficiently described the pharmacokinetics of infliximab in the studied populations and it can be used to support the current application.

2.4. Clinical efficacy

2.4.1. Dose response studies

Dose response for CT-P13 SC was evaluated in RA patients in Study CT-P13 3.5 Part 1 and in CD patients in study CT-P13 1.6 Part 1. The results of these two open-label studies were assessed in connection with the line extension application (EMEA/H/C/002576/X/0062). Dose response regarding the other indications now sought is discussed in section 2.4.3.

2.4.2. Main studies

This indication extension variation is based on the whole clinical package presented in before. The efficacy and safety of CT-P13 SC has previously been studied in RA patients in Study CT-P13 3.5 Part 1 and 2 and in CD patients in Study CT-P13 1.6 Part 1. These studies have been assessed within the initial line extension application. This assessment report will focus on Part 2 of Study CT-P13 1.6. Extrapolation of the combined results from the whole clinical package to indications not studied (ankylosing spondylitis, psoriatic arthritis and psoriasis), is discussed in relevant PK, Efficacy and Safety sections and also in the benefit risk section.

Study CT-P13 1.6 Part 2

Methods

Study CT-P13 1.6 was an open-label, randomized, multicenter, parallel group, Phase I study designed to evaluate PK, efficacy, PD, and safety between CT-P13 SC and CT-P13 IV in patients with active Crohn's disease (CD) or active ulcerative colitis (UC) up to Week 54.

The study consisted of the following 2 parts, Part 1 and Part 2. Part 1 was designed to find the optimal dose of CT-P13 SC whereas Part 2 was designed to demonstrate that CT-P13 SC was non-inferior to CT-P13 IV, in terms of PK.

In the induction phase, all enrolled patients received two loading doses of 5mg/kg CT-P13 IV infusion at Weeks 0 and 2. Patients who received two full doses and for whom there were no safety concerns were randomly assigned to receive either CT-P13 SC or CT-P13 IV.

The duration of Study CT-P13 1.6 Part 2 was up to 62 weeks, which included screening (up to 6 weeks) and the last dose at 54 weeks, plus the following 2 weeks off-dose period, prior to the EOS visit.

Figure 20 Overview of Study Design of CT-P13 1.6 Part 2
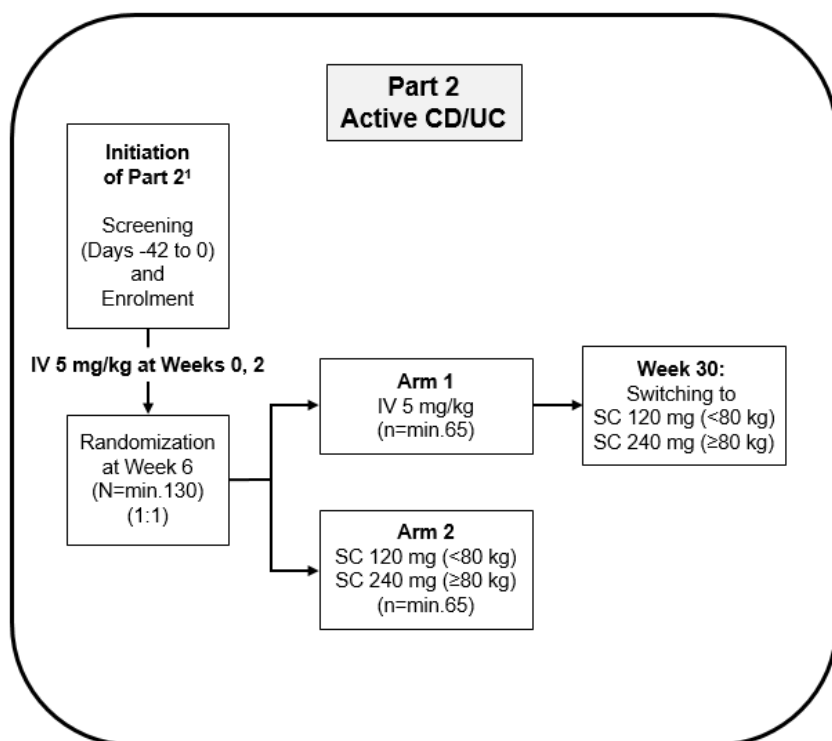
[1] Part 2 was initiated based upon the independent Data Safety Monitoring Board's review of the pharmacokinetics as well as efficacy, pharmacodynamics, and safety data found over the first 30 weeks from Part 1.
CD: Crohn's disease, IV: Intravenous, SC: Subcutaneous, UC: Ulcerative Colitis

Study participants

A total of 195 patients from 62 study centers in 16 countries were screened and 136 patients from 50 study centers in 15 countries were enrolled in this study. Study centers included university hospitals, county hospitals, and several forms of medical centers and private clinics.

Male or female patients aged 18 to 75 years old, inclusive, with active CD or UC of at least 3 months' disease duration prior to the first administration of the study drug (Day 0) were eligible. A patient who had active CD with a Crohn's Disease Activity Index (CDAI) score between 220 and 450 points or who had active UC with total Mayo score between 6 and 12 points with endoscopic subscore of ≥2 at screening was considered for enrolment in the study.

For CD patients, the patient had to have 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.

CD-patients met at least one of the following at screening:

- C-reactive protein (CRP) concentration >0.5 mg/dL

- Fecal calprotectin (FC) >100 µg/g

- Simplified Endoscopic Activity Score for CD (SES-CD) of ≥6 points for ileal-colonic CD or ≥4 points including ulcer score from at least 1 segment for ileal CD or colonic CD

For UC patients, the patient had to have been treated for active UC, but not responded despite conventional therapy including corticosteroids alone or in combination with 6-mercaptopurine (6-MP) or azathioprine (AZA) and medications containing 5-aminosalicylates (5-ASA), or who was intolerant to or had medical contraindications for such therapies. If the patient had more than 8 years of disease

duration of UC, the patient must have had documented evidence for absence of colorectal cancer or dysplasia by full colonoscopy examination performed within a year prior to the first administration of the study drug (Day 0).

The patient had to have stable doses of the following CD or UC treatments or currently not receiving them during the specified time frame: AZA or 6-MP at least for 8 weeks prior to the first administration of the study drug (Day 0); methotrexate (MTX) at least for 6 weeks prior to the first administration of the study drug (Day 0); oral corticosteroids at the equivalent dose of 20 mg/day of prednisone or less at least for 2 weeks prior to the first administration of the study drug (Day 0); oral budesonide at the dose of 6 mg/day or less at least for 4 weeks prior to the first administration of the study drug (Day 0); 5-ASA (oral 5-ASA for UC) at least for 4 weeks prior to the first administration of the study drug (Day 0).

Main exclusion criteria were as follows:

- Patient had previously received a biological agent for the treatment of CD or UC and/or a TNFα inhibitor for the treatment of other diseases.

- Patient had a current or past history of one of several specified infections, including HIV, hepatitis B or C, tuberculosis.

- Patient with CD had active entero-vesical, entero-retroperitoneal, entero-cutaneous, and entero-vaginal fistulae within 6 months prior to the first administration of the study drug (Day 0). Entero-enteral fistulae without clinical significant symptoms upon investigator's opinion and anal fistulae without draining problems were allowed.

- Patient with CD had more than three small-bowel resection procedures prior to the first administration of the study drug (Day 0).

- Patient with UC was taking rectally administered medications containing corticosteroids or 5-ASA for the treatment of UC within 2 weeks prior to screening.

Treatments

During the dose-loading phase, all enrolled patients initially received a 2-hour CT-P13 IV infusion at Weeks 0 and 2. Before treatment on 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 CT-P13 SC or CT-P13 IV.

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 (Arm 1): further 3 doses of CT-P13 IV were administered at Week 6 and every 8 weeks thereafter up to Week 22 (Weeks 14 and 22). CT-P13 IV was then switched to CT-P13 SC at Week 30 with CT-P13 SC dose based on body weight at Week 30. Further doses of study treatment with CT-P13 SC were given every 2 weeks up to Week 54.

- Subcutaneous 120 mg or 240 mg (Arm 2): CT-P13 SC dose based on body weight at Week 6 was administered by PFS at Week 6 and then every 2 weeks up to Week 54. Patients weighing < 80kg were given 120 mg and patients weighing ≥80 kg were given 240 mg.

For patients receiving CT-P13 SC 120 mg every 2 weeks, dose escalation to CT-P13 SC 240 mg every 2 weeks was allowed from Week 30 if the patient initially responded, but then lost response at the

Week 30, 38, 46, or 54 visits. Dose escalation was not allowed for patients receiving CT-P13 SC 240 mg every 2 weeks.

Concomitant medication

Immunomodulators (such as AZA, 6-MP, or MTX) were allowed if patients maintained stable doses for the specified time frame according to the inclusion criteria and the stable dose was maintained throughout the study.

Oral corticosteroids at the equivalent dose of 20 mg/day of prednisone or less were allowed if the patient had received a stable dose for at least 2 weeks prior to the first administration of the study drug (Day 0). For patients receiving corticosteroids at the first administration of the study drug (Day 0), corticosteroid treatment was kept up to Week 6 at the same dose level. After Week 6, a specific tapering regimen could be followed if the patient's condition had improved.

For CD, 5-ASA was allowed if patients maintained stable doses for the specified timeframe according to the inclusion criteria and the stable dose was maintained throughout the study.

For UC, only oral 5-ASA was allowed if patients maintained stable doses for the specified timeframe according to the inclusion criteria and the stable dose was maintained throughout the study.

The following medications and treatments during the study period were prohibited: antibiotics for the treatment of CD or UC and for UC patients, rectally administered medications containing corticosteroids or 5-ASA.

The CHMP considered that the use of a concomitant immunomodulatory medication was evenly distributed between treatment arms in both patient groups. Data on tapering of corticosteroid dose was not provided or included in efficacy estimands. In this small open-label setting, where efficacy was a secondary outcome, this was considered acceptable.

Objectives

The overall objective of this study was to evaluate pharmacokinetics (PK), efficacy, and safety between subcutaneous (SC) CT-P13 and intravenous (IV) CT-P13 in patients with inflammatory bowel disease (IBD). With this purpose, this study was divided into 2 parts, Part 1 and Part 2. The results from Part 1 of the study were presented in a separate report.

The study objectives of Part 2 are described as below:

Primary objective:

- 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).

Secondary objectives:

- To evaluate efficacy, PK, pharmacodynamics (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

Tertiary objectives:

- To evaluate genotypes as biomarkers (optional)
- To evaluate amino acids as biomarkers
- To evaluate patient overall satisfaction of CT-P13 IV and CT-P13 SC

Outcomes/endpoints

The primary endpoint for Study 1.6 Part 2 was $C_{trough,week22}$. PK endpoints are described in more detail in section 2.3.2.

The following secondary endpoints were assessed to evaluate efficacy:

Patients with active CD:

- 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 overall Simplified Endoscopic Activity Score for Crohn's Disease (SES-CD) score from the baseline value. (Weeks 22 and 54)

- Endoscopic remission, defined as an absolute SES-CD score of 2 points or less

- Short Inflammatory Bowel Disease Questionnaire (SIBDQ)

Patients with active UC:

- Clinical response, defined as a decrease from baseline in total Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point or an absolute subscore for rectal bleeding of 0 or 1

- Clinical response, defined as a decrease from baseline in partial Mayo score of at least 2 points, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point or an absolute subscore for rectal bleeding of 0 or 1

- Clinical remission, defined as a total Mayo score of 2 points or lower with no individual subscore exceeding 1 point, or partial Mayo score of 1 point or lower

- Mucosal healing, defined as absolute endoscopic subscore of 0 or 1 from Mayo Scoring System (MSS). (Weeks 22 and 54)

- SIBDQ

The following PD parameters were determined as secondary PD endpoints (up to EOS visit):

- Fecal calprotectin (FC)

- C-reactive protein (CRP)

Safety assessments were secondary endpoints and were performed on immunogenicity tests, hypersensitivity monitoring (including delayed hypersensitivity monitoring), vital sign measurements (including blood pressure, heart and respiratory rates, and body temperature), weight, body mass index (BMI), interferon-γ release assay (IGRA), diabetes mellitus assessment, congestive heart failure assessment, chest x-ray, hepatitis B and C and HIV -1 and -2 status, physical examination findings, electrocardiograms (ECG), adverse events (AEs; including serious AEs [SAEs]), AEs of special interest (infusion related reaction [IRR]/systemic injection reaction [SIR], delayed hypersensitivity, localised injection site reactions [ISRs], infections, and malignancies), clinical laboratory analyses, pregnancy testing, local site pain using the 100-mm Visual Analogue Scale (VAS), and signs and symptoms of tuberculosis (TB).

Sample size

The primary endpoint was the $C_{trough,week22}$ (pre-dose level at Week 22). A sample size of 104 patients (52 patients each in the SC 120/240 mg and IV 5 mg/kg treatment arms) provided 90% power to demonstrate non-inferiority of CT-P13 SC to CT-P13 IV based on the 95% one-sided CI for the geometric mean ratio of CT-P13 SC to CT-P13 IV in $C_{trough,week22}$. In the sample size calculation, non-inferiority margin of 80%, one-sided alpha level 5%, expected ratio of 1.3, and CV of 100% were assumed. Considering a 20% drop-out rate, a total of 130 patients (65 patients each in the SC 120/240 mg and IV 5 mg/kg treatment arms) were required.

A reassessment of sample size accounting for the actual ratio of geometric means and CV was made using the results from Part 1. The sample size was not to be decreased from the initial 130 total sample size, but could be increased up to 200 patients in case that actual ratio of geometric means decreased to 1.18 or actual CV increased up to 140%. The minimum sample size was determined as initial 130 total, considering DSMB's recommendation based upon the review of PK, efficacy, PD, and safety data found over the first 30 weeks from Part 1 of the study.

Randomisation

An interactive web response system (IWRS) was used for the randomisation at Week 6. The randomisation was stratified by 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 or partial Mayo score for UC), body weight at Week 6 (<80 kg or ≥80 kg), and disease (CD or UC). The randomisation numbers were blocked, and within each block the same number of patients was allocated to each treatment arm. The block size, four, was not revealed.

Initially, per protocol amendment 1, the body weight cut-off was 100 kg, thus the stratification principle was changed during the conduct of the trial.

Blinding (masking)

Blinding was not included in Part 2 of the study, because it was an open-label study.

Statistical methods

The principles of the statistical analyses were described in the protocol amendment 1 (17Jan2017), which was issued before first patient first visit. The details were further described in SAP (final version 15Jan2020).

There were six analysis populations: intent-to-treat (ITT), all-randomized, PK, PD, efficacy, and safety populations. Analysis of the ITT population and all-randomized population was performed according to the treatment they were randomized to at Week 6. The other populations were analysed according to actual treatment arm. There was no difference in actual and randomised treatments.

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 primary PK endpoint of the $C_{trough,week22}$ (pre-dose level at Week 22) was analysed in patients who received all doses (full) of study drug up to Week 22 (prior to Week 22) in the PK

population. A patient was considered as receiving full dose if the actual administered dose (mg) of the patient was greater than or equal to 95% of prescribed dose (mg).

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 (FC or CRP) 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 (in respective indication) result after Week 6 treatment.

The safety population consisted of all patients who received at least one dose (full or partial) of study drug at Week 6 or thereafter.

The primary PK endpoint, $C_{trough,week22}$ (pre-dose level at Week 22) was analysed using an analysis of covariance (ANCOVA) as described in section 2.3.2.

All other endpoints were summarized in terms of descriptive statistics. Numerical endpoints were reported as observed, thus, no imputation was applied. For response type of endpoints, the percentage of responders was calculated using the number of subjects in the specific analysis population as denominator.

Results

Participant flow

Figure 21 Patient Disposition: All-Randomized Population
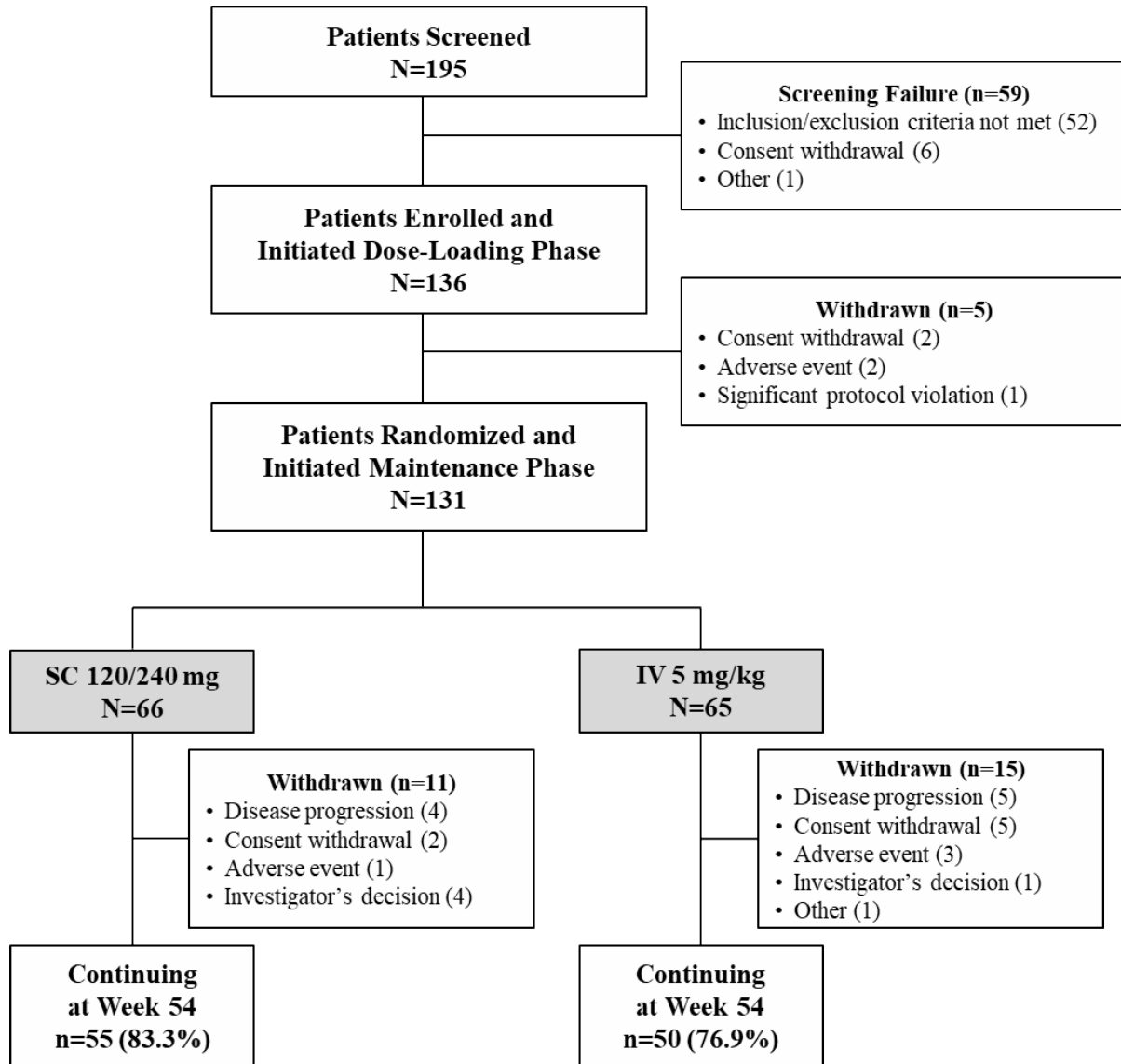
IV: Intravenous, SC: Subcutaneous

136 patients were enrolled in the study and were treated in the dose-loading phase. 131 patients initiated the maintenance phase at Week 6 (66 and 65 patients in the SC 120/240 mg and IV 5 mg/kg treatment arms, respectively). Of the patients initiating the maintenance phase 53 were CD patients and 78 were UC patients. The majority of patients in each treatment arm were continuing the study at Week 54. During the maintenance phase, 11 [16.7%] patients in the SC 120/240 mg arm and 15 [23.1%] patients in the IV 5 mg/kg treatment arm discontinued the study.

During the maintenance phase, 13 CD patients discontinued (6 [21.4%] and 7 [28.0%] patients in the SC 120/240 mg and IV 5 mg/kg treatment arms, respectively) and 13 UC patients discontinued (5 [13.2%] and 8 [20.0%] patients in the SC 120/240 mg and IV 5 mg/kg treatment arms, respectively).

For patients who dropped out for any reason, all study procedures were performed on the day of withdrawal (or the day after withdrawal) and all attempts were made to complete all EOS assessments at planned time points of the EOS visit.

Recruitment

The study period was 07 May 2018 (first patient's first study drug administration date) to 16 September 2019 (last patient's Week 54 visit). The Week 54 visit date of the last patient was 16 September 2019 and after further data cleaning, the database was locked on 25 October 2019.

Baseline data

Demographic characteristics at screening and stratification details are summarised for the all-randomised population in Table 16.

Table 16 Demographics and Stratification Details at screening: All-Randomised Population

Parameter	CT-P13 IV 5 mg/kg (N=65)	CT-P13 SC 120/ 240 mg (N=66)	Total (N=131)
Demographic Characteristics			
Age (years)			
Mean (SD)	39.4 (14.02)	37.8 (15.13)	38.6 (14.55)
Median	36.0	33.0	36.0
Min, Max	18, 70	18, 69	18, 70
Sex, no. (%)			
Male	35 (53.8)	36 (54.5)	71 (54.2)
Female	30 (46.2)	30 (45.5)	60 (45.8)
Race, no. (%)			
Caucasian/ White	60 (92.3)	62 (93.9)	122 (93.1)
Asian/ Oriental	4 (6.2)	3 (4.5)	7 (5.3)
Other	1 (1.5)	1 (1.5)	2 (1.5)
Screening height (cm)			
Mean (SD)	172.2 (9.05)	170.8 (8.65)	171.5 (8.84)
Median	171.0	170.0	171.0
Min, Max	157.0, 198.0	144.0, 187.0	144.0, 198.0
Screening weight (kg)			
Mean (SD)	72.0 (16.92)	69.4 (14.51)	70.7 (15.74)
Median	69.0	66.1	68.0
Min, Max	43.2, 116.2	45.2, 117.0	43.2, 117.0
Screening BMI (kg/m^2)			
Mean (SD)	24.2 (4.68)	23.7 (4.07)	23.9 (4.37)
Median	23.6	23.6	23.6
Min, Max	15.3, 38.3	16.4, 34.9	15.3, 38.3

Parameter	CT-P13 IV 5 mg/kg (N=65)	CT-P13 SC 120/ 240 mg (N=66)	Total (N=131)
Stratification Factor			
Current use of treatment with AZA or 6-MP or MTX			
Used	29 (44.6)	29 (43.9)	58 (44.3)
Not used	36 (55.4)	37 (56.1)	73 (55.7)
Disease			
CD	25 (38.5)	28 (42.4)	53 (40.5)
UC	40 (61.5)	38 (57.6)	78 (59.5)
Clinical Response at Week 6[1]			
Responder	52 (80.0)	49 (74.2)	101 (77.1)
Non-responder	13 (20.0)	17 (25.8)	30 (22.9)
Body Weight at Week 6			
< 80 kg	45 (69.2)	48 (72.7)	93 (71.0)
≥ 80 kg	20 (30.8)	18 (27.3)	38 (29.0)

[1] Clinical response as defined by CDAI-70 for CD or partial Mayo score for UC.
6-MP: 6-mercaptopurine, AZA: Azathioprine, BMI: Body mass index, CD: Crohn's disease, CDAI: Crohn's disease activity index, IV: Intravenous, Max: Maximum, Min: Minimum, MTX: Methotrexate, SC: Subcutaneous, SD: Standard deviation, UC: Ulcerative colitis

Baseline data in CD patients

In CD patients, the mean (SD) age of patients was 38.4 (15.78) and 35.5 (11.41) years in the SC 120/240 mg and IV 5 mg/kg treatment arms, respectively. The proportion of male patients compared to the female patients were similar in total (27 [50.9%] male and 26 [49.1%] female patients). However, in the SC treatment arm 16/28 patients (57.1%) were male. In the IV treatment arm 11/25 (44%) were male. The mean weight was 68.93 (16.32) kg.

Baseline CDAI scores were similar in the two treatment arms (296.38 and 294.75 in the SC and IV arms, respectively). However, at randomisation, after 6 weeks of identical IV treatment, patients in the SC arm had higher CDAI scores. In the SC treatment arm 75% of patients were responders at week 6, while 84% of patients in the IV arm were responders. The difference between treatment arms was driven mainly by patients weighing ≥ 80kg, i.e. patients who would subsequently receive SC 240 mg. These patients had a significantly higher baseline CDAI score than patients with a body weight <80kg (320.4 vs. 286.8). Baseline CDAI score for patients in the IV arm with a body weight ≥ 80kg was 296.7.

Baseline data in UC patients

In UC patients, the mean (SD) age of patients was 37.4 (14.83) and 41.8 (15.06) years in the SC 120/240 mg and IV 5 mg/kg treatment arms, respectively. The proportion of male patients were slightly higher than the female (44 [56.4%] male and 34 [43.6%] female patients). In the SC arm 52,6% were male, while 60% were male in the IV arm. The mean weight was 71.93 (15.32) kg.

In the SC treatment arm 73.7% of patients were responders at week 6, while 77.5% of patients in the IV arm were responders. Baseline total Mayo scores were similar in the two treatment arms (7.9 and 8.3 in the SC and IV arms, respectively).

Medical history, prior medication and concomitant treatment

The total number of medical histories at screening was higher in the SC 120/240 mg treatment arm (277 and 180 medical histories reported in the SC 120/240 mg and IV 5 mg/kg treatment arms, respectively). Gastrointestinal disorders were recorded for 45.5% of patients in the SC arm and 35.4% on the IV arm. In the SC arm, 12 patients (18.2%) had a recording of anaemia, in the IV arm, 7 patients (10.8%).

In CD patients, a total of 46 (86.8%) patients had taken at least 1 prior medication. The most commonly reported prior medications by drug class were corticosteroids for systemic use (15 [53.6%] and 13 [52.0%] patients in the SC 120/240 mg and IV 5 mg/kg treatment arms, respectively). During maintenance phase, the most commonly reported concomitant medications were corticosteroids for systemic use (15 [53.6%] and 16 [64.0%] patients in the SC and IV treatment arms, respectively).

In UC patients, a total of 71 (91.0%) patients had taken at least 1 prior medication. The most commonly reported prior medications by drug class were antidiarrheal, intestinal anti-inflammatory/anti-infective agents (24 [63.2%] and 23 [57.5%] patients in the SC 120/240 mg and IV 5 mg/kg treatment arms, respectively). During maintenance phase, the most commonly reported concomitant medications were antidiarrheal, intestinal anti-inflammatory/anti-infective agents (35 [92.1%] and 38 [95.0%] patients in the SC and IV treatment arms, respectively). Corticosteroids for systemic use were used by 52.6% and 52.5%of patients prior to study initiation, while they were used by 14 (36.8%) and 28 (70%) patients in the SC and IV treatment arms, respectively during maintenance phase.

Among CD patients, 50.9% had a concomitant immunosuppressant (AZA or MTX or hydroxychloroquine sulfate); 15/28 (53.6%) in the SC arm and 12/25 (48%) in the IV arm. Among UC patients, the amount of patients with concomitant immunosuppressant medication (AZA or cyclosporine) was 39.7%; SC 14/38 (36.8%) in the SC arm and 17/40 (42.5%) in the IV arm. In addition, one patient in the UC group used mercaptopurine, which was classified as an antineoplastic agent.

Hence, data on patients treated without concomitant immunosuppressant is still limited (13 CD patients and 24 UC patients treated with Remsima SC).

Numbers analysed

The number of patients in each population of analysis are presented in Table 17 For further description of the populations see section on statistical methods.

Table 17 Populations of Analysis

Number of patients	CT-P13 SC 120/ 240 mg	CT-P13 IV 5 mg/kg	Total
Intent-to-treat population	-	-	136
Intent-to-treat population – CD	-	-	57
Intent-to-treat population – UC	-	-	79
All-randomized population	66	65	131
All-randomized population – CD	28	25	53
All-randomized population – UC	38	40	78
Pharmacokinetic population	63	64	127
Pharmacokinetic population – CD	27	25	52
Pharmacokinetic population – UC	36	39	75
Pharmacodynamic population	66	64	130

Number of patients	CT-P13 SC 120/ 240 mg	CT-P13 IV 5 mg/kg	Total
Pharmacodynamic population – CD	28	25	53
Pharmacodynamic population – UC	38	39	77
Efficacy population	66	64	130
Efficacy population – CD	28	25	53
Efficacy population – UC	38	39	77
Safety population	66	65	131
Safety population – CD	28	25	53
Safety population – UC	38	40	78

Note: The randomized treatment at Week 6 was used for the all-randomized population. Actual treatment was used for pharmacokinetic, pharmacodynamic, efficacy, and safety populations.
CD: Crohn's disease, IV: intravenous, SC: subcutaneous, UC: ulcerative colitis

Outcomes and estimation

Efficacy in Patients with Active Crohn's Disease

Efficacy was the secondary endpoint of the study, where active CD was assessed by the evaluation of CDAI, colonoscopy (SES-CD), and SIBDQ. In addition, CRP and faecal calprotectin were assessed as pharmacodynamic parameters.

CDAI

The proportions of CD patients achieving clinical response according to the CDAI-70 and CDAI-100 criteria in the two treatment arms up to Week 54 are shown in Table 18 and the proportion of patients achieving clinical remission are shown in Table 20. Clinical remission was defined as an absolute CDAI score < 150 points.

Table 18 Proportions of Patients Achieving Clinical Response according to CDAI-70 and CDAI-100 Criteria (95% CI) based on the Adjusted CDAI Score in Study CT-P13 1.6 Part 2: Efficacy Population-CD

Parameter Visit	CT-P13 IV 5 mg/kg (N=25)	CT-P13 SC 120/ 240 mg (N=28)	CT-P13 SC 120 mg (N=20)
CDAI-70			
Week 6[1]			
Responder, n (%)	21 (84.0)	21 (75.0)	17 (85.0)
Exact 95% CI of Proportion	63.92, 95.46	55.13, 89.31	62.11, 96.79
Week 22			
Responder, n (%)	21 (84.0)	22 (78.6)	18 (90.0)
Exact 95% CI of Proportion	63.92, 95.46	59.05, 91.70	68.30, 98.77
Week 30			
Responder, n (%)	17 (68.0)	19 (67.9)	15 (75.0)
Exact 95% CI of Proportion	46.50, 85.05	47.65, 84.12	50.90, 91.34
Week 54			
Responder, n (%)	17 (68.0)	20 (71.4)	15 (75.0)
Exact 95% CI of Proportion	46.50, 85.05	51.33, 86.78	50.90, 91.34
CDAI-100			
Week 6[1]			
Responder, n (%)	18 (72.0)	15 (53.6)	14 (70.0)
Exact 95% CI of Proportion	50.61, 87.93	33.87, 72.49	45.72, 88.11
Week 22			
Responder, n (%)	20 (80.0)	21 (75.0)	17 (85.0)
Exact 95% CI of Proportion	59.30, 93.17	55.13, 89.31	62.11, 96.79
Week 30			
Responder, n (%)	16 (64.0)	19 (67.9)	15 (75.0)
Exact 95% CI of Proportion	42.52, 82.03	47.65, 84.12	50.90, 91.34
Week 54			
Responder, n (%)	16 (64.0)	18 (64.3)	14 (70.0)
Exact 95% CI of Proportion	42.52, 82.03	44.07, 81.36	45.72, 88.11

Note: A patient was defined as having a CDAI-70 response if there was a decrease in CDAI score of ≥ 70 points from the baseline value. A patient was defined as having a CDAI-100 response if there was a decrease in CDAI score of ≥ 100 points from the baseline value. The baseline value was considered to be the last non-missing value before the first administration.

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

CI: Confidence interval, CDAI: Crohn's disease activity Index, IV: Intravenous, SC: Subcutaneous

Table 19 Proportion of Patients Achieving Clinical Response according to Adjusted CDAI-70 Criteria for 120mg and 240mg SC separately

Visit, n (%)	CT-P13 IV 5 mg/kg (N=25)	CT-P13 SC 120/ 240 mg (N=28)	CT-P13 SC 120 mg (N=20)	CT-P13 SC 240mg (N=8)
Week 2	14 (56.0)	16 (57.1)	12 (60.0)	4 (50.0)
Exact 95% CI of Proportion	34.93, 75.60	37.18, 75.54	36.05, 80.88	15.70, 84.30
Week 6	21 (84.0)	21 (75.0)	17 (85.0)	4 (50.0)
Exact 95% CI of Proportion	63.92, 95.46	55.13, 89.31	62.11, 96.79	15.70, 84.30
Week 14	22 (88.0)	22 (78.6)	17 (85.0)	5 (62.5)
Exact 95% CI of Proportion	68.78, 97.45	59.05, 91.70	62.11, 96.79	24.49, 91.48
Week 22	21 (84.0)	22 (78.6)	18 (90.0)	4 (50.0)
Exact 95% CI of Proportion	63.92, 95.46	59.05, 91.70	68.30, 98.77	15.70, 84.30
Week 30	17 (68.0)	19 (67.9)	15 (75.0)	4 (50.0)
Exact 95% CI of Proportion	46.50, 85.05	47.65, 84.12	50.90, 91.34	15.70, 84.30
Week 38	17 (68.0)	21 (75.0)	16 (80.0)	5 (62.5)
Exact 95% CI of Proportion	46.50, 85.05	55.13, 89.31	56.34, 94.27	24.49, 91.48
Week 46	14 (56.0)	20 (71.4)	16 (80.0)	4 (50.0)
Exact 95% CI of Proportion	34.93, 75.60	51.33, 86.78	56.34, 94.27	15.70, 84.30
Week 54	17 (68.0)	20 (71.4)	15 (75.0)	5 (62.5)
Exact 95% CI of Proportion	46.50, 85.05	51.33, 86.78	50.90, 91.34	24.49, 91.48

Note: A patient is defined as having a CDAI-70 response if there is a decrease in CDAI score of 70 points or more from the baseline value. The baseline value was considered to be the last non-missing value before the first administration. Weight at Week 6 was used for categorization of SC group. CI=Confidence Interval.

At week 22 the mean response rate was slightly lower in the SC 120/240 arm compared to the IV arm. However, by week 30, the rates were similar. In the 120mg arm (the proposed dose) the response rate after week 6 was constantly slightly higher or similar compared to the IV arm.

Table 19 shows that the proportion of patients reaching clinical response was significantly lower among patients weighing ≥80 kg than among patients weighing <80 kg in the SC arm. Their response rates remained lower compared to <80kg SC patients and compared to average IV patients throughout the study.

Table 20 Proportions of Patients Achieving Clinical Remission based on Adjusted CDAI Score (95% CI) in Study CT-P13 1.6 Part 2: Efficacy Population-CD

Visit, n (%)	CT-P13 IV 5 mg/kg (N=25)	CT-P13 SC 120/ 240 mg (N=28)	CT-P13 SC 120 mg (N=20)
Week 6[1]	11 (44.0)	14 (50.0)	12 (60.0)
Exact 95% CI of Proportion	24.40, 65.07	30.65, 69.35	36.05, 80.88
Week 22	15 (60.0)	16 (57.1)	13 (65.0)
Exact 95% CI of Proportion	38.67, 78.87	37.18, 75.54	40.78, 84.61
Week 30	14 (56.0)	17 (60.7)	13 (65.0)
Exact 95% CI of Proportion	34.93, 75.60	40.58, 78.50	40.78, 84.61
Week 54	14 (56.0)	15 (53.6)	12 (60.0)
Exact 95% CI of Proportion	34.93, 75.60	33.87, 72.49	36.05, 80.88

Note: Clinical remission was defined as an absolute CDAI score < 150 points.
[1] Results at Week 6 were obtained following 2 IV infusions in the Dose-Loading Phase.
CDAI: Crohn's disease activity index, CI: Confidence interval, IV: Intravenous, SC: Subcutaneous

Figure 22 Mean of Actual Score and Change from Baseline of Adjusted CDAI Score (95% CI) in Study CT-P13 1.6 Part 2: Efficacy Population-CD
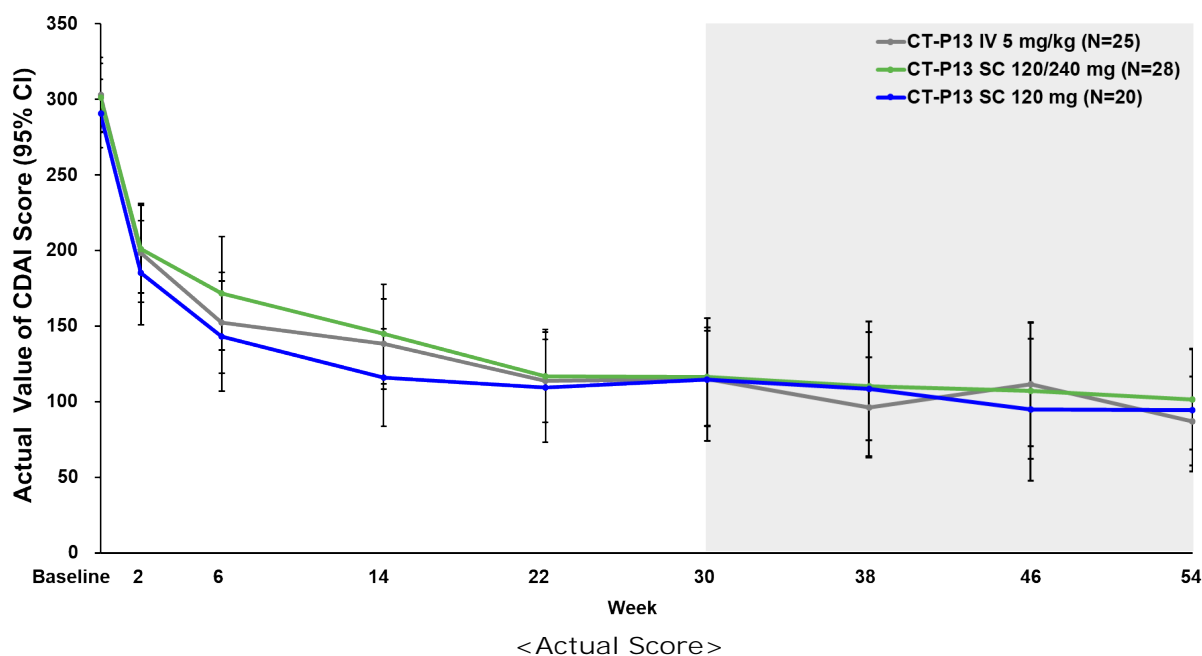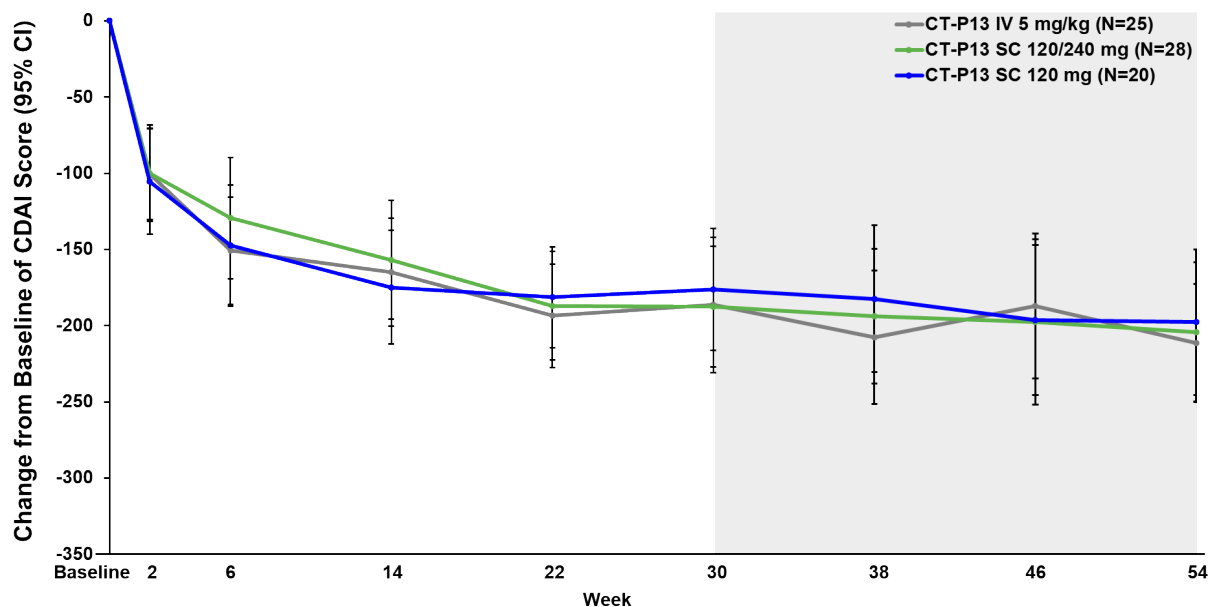
<Actual Score>

\<Change from Baseline\>

Note: Shaded area represents patients in the CT-P13 IV 5 mg/kg arm switched to CT-P13 SC treatment at Week 30.
CDAI: Crohn's disease activity index, CI: Confidence interval, IV: Intravenous, SC: Subcutaneous

Figure 22 shows that patients who received 240mg SC treatment (per protocol ≥80kg) have a less favourable outcome compared to the combined SC treatment arm. This is explained by the fact that these eight patients had poorer baseline CDAI scores than patients in the other groups and they also showed a poorer response than other patients in the SC arm and compared to the whole IV arm. However, compared to patients in the IV arm with body weight ≥80kg, their response was not worse according to actual values of CDAI score (Table 29). Baseline CDAI among SC patients ≥80kg was 326.71; among IV patients ≥80kg baseline CDAI was 305.86.

Colonoscopy (SES-CD) and SIBDQ

The mean (SD) overall SES-CD scores were similar at baseline and decreased at Week 22 in a similar trend between the 2 treatment arms.

Table 21 Mean (SD) Actual Values and Changes from Baseline of Overall SES-CD Score: Efficacy Population – CD

Visit Statistics	CT-P13 IV 5 mg/kg (N=25)		CT-P13 SC 120/ 240 mg (N=28)		CT-P13 SC 120 mg (N=20)	
	Actual Value	CfB	Actual Value	CfB	Actual Value	CfB
Baseline						
n	16	-	21	-	14	-
Mean (SD)	8.1 (5.83)	-	10.9 (8.28)	-	9.6 (7.83)	-
95% CI of Mean	4.96, 11.17	-	7.09, 14.63	-	5.12, 14.16	-
Week 22						
n	12	7	19	15	15	12
Mean (SD)	4.6 (3.97)	-4.4 (4.76)	3.2 (2.43)	-8.9 (7.59)	3.2 (2.68)	-7.8 (6.37)
95% CI of	2.06, 7.10	-8.83, -0.03	1.99, 4.33	-13.07, -4.67	1.72, 4.68	-11.80, -3.70

Visit Statistics	CT-P13 IV 5 mg/kg (N=25)		CT-P13 SC 120/ 240 mg (N=28)		CT-P13 SC 120 mg (N=20)	
	Actual Value	CfB	Actual Value	CfB	Actual Value	CfB
Mean						
Week 54						
n	14[1]	10	17	13	13	9
Mean (SD)	2.7 (2.79)	-6.4 (4.90)	2.2 (2.36)	-10.2 (8.75)	2.2 (2.62)	-9.8 (7.78)
95% CI of Mean	1.11, 4.32	-9.91, -2.89	1.02, 3.45	-15.44, -4.86	0.65, 3.81	-15.75, -3.80

CD: Crohn's disease, CI: Confidence interval, IV: Intravenous, CfB: Change from baseline, SC: Subcutaneous, SD: Standard deviation, SES-CD: Simplified endoscopic activity score for Crohn's disease

The proportion of patients achieving endoscopic remission according to the SES-CD score at Week 22 was slightly higher in the SC 120/240 mg treatment arm compared to the IV 5 mg/kg treatment arm.

Table 22 Proportion of Patients Achieving Endoscopic Remission According to the SES-CD Score: Efficacy Population – CD

Visit, n (%)	CT-P13 IV 5 mg/kg (N=25)	CT-P13 SC 120/ 240 mg (N=28)	CT-P13 SC 120 mg (N=20)
Week 22	1/7 (14.3)	5/14 (35.7)	4/11 (36.4)
Exact 95% CI of Proportion	0.36, 57.87	12.76, 64.86	10.93, 69.21
Week 54	5/10 (50.0)	6/12 (50.0)	4/8 (50.0)
Exact 95% CI of Proportion	18.71, 81.29	21.09, 78.91	15.70, 84.30

CD: Crohn's disease, CI: Confidence interval, IV: Intravenous, SC: Subcutaneous, SES-CD: Simplified endoscopic activity score for Crohn's disease

The unblinded local and the blinded centralised assessments of SES-CD score resulted in similar outcomes.

The mean scores of Short Inflammatory Bowel Disease Questionnaire (SIBDQ) were similar between the two treatment arms and similar levels of improvement in the quality were observed in both treatment arms up to Week 54.

CRP and FC concentrations

The mean change from baseline in CRP was similar between the 2 treatment arms up to Week 22 with slightly greater decrease in the SC 120/240 mg treatment arm than the IV 5 mg/kg treatment arm at Week 30.

Baseline FC levels varied in CD patients but decreased to similar levels in the two treatment arms after CT-P13 administration and well maintained up to Week 54.

Figure 23 Mean (+/- SE) of C - Reactive Protein, Pharmacodynamic Population - CD patients
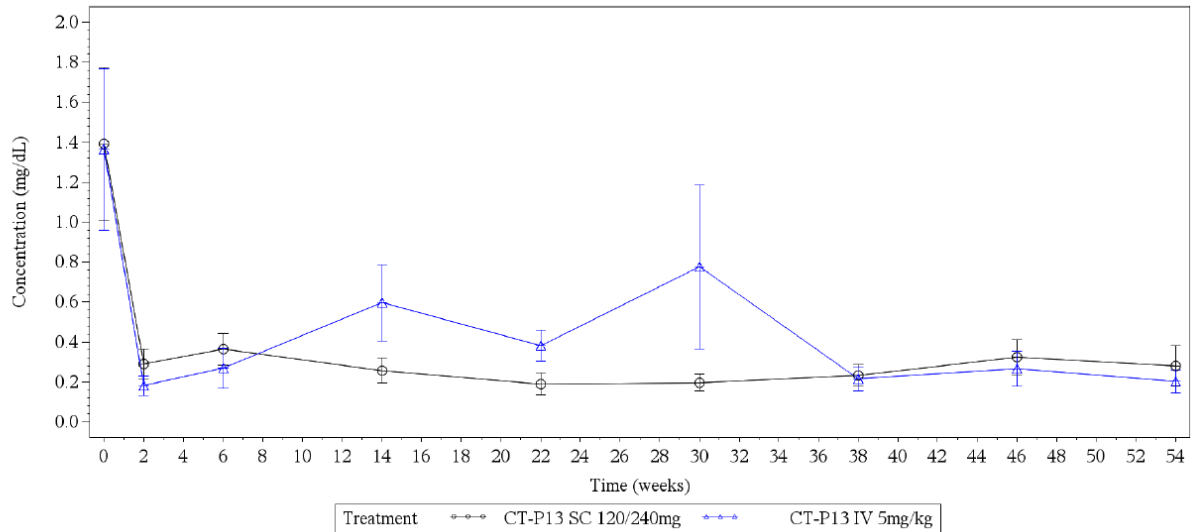
Figure 24 Mean (+/- SE) of Fecal Calprotectin, Pharmacodynamic Population - CD patients
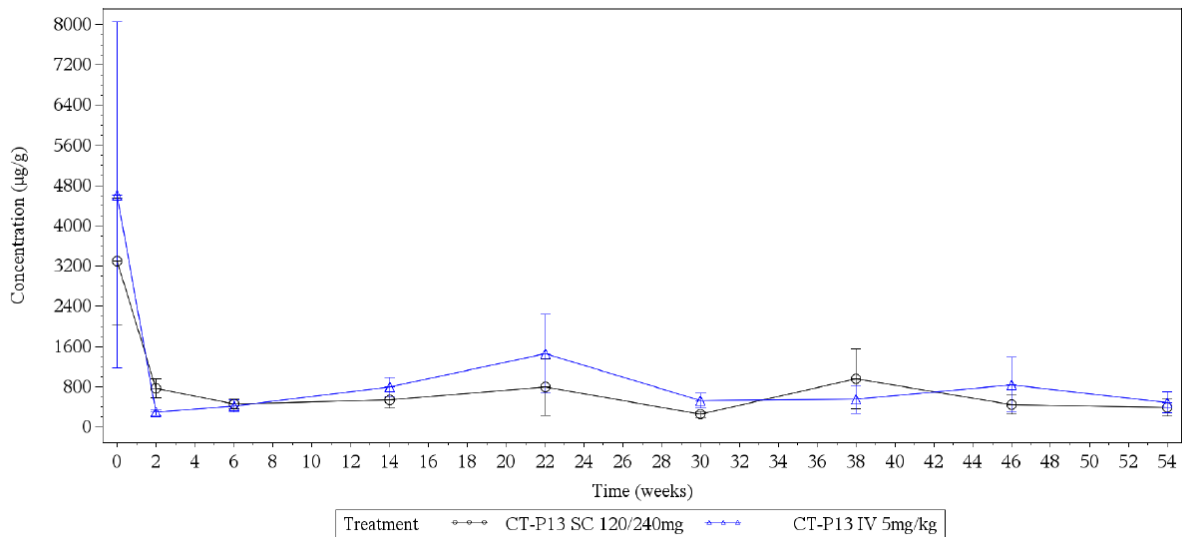
The FcRn genotypes were provided in the final study report. Genotype results are summarized for the safety population in the table below. Based on the data provided, the treatment arms were well balanced in terms of FcRn genotype.

Table 23 Genotype results

Test (Visit) Result	CT-P13 IV 5mg/kg (N=65)	CT-P13 SC 120/ 240mg (N=66)	Total (N=131)
FcRN (Week 0)			
VNTR2/VNTR2	0	1 (1.5%)	1 (0.8%)
VNTR2/VNTR3	7 (10.8%)	8 (12.1%)	15 (11.5%)
VNTR3/VNTR3	41 (63.1%)	38 (57.6%)	79 (60.3%)
VNTR3/VNTR4	1 (1.5%)	0	1 (0.8%)

Note: Percentages are calculated by using the number of patients in the Safety Population as the denominator.

Efficacy in Patients with Active Ulcerative Colitis

Active UC was assessed by the evaluation of Mayo scoring system, mucosal healing, and SIBDQ. In addition, CRP and faecal calprotectin were assessed as pharmacodynamic parameters.

Mayo score

The mean scores for total and partial Mayo scores were similar between the 2 treatment arms at baseline. At Week 22, there was a slightly greater improvement in the SC 120/240 mg treatment arm in terms of both response and remission rates according to both total and partial Mayo scores. After switching to CT-P13 SC 120/240 mg at Week 30 in the IV 5 mg/kg treatment arm, the response and remission rates were comparable between the two treatment arms up to Week 54.

Table 24 Proportion of Patients Achieving Clinical Response According to the Mayo Scoring System: Efficacy Population – UC

Parameter Visit, n (%)	CT-P13 IV 5 mg/kg (N=39)	CT-P13 SC 120/ 240 mg (N=38)	CT-P13 SC 120 mg (N=28)
Total Mayo Score			
Week 22	17 (43.6)	24 (63.2)	15 (53.6)
Exact 95% CI of Proportion	27.81, 60.38	45.99, 78.19	33.87, 72.49
Week 54	24 (61.5)	24 (63.2)	18 (64.3)
Exact 95% CI of Proportion	44.62, 76.64	45.99, 78.19	44.07, 81.36
Partial Mayo Score			
Week 2	25 (64.1)	20 (52.6)	13 (46.4)
Exact 95% CI of Proportion	47.18, 78.80	35.82, 69.02	27.51, 66.13
Week 6[1]	31 (79.5)	28 (73.7)	19 (67.9)
Exact 95% CI of Proportion	63.54, 90.70	56.90, 86.60	47.65, 84.12
Week 14	33 (84.6)	30 (78.9)	21 (75)
Exact 95% CI of Proportion	69.47, 94.14	62.68, 90.45	55.13, 89.31
Week 22	30 (76.9)	32 (84.2)	22 (78.6)
Exact 95% CI of Proportion	60.67, 88.87	68.75, 93.98	59.05, 91.70
Week 30	29 (74.4)	33 (86.8)	23 (82.1)
Exact 95% CI of Proportion	57.87, 86.96	71.91, 95.59	63.11, 93.94
Week 38	31 (79.5)	33 (86.8)	23 (82.1)
Exact 95% CI of Proportion	63.54, 90.70	71.91, 95.59	63.11, 93.94
Week 46	30 (76.9)	32 (84.2)	23 (82.1)
Exact 95% CI of Proportion	60.67, 88.87	68.75, 93.98	63.11, 93.94
Week 54	28 (71.8)	31 (81.6)	22 (78.6)
Exact 95% CI of Proportion	55.13, 85.00	65.67, 92.26	59.05, 91.70

Note: A patient is defined as having a clinical response according to total Mayo score if there is a decrease from baseline in total Mayo score at least 3 points and at least 30%, with an accompanying decrease from baseline in the subscore for rectal bleeding of at least 1 point or absolute subscore for rectal bleeding of 0 or 1. A patient is defined as having a clinical response according to partial Mayo score if there is a decrease from baseline in partial Mayo score at least 2 points, with an accompanying decrease from baseline in the subscore for rectal bleeding of at least 1 point, or an absolute subscore for rectal bleeding of 0 or 1. Weight at Week 6 was used for categorization of SC group.
[1] Results at Week 6 were obtained following 2 IV infusions in the Dose-Loading Phase.
CI: Confidence interval, IV: Intravenous, SC: Subcutaneous, UC: Ulcerative colitis

Table 25 Proportion of Patients Achieving Clinical Remission According to the Mayo Scoring System: Efficacy Population – UC

Parameter Visit, n (%)	CT-P13 IV 5 mg/kg (N=39)	CT-P13 SC 120/ 240 mg (N=38)	CT-P13 SC 120 mg (N=28)
Total Mayo Score			
Week 22	10 (25.6)	17 (44.7)	11 (39.3)
Exact 95% CI of Proportion	13.04, 42.13	28.62, 61.70	21.50, 59.42
Week 54	19 (48.7)	20 (52.6)	15 (53.6)
Exact 95% CI of Proportion	32.42, 65.22	35.82, 69.02	33.87, 72.49
Partial Mayo Score			
Week 2	7 (17.9)	9 (23.7)	7 (25.0)
Exact 95% CI of Proportion	7.54, 33.53	11.44, 40.24	10.69, 44.87
Week 6[1]	12 (30.8)	14 (36.8)	10 (35.7)
Exact 95% CI of Proportion	17.02, 47.57	21.81, 54.01	18.64, 55.93
Week 14	17 (43.6)	17 (44.7)	10 (35.7)
Exact 95% CI of Proportion	27.81, 60.38	28.62, 61.70	18.64, 55.93
Week 22	15 (38.5)	23 (60.5)	14 (50.0)
Exact 95% CI of Proportion	23.36, 55.38	43.39, 75.96	30.65, 69.35
Week 30	21 (53.8)	26 (68.4)	18 (64.3)
Exact 95% CI of Proportion	37.18, 69.91	51.35, 82.50	44.07, 81.36
Week 38	25 (64.1)	26 (68.4)	18 (64.3)
Exact 95% CI of Proportion	47.18, 78.80	51.35, 82.50	44.07, 81.36
Week 46	26 (66.7)	26 (68.4)	18 (64.3)
Exact 95% CI of Proportion	49.78, 80.91	51.35, 82.50	44.07, 81.36
Week 54	24 (61.5)	26 (68.4)	18 (64.3)
Exact 95% CI of Proportion	44.62, 76.64	51.35, 82.50	44.07, 81.36

Note: Clinical remission according to total Mayo score is defined as a total Mayo score of 2 points or lower with no individual subscore exceeding 1 point. Clinical remission according to partial Mayo socre is defined as a parital Mayo of 1 point or lower.
[1] Results at Week 6 were obtained following 2 IV infusions in the Dose-Loading Phase.
CI: Confidence interval, IV: Intravenous, SC: Subcutaneous, UC: Ulcerative colitis

Figure 25 Change from Week 6 of Partial Mayo Score (95% CI) Efficacy Population – UC
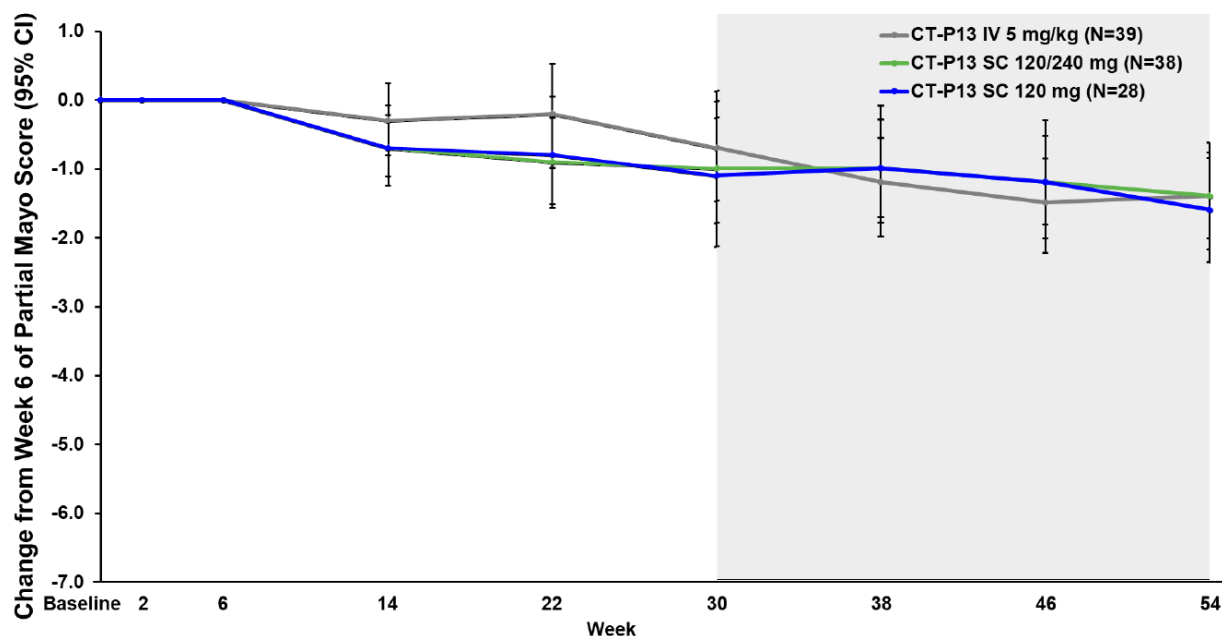
Note: Shaded area represents patients in the CT-P13 IV 5 mg/kg arm switched to CT-P13 SC treatment at Week 30.
CI: Confidence interval, IV: Intravenous, SC: Subcutaneous, UC: Ulcerative colitis

The unblinded local and the blinded centralised assessments of mucosal healing resulted in similar Mayo score and remission outcomes.

Mucosal healing

Mucosal healing was assessed by endoscopic subscore of the MSS which evaluated the degree of endoscopic rectal inflammation based on a 4-point scale according to flexible proctosigmoidoscopy findings. Mucosal healing was defined as an absolute endoscopic subscore of 0 or 1.

The proportion of patients achieving mucosal healing was higher in the CT-P13 SC 120/ 240 mg arm than the CT-P13 IV 5 mg/kg arm at Week 22. After switching from CT-P13 IV to CT-P13 SC treatment at Week 30 in the CT-P13 IV 5 mg/kg arm, the proportions of patients achieving mucosal healing were similar between the two treatment arms at Week 54. Unblinded local and blinded centralised endoscopy results are presented in Table 26.

Table 26 Proportion of Patients with Mucosal Healing: Efficacy Population – UC

Visit, n (%)	CT-P13 IV 5 mg/kg (N=39)	CT-P13 SC 120/ 240 mg (N=38)	CT-P13 SC 120 mg (N=28)
Week 22	12 (30.8)	18 (47.4)	12 (42.9)
Exact 95% CI of Proportion	17.02, 47.57	30.98, 64.18	24.46, 62.82
Week 54	22 (56.4)	21 (55.3)	16 (57.1)
Exact 95% CI of Proportion	39.62, 72.19	38.30, 71.38	37.18, 75.54

Note: Mucosal healing was defined as absolute endoscopic subscore of 0 or 1 from Mayo Scoring System.
CI: Confidence interval, IV: Intravenous, SC: Subcutaneous, UC: Ulcerative colitis

The MAH states that the relatively lower proportion of patients achieving mucosal healing at Week 22 in the IV treatment arm is a reflection of greater missing rates in the IV arm. The number of patients who discontinued from the study prior to Week 22 or missed endoscopy subscore at Week 22 in the SC 120/240 mg and IV 5 mg/kg treatment arms was 4 (10.5%) and 11 (28.2%) patients, respectively.

The CHMP noted that when calculating only the results for patients who remained in the study and had endoscopy scores, the proportion of patients achieving response and mucosal healing was still numerically greater among SC treated patients.

CRP and FC concentrations

Figure 26 Mean (+/- SE) of C - Reactive Protein, Pharmacodynamic Population - UC patients
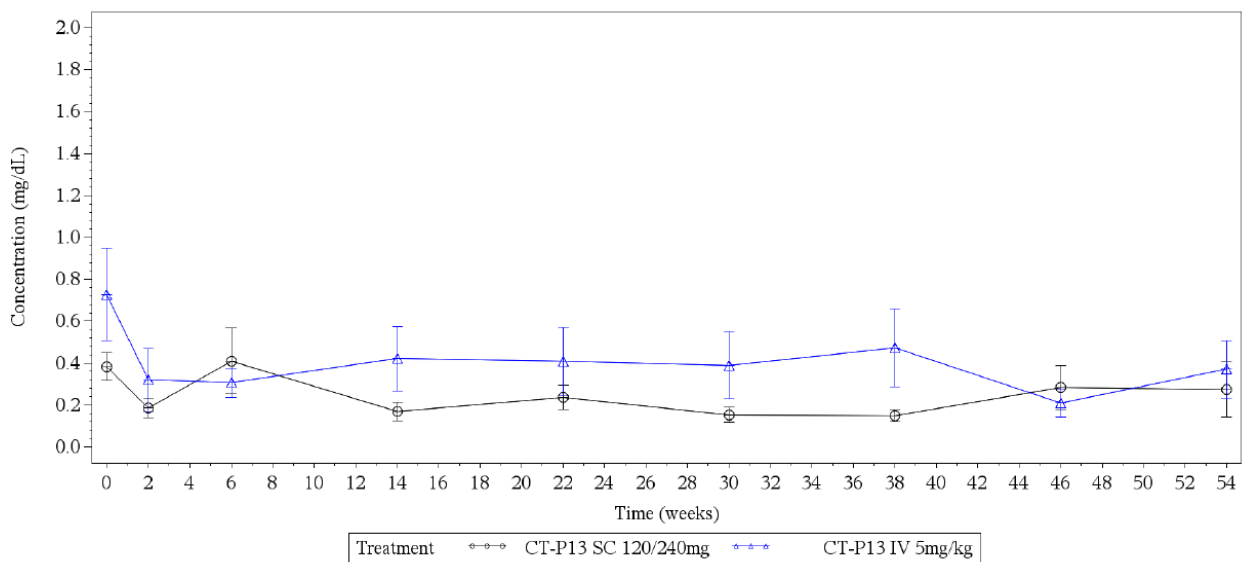
Figure 27 Mean (+/- SE) of Fecal Calprotectin, Pharmacodynamic Population - UC patients
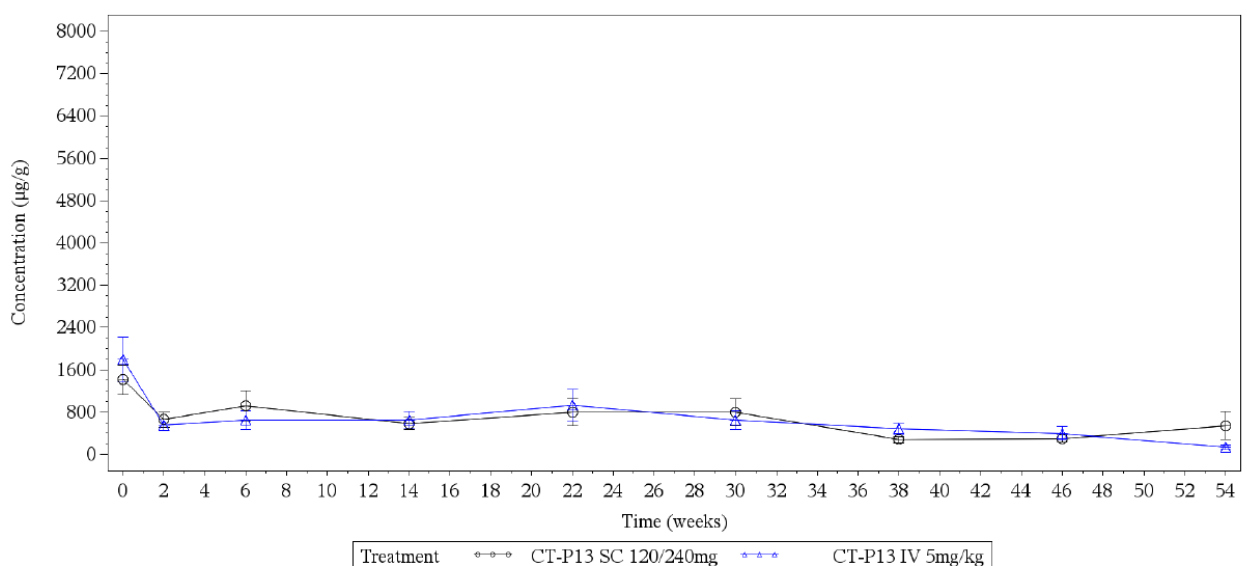
Ancillary analyses

Efficacy results after dose escalation

Dose escalation to CT-P13 SC 240 mg every 2 weeks was allowed starting at Week 30 if the patient initially responded but then lost response. Among patients who were planned to receive CT-P13 SC 120 mg on or after Week 30 regardless of the treatment arm, a total of 14 patients (5 CD patients [2 and 3 from CT-P13 IV and CT-P13 SC arms, respectively] and 9 UC patients [6 and 3 from CT-P13 IV and CT-P13 SC arms, respectively]) received at least one escalated dose.

Table 27 CDAI Score from CD Patients Administered with Escalated Dose in Study CT-P13 1.6 Part 2

Arm	CT-P13 IV 5mg/kg		CT-P13 SC 120/240mg		
Week 0	232	276.7	387.7	266	307.4
Week 2	180	132.9	256.7	49.4	251
Week 6	121	37.3	194.8	117.2	255
Week 14	99.8	64.7	139.6	73	144
Week 22	46.4	40.5	272.3	71.6	173
Week 30	125.8	55.4	325.1	147	137.8
Week 38	61.4	9.6	108.4	140	321.6
Week 46	172	246.8	84	46.4	340.2
Week 54	58	91.6	62.9	N/A*	263.4

Note: Patients in the CT-P13 IV 5 mg/kg arm switched to CT-P13 SC treatment at Week 30. Efficacy results assessed following administration of CT-P13 SC 120 mg after Week 30 are highlighted in grey, and efficacy results assessed after dose escalation to CT-P13 SC 240 mg were highlighted in yellow. * Patient discontinued the study due to AE.

Table 28 Partial Mayo Score from UC Patients Administered with Escalated Dose in Study CT-P13 1.6 Part 2

Arm	CT-P13 IV 5mg/kg						CT-P13 SC 120/240mg		
Week 0	6	6	7	8	4	6	3	7	6
Week 2	6	5	1	5	4	5	1	5	2
Week 6	4	4	1	1	2	2	0	2	1
Week 14	6	7	2	0	1	1	3	2	2
Week 22	6	5	7	5	2	1	2	4	3
Week 30	6	4	6	3	5	0	6	2	5
Week 38	6	N/A*	N/A*	1	4	1	6	5	0
Week 46	5	N/A*	N/A*	1	3	0	5	3	0
Week 54	6	N/A*	N/A*	1	5	0	N/A*	0	0

Note: Patients in the CT-P13 IV 5 mg/kg arm switched to CT-P13 SC treatment at Week 30. Efficacy results assessed following administration of CT-P13 SC 120 mg after Week 30 are highlighted in grey, and efficacy results assessed after dose escalation to CT-P13 SC 240 mg were highlighted in yellow. * Patient discontinued the study due to AE.

In all, 14 patients received the escalated dose and 7 of these patients showed some sign of improvement, All CD patients had C_{trough} concentrations well above the target of 5 µg/mL (range 8.9-29.6 µg/mL) immediately before loss of response.

Among UC patients, three patients showed improvement according to Mayo score after dose escalation. Three patients discontinued due to signs of disease progression despite the double dose.

<u>Subgroup analysis by body weight</u>

For subgroup analysis, patients with body weight < 80 kg who were administered CT-P13 SC 120 mg for maintenance treatment were divided into tertiles by weight: < 60 kg (first subgroup), 60 kg ≤ weight < 67 kg (second subgroup) and 67 kg ≤ weight < 80 kg (third subgroup). In addition to the three subgroups above, patients ≥ 80 kg who were administered CT-P13 SC 240 mg for maintenance treatment were included as a fourth subgroup for analysis.

Table 29 95% CI for the Mean of Actual Score of CDAI up to Week 30 by Body Weight in Study CT-P13 1.6 Part 2: Efficacy Population-CD

Category	Weight < 60.0 kg		60.0 kg ≤ Weight < 67.0 kg		67.0 kg ≤ Weight < 80.0 kg		Weight ≥ 80.0 kg	
Statistics	CT-P13 IV 5 mg/kg	CT-P13 SC 120 mg	CT-P13 IV 5 mg/kg	CT-P13 SC 120 mg	CT-P13 IV 5 mg/kg	CT-P13 SC 120 mg	CT-P13 IV 5 mg/kg	CT-P13 SC 240 mg
Baseline								
n	7	5	7	8	4	7	7	8
Mean (SD)	312.5 (72.98)	323.2 (68.94)	263.3 (59.93)	271.3 (27.61)	315.2 (31.48)	278.5 (46.28)	296.7 (56.02)	320.4 (77.46)
95% CI for Mean	245.01, 379.99	237.58, 408.78	207.92, 318.77	248.22, 294.38	265.09, 365.26	235.69, 321.31	244.94, 348.55	255.61, 385.12
Week 6								
n	7	5	7	8	4	7	7	8
Mean (SD)	128.8 (68.30)	110.8 (57.87)	113.8 (98.15)	148.2 (95.35)	131.4 (57.70)	143.3 (78.30)	200.1 (67.88)	234.6 (105.50)
95% CI for Mean	65.60, 191.94	38.99, 182.69	22.98, 204.53	68.45, 227.87	39.54, 223.16	70.91, 215.75	137.28, 262.84	146.40, 322.80
Week 22								
n	7	5	6	7	2	7	6	5
Mean (SD)	101.7 (61.07)	92.8 (128.06)	77.6 (67.07)	129.2 (70.96)	96.9 (9.76)	71.3 (60.92)	139.2 (59.38)	137.9 (56.32)
95% CI for Mean	45.23, 158.20	-66.16, 251.84	7.18, 147.95	63.55, 194.80	9.23, 184.57	14.96, 127.64	76.92, 201.55	67.99, 207.85
Week 30								
n	6	5	6	7	2	7	6	5
Mean (SD)	116.4 (73.83)	92.9 (153.46)	80.3 (63.31)	110.1 (80.95)	88.8 (9.62)	96.7 (76.99)	128.5 (79.34)	115.8 (47.07)
95% CI for Mean	38.87, 193.83	-97.62, 283.46	13.88, 146.75	35.26, 184.99	2.40, 175.20	25.54, 167.95	45.27, 211.79	57.31, 174.21

Note: Weight at Week 6 was used for categorisation of subgroup. The baseline value was considered to be the last non-missing value before the first administration.
CD: Crohn's disease, CDAI: Crohn's disease activity index, CI: Confidence interval, IV: Intravenous, SC: Subcutaneous, SD: Standard deviation

There was no clear trend in efficacy results according to body weight. However, among CD patients, improvement in actual values of CDAI score was slightly poorer among patients with body weight ≥80kg.

In patients weighing ≥ 80 kg, the proportion of patients achieving clinical response according to CDAI-70 and CDAI-100 was smaller in the SC arm than in the IV arm. However, this difference was seen already at week 6 when treatments were identical, and also remained at week 54 (identical treatments from week 30 to week 54) (Table 19).

Table 30 Proportions of Patients Achieving Clinical Response based on Partial Mayo Score (95% CI) by Weight in Study CT-P13 1.6 Part 2: Efficacy Population-UC

Category	Weight < 60 kg		60 kg ≤ Weight < 67 kg		67 kg ≤ Weight < 80 kg		Weight ≥ 80 kg	
Statistics	CT-P13 IV 5 mg/kg (N=5)	CT-P13 SC 120 mg (N=9)	CT-P13 IV 5 mg/kg (N=8)	CT-P13 SC 120 mg (N=10)	CT-P13 IV 5 mg/kg (N=13)	CT-P13 SC 120 mg (N=9)	CT-P13 IV 5 mg/kg (N=13)	CT-P13 SC 240 mg (N=10)
Week 6[1]								
Responder, n (%)	4 (80.0)	6 (66.7)	5 (62.5)	7 (70.0)	10 (76.9)	6 (66.7)	12 (92.3)	9 (90.0)
Exact 95% CI of Proportion	28.36, 99.49	29.93, 92.51	24.49, 91.48	34.75, 93.33	46.19, 94.96	29.93, 92.51	63.97, 99.81	55.50, 99.75
Week 22								
Responder, n (%)	4 (80.0)	8 (88.9)	8 (100.0)	8 (80.0)	8 (61.5)	6 (66.7)	10 (76.9)	10 (100.0)
Exact 95% CI of Proportion	28.36, 99.49	51.75, 99.72	63.06, 100.00	44.39, 97.48	31.58, 86.14	29.93, 92.51	46.19, 94.96	69.15, 100.00
Week 30								
Responder, n (%)	4 (80.0)	8 (88.9)	7 (87.5)	9 (90.0)	9 (69.2)	6 (66.7)	9 (69.2)	10 (100.0)
Exact 95% CI of Proportion	28.36, 99.49	51.75, 99.72	47.35, 99.68	55.50, 99.75	38.57, 90.91	29.93, 92.51	38.57, 90.91	69.15, 100.00
Week 54								
Responder, n (%)	4 (80.0)	7 (77.8)	8 (100)	8 (80.0)	6 (46.2)	7 (77.8)	10 (76.9)	9 (90.0)
Exact 95% CI of Proportion	28.36, 99.49	39.99, 97.19	63.06, 100.00	44.39, 97.48	19.22, 74.87	39.99, 97.19	46.19, 94.96	55.50, 99.75

Note: Weight at Week 6 was used for categorisation of subgroup. A patient was defined as having a clinical response according to partial Mayo score if there was a decrease from baseline in partial Mayo score at least 2 points, with an accompanying decrease from baseline in the subscore for rectal bleeding of at least 1 point, or an absolute subscore for rectal bleeding of 0 or 1.
[1] Results at Week 6 were obtained following 2 IV infusions in the Dose-Loading Phase.
CI: Confidence interval, IV: Intravenous, SC: Subcutaneous, UC: Ulcerative colitis

Table 31 95% CI for the Mean of Actual Score of Partial Mayo Score up to Week 30 by Body Weight in Study CT-P13 1.6 Part 2: Efficacy Population-UC

Category	Weight < 60.0 kg		60.0 kg ≤ Weight < 67.0 kg		67.0 kg ≤ Weight < 80.0 kg		Weight ≥ 80.0 kg	
Statistics	CT-P13 IV 5 mg/kg	CT-P13 SC 120 mg	CT-P13 IV 5 mg/kg	CT-P13 SC 120 mg	CT-P13 IV 5 mg/kg	CT-P13 SC 120 mg	CT-P13 IV 5 mg/kg	CT-P13 SC 240 mg
Baseline								
n	5	9	8	10	13	9	13	10
Mean (SD)	6.0 (1.00)	5.4 (0.88)	6.1 (1.46)	5.5 (1.78)	5.5 (1.33)	5.0 (1.32)	6.1 (1.04)	5.8 (1.14)
95% CI for Mean	4.76, 7.24	4.77, 6.12	4.91, 7.34	4.23, 6.77	4.73, 6.34	3.98, 6.02	5.45, 6.70	4.99, 6.61
Week 6								
n	5	9	8	10	13	9	13	10
Mean (SD)	2.0 (1.22)	3.2 (2.68)	3.4 (2.50)	3.1 (2.38)	2.4 (1.85)	2.1 (1.76)	2.4 (1.19)	1.9 (1.52)
95% CI for Mean	0.48, 3.52	1.16, 5.28	1.28, 5.47	1.40, 4.80	1.27, 3.50	0.76, 3.47	1.66, 3.11	0.81, 2.99
Week 22								
n	4	8	8	9	13	8	11	10
Mean (SD)	1.5 (0.58)	1.4 (1.77)	2.5 (1.69)	2.2 (2.11)	2.8 (2.48)	1.1 (1.36)	1.9 (1.81)	0.7 (0.95)
95% CI for Mean	0.58, 2.42	-0.10, 2.85	1.09, 3.91	0.60, 3.84	1.35, 4.34	-0.01, 2.26	0.69, 3.13	0.02, 1.38
Week 30								
n	4	8	8	9	13	8	11	10
Mean (SD)	1.0 (0.82)	0.9 (1.13)	1.8 (1.83)	1.2 (1.64)	2.5 (2.37)	1.8 (2.38)	1.5 (1.44)	1.0 (1.15)
95% CI for Mean	-0.30, 2.30	-0.07, 1.82	0.22, 3.28	-0.04, 2.48	1.11, 3.97	-0.24, 3.74	0.58, 2.51	0.17, 1.83

Note: Weight at Week 6 was used for categorisation of subgroup. The baseline value was considered to be the last non-missing value before the first administration.

CI: confidence interval, IV: Intravenous, SC: Subcutaneous, SD: Standard deviation, UC: Ulcerative

Table 32 Proportions of Patients Achieving Clinical Remission based on Partial Mayo Score (95% CI) by Weight in Study CT-P13 1.6 Part 2: Efficacy Population-UC

Category Statistics	Weight < 60 kg		60 kg ≤ Weight < 67 kg		67 kg ≤ Weight < 80 kg		Weight ≥ 80 kg	
	CT-P13 IV 5 mg/kg (N=5)	CT-P13 SC 120 mg (N=9)	CT-P13 IV 5 mg/kg (N=8)	CT-P13 SC 120 mg (N=10)	CT-P13 IV 5 mg/kg (N=13)	CT-P13 SC 120 mg (N=9)	CT-P13 IV 5 mg/kg (N=13)	CT-P13 SC 240 mg (N=10)
Week 6[1]								
Responder, n (%)	2 (40.0)	2 (22.2)	2 (25.0)	4 (40.0)	5 (38.5)	4 (44.4)	3 (23.1)	4 (40.0)
Exact 95% CI of Proportion	5.27, 85.34	2.81, 60.01	3.19, 65.09	12.16, 73.76	13.86, 68.42	13.70, 78.80	5.04, 53.81	12.16, 73.76
Week 22								
Responder, n (%)	2 (40.0)	5 (55.6)	2 (25.0)	4 (40.0)	5 (38.5)	5 (55.6)	6 (46.2)	9 (90.0)
Exact 95% CI of Proportion	5.27, 85.34	21.20, 86.30	3.19, 65.09	12.16, 73.76	13.86, 68.42	21.20, 86.30	19.22, 74.87	55.50, 99.75
Week 30								
Responder, n (%)	3 (60.0)	6 (66.7)	5 (62.5)	6 (60.0)	5 (38.5)	6 (66.7)	8 (61.5)	8 (80.0)
Exact 95% CI of Proportion	14.66, 94.73	29.93, 92.51	24.49, 91.48	26.24, 87.84	13.86, 68.42	29.93, 92.51	31.58, 86.14	44.39, 97.48
Week 54								
Responder, n (%)	4 (80.0)	6 (66.7)	6 (75.0)	6 (60.0)	6 (46.2)	6 (66.7)	8 (61.5)	8 (80.0)
Exact 95% CI of Proportion	28.36, 99.49	29.93, 92.51	34.91, 96.81	26.24, 87.84	19.22, 74.87	29.93, 92.51	31.58, 86.14	44.39, 97.48

Note: Weight at Week 6 was used for categorisation of subgroup. Clinical remission according to partial Mayo score was defined as a partial Mayo of 1 point or lower.

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

CI: Confidence interval, IV: Intravenous, SC: Subcutaneous, UC: Ulcerative colitis

All CD subjects had moderate disease severity (CDAI score between 220 and 450 points) and all but 3 UC patients had moderate disease severity (6-10 points on Mayo score). Hence, no subgroup analysis for disease severity was conducted.

Summary of main study

The following table 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 33 Summary of Efficacy for Trial CT-P13 1.6 Part 2

Title: An Open-label, Randomized, Parallel-Group, Phase I Study to Evaluate Pharmacokinetics, Efficacy and Safety between Subcutaneous CT-P13 and Intravenous CT-P13 in Patients with Active Crohn's Disease and Active Ulcerative Colitis			
Study identifier	Project code: CT-P13 SC EudraCT number: 2016-002124-89		
Design	Randomised, parallel- group, open-label, multicentre study		
	Duration of main phase:	54 weeks Dose-Loading Phase: 6 weeks (all patients received CT-P13 IV 5 mg/kg at weeks 0 and 2) Maintenance Phase: 48 weeks (patients were randomised 1:1 ratio into CT-P13 IV 5 mg/kg or CT-P13 SC 120/240 mg)	
	Duration of Run-in phase:	not applicable	
	Duration of Extension	not applicable	
Hypothesis	To demonstrate that CT-P13 SC is noninferior to CT-P13 IV		
Treatments groups	CT-P13 IV 5 mg/kg	Dose-loading Phase: CT-P13 IV (5 mg/kg) at Weeks 0 and 2 Maintenance Phase: CT-P13 IV (5 mg/kg) at Week 6 and every 8 weeks up to Week 22. CT-P13 IV was switched to CT-P13 SC at Week 30 and thereafter further doses of CT-P13 SC were administered up to Week 54. The dosage of CT-P13 SC was determined based on the patient's body weight at Week 30 (CT-P13 SC 120 mg for patients < 80 kg; 240 mg for patients ≥ 80 kg). Number of randomised=65 (CD: 25, UC: 40)	
	CT-P13 SC 120/240 mg	Dose-loading Phase: CT-P13 IV (5 mg/kg) at Weeks 0 and 2 Maintenance Phase: CT-P13 SC 120/240 mg Week 6 and every 2 weeks up to Week 54 The dosage of CT-P13 SC was determined based on the patient's body weight at Week 6 (CT-P13 SC 120 mg for patients < 80 kg; 240 mg for patients ≥ 80 kg). Number of randomised=66 (CD: 28, UC: 38)	
Endpoints and definitions	Secondary endpoint for CD patients	CDAI-70	defined as a decrease in CDAI score of ≥ 70 points from the baseline value
		CDAI-100	defined as a decrease in CDAI score of ≥ 100 points from the baseline value
		Clinical remission	defined as an absolute CDAI score of < 150 points
		Endoscopic response	defined as a decrease in ≥ 50% of SES-CD score from the baseline
		Endoscopic remission	defined as an absolute SES-CD score of ≤ 2 points

		SIBDQ	Short Inflammatory Bowel Disease Questionnaire
	Secondary endpoint for UC patients	Clinical response by total Mayo score	defined as a decrease in total Mayo score from baseline of at least 3 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point or an absolute subscore for rectal bleeding of 0 or 1 point
		Clinical response by partial Mayo score	defined as a decrease in partial Mayo score from baseline of at least 2 points, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point, or an absolute subscore for rectal bleeding of 0 or 1 point
		Clinical remission by total Mayo score	defined as a total Mayo score of ≤ 2 points with no individual subscore exceeding 1 point
		Clinical remission by partial Mayo score	defined as a partial Mayo score of ≤ 1 point
		Mucosal healing	defined as an absolute endoscopic subscore of 0 or 1 point from Mayo scoring system
		SIBDQ	Short Inflammatory Bowel Disease Questionnaire
Database lock	16 September 2019 as the last patient's Week 54 visit for Week 54 CSR 17 January 2020 as the last patient's visit for Final CSR		

Results and Analysis

Analysis description	Secondary analysis
Analysis population and time point description	• 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 treatment • Secondary endpoints were analysed at Weeks 0, 2, 6, 14, 22, 30, 38, 46 and 54

Descriptive statistics and estimate variability	Number (%) of patients	
	Secondary analysis for CD patients	
	Treatment group	CT-P13 IV 5 mg/kg (N=25)	CT-P13 SC 120 mg (N=20)
	CDAI-70 at Week 6	21 (84.0)	17 (85.0)
	CDAI-70 at Week 22	21 (84.0)	18 (90.0)
	CDAI-70 at Week 30	17 (68.0)	15 (75.0)
	CDAI-70 at Week 54	17 (68.0)	15 (75.0)
	CDAI-100 at Week 6	18 (72.0)	14 (70.0)
	CDAI-100 at Week 22	20 (80.0)	17 (85.0)
	CDAI-100 at Week 30	16 (64.0)	15 (75.0)
	CDAI-100 at Week 54	16 (64.0)	14 (70.0)
	Clinical remission at Week 6	11 (44.0)	12 (60.0)

Clinical remission at Week 22	15 (60.0)	13 (65.0)
Clinical remission at Week 30	14 (56.0)	13 (65.0)
Clinical remission at Week 54	14 (56.0)	12 (60.0)
Secondary analysis for UC patients		
Treatment group	CT-P13 IV 5 mg/kg (N=39)	CT-P13 SC 120 mg (N=28)
Clinical response (partial Mayo score) at Week 6	31 (79.5)	19 (67.9)
Clinical response (partial Mayo score) at Week 22	30 (76.9)	22 (78.6)
Clinical response (partial Mayo score) at Week 30	29 (74.4)	23 (82.1)
Clinical response (partial Mayo score) at Week 54	28 (71.8)	22 (78.6)
Clinical remission (partial Mayo score) at Week 6	12 (30.8)	10 (35.7)
Clinical remission (partial Mayo score) at Week 22	15 (38.5)	14 (50.0)
Clinical remission (partial Mayo score) at Week 30	21 (53.8)	18 (64.3)
Clinical remission (partial Mayo score) at Week 54	24 (61.5)	18 (64.3)

Note: The IV 5 mg/kg treatment arm included 7 CD and 13 UC patients with a body weight ≥ 80kg, while all patients in the SC 120mg treatment arm were < 80kg. The efficacy of Remsima SC 120mg in patients weighing ≥ 80kg was estimated to be non-inferior to the efficacy of Remsima IV 5mg/kg based on PK and extrapolation exercise.

Analysis performed across trials

Integrated Efficacy Analysis of Study CT-P13 1.6 Part 1 and Part 2 in CD Patients

Table 34 Proportions of Patients Achieving Clinical Response according to CDAI-70 and CDAI-100 Criteria (95% CI) in Study CT-P13 1.6 Parts 1 & 2: Efficacy Population-CD

Parameter Visit	Pooled CT-P13 IV 5 mg/kg (N=37)	Pooled CT-P13 SC 120 mg (N=31)	Pooled CT-P13 SC 120/ 180/ 240 mg (N=58)
CDAI-70, n (%)			
Week 6[1]			
Responder, n (%)	28 (75.7)	26 (83.9)	42 (72.4)
Exact 95% CI of Proportion	58.80, 88.23	66.27, 94.55	59.10, 83.34
Week 22			
Responder, n (%)	30 (81.1)	27 (87.1)	45 (77.6)
Exact 95% CI of Proportion	64.84, 92.04	70.17, 96.37	64.73, 87.49
Week 30			
Responder, n (%)	25 (67.6)	24 (77.4)	43 (74.1)
Exact 95% CI of Proportion	50.21, 81.99	58.90, 90.41	60.96, 84.74

Week 54				
Responder, n (%)	7 (58.3)[2]	17 (68.0)[3]	24 (77.4)	42 (72.4)
Exact 95% CI of Proportion	27.67, 84.83	46.50, 85.05	58.90, 90.41	59.10, 83.34
CDAI-100, n (%)				
Week 6[1]				
Responder, n (%)	24 (64.9)		20 (64.5)	30 (51.7)
Exact 95% CI of Proportion	47.46, 79.79		45.37, 80.77	38.22, 65.05
Week 22				
Responder, n (%)	28 (75.7)		24 (77.4)	39 (67.2)
Exact 95% CI of Proportion	58.80, 88.23		58.90, 90.41	53.66, 78.99
Week 30				
Responder, n (%)	23 (62.2)		24 (77.4)	43 (74.1)
Exact 95% CI of Proportion	44.76, 77.54		58.90, 90.41	60.96, 84.74
Week 54				
Responder, n (%)	6 (50.0)[2]	16 (64.0)[3]	23 (74.2)	39 (67.2)
Exact 95% CI of Proportion	21.09, 78.91	42.52, 82.03	55.39, 88.14	53.66, 78.99

Note: A patient was defined as having a CDAI-70 response if there was a decrease in CDAI score of ≥ 70 points from the baseline value. A patient was defined as having a CDAI-100 response if there was a decrease in CDAI score of ≥ 100 points from the baseline value. The baseline value was considered to be the last non-missing value before the first administration.

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

[2] Patients from Part 1 were included. The patients administered CT-P13 IV 5 mg/kg up to Week 54. [3] Patients from Part 2 were included. The patients administered CT-P13 IV 5 mg/kg up to Week 22. From Week 30, the patients were switched to CT-P13 SC 120 or 240 mg based on their weight at Week 30. Further doses of CT-P13 SC every 2 weeks were given up to Week 54.

CDAI: Crohn's disease activity Index, CI: Confidence interval, IV: Intravenous, SC: Subcutaneous

2.4.3. Discussion on clinical efficacy

The efficacy of infliximab IV is well established. As a biosimilar to Remicade IV, 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). Following a line extension application (EMEA/H/C/002576/X/0062), the subcutaneous formulation Remsima SC was approved for treatment of RA. Notably, the originator Remicade does not have a SC-formulation. With this variation, the MAH has presented data to support an indication extension to cover all the indications approved for Remsima IV (and Remicade IV). The recommended dose is 120 mg administered as a subcutaneous (SC) injection every 2 weeks (Q2W) for all patients in all indications.

The efficacy and dose finding data supporting the proposed extension of indications are from Study CT-P13 1.6 Parts 1/2 (CD and UC patients) with pivotal data coming from Study CT-P13 3.5 Parts 1/2 (RA patients). Studies 3.5 Parts 1/2 and 1.6 Part 1 have been assessed within the initial line extension application. Efficacy data from Study CT-P13 1.6 Part 2, as well as the basis for extrapolation of efficacy and dosing to indications not studied, are discussed in more detail below.

Design and conduct of Study CT-P13 1.6 Part 2

Study design

Study CT-P13 1.6 Part 2 was an open-label, randomized, parallel-group, study designed to demonstrate that CT-P13 SC was non-inferior to CT-P13 IV, in terms of PK in patients with active Crohn's disease (CD) or active ulcerative colitis (UC) up to Week 54. Efficacy endpoints were evaluated

as supportive data. The open label design is acceptable, since the primary endpoint (C_{trough}) is not expected to be subject to bias due to lack of blinding. The study design was discussed and agreed with the CHMP through Scientific Advice (SA).

Participants

The study population (as captured by the inclusion/exclusion criteria) is overall appropriate for the study purpose and the studied indications CD and UC. In addition to the subjective rating scales (CDAI for CD patients and total Mayo score for UC patients), current disease activity was ensured by objective measures, such as CRP and endoscopic findings. The exclusion criteria are in line with contraindications and warnings in the current SmPC.

CD patients with severe disease activity or fistulating CD were not included in the study. Such patients are expected to have a high inflammatory burden and possibly an accelerated drug clearance. However, the route of administration is not expected to affect the level of influence of inflammatory burden on PK and, therefore, the exclusion of patients with severe disease activity is acceptable.

Patients with a BMI>35 were excluded from this study and have not been included in any of the other clinical studies in the development of Remsima SC. Thus, drug exposure and efficacy among the heaviest patients is based on simulations.

Among CD patients, 8 patients in the SC arm and 7 in IV arm had a body weight ≥80kg at week 6. Among UC patients, 10 and 13 patients in the SC and IV arms, respectively had a body weight ≥80kg.

Treatments

CT-P13 120 mg by SC injection every 2 weeks after loading doses, was compared to CT-P13 5mg/kg every 8 weeks during 54 weeks of treatment. The 54 week duration is sufficient to determine efficacy and immunogenicity during treatment. There was only a 2 weeks off-dose period, prior to the EOS visit. This means that no ADA samples were taken post immunosuppression. This is further discussed in section 2.5.1.

The dose chosen for the investigational drug was 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), RA patients (CT-P13 3.5 [Part 1 up to Week 30]) and CD patients (CT-P13 1.6 [Part 1 up to Week 30]). The method of dose selection was agreed in CHMP SA. The dosing of the comparator, Remsima IV, was in line with the SmPC for all intended indications.

All stratification parameters are factors, which may affect drug concentration. Hence, the stratification scheme is adequate.

Objectives and endpoints

The mode of action in all proposed indications is the same, namely neutralisation of TNFα (soluble and/or membrane bound). However, due to differences between target populations in age, disease specific variation in amount of target molecule (TNFα), inflammatory burden, comorbidities and concomitant medication, there may be differences between the two formulations regarding PK and immunogenicity, which might shift the benefit/risk. Therefore, the purpose of this study was to show that Remsima SC has a similar PK, efficacy and safety profile, including immunogenicity, as Remsima IV in also IBD patients, though it has already been shown in RA.

The primary objective to demonstrate non-inferiority of C_{trough} at week 22 with Remsima SC compared to Remsima IV in CD and UC patients was agreed by CHMP through scientific advice (EMA - Follow-up Scientific Advice (EMEA/H/SA/3220/1/FU/1/2016/II; 15 Sep 2016)). Efficacy of infliximab has

previously been shown to correlate with C_{trough} in IBD patients. Although the exact target concentration for infliximab in IBD is unknown, the current evidence suggests that targeting a concentration greater than 5 μg/mL is appropriate when aiming at both symptomatic and endoscopic response. Of note, this target is often not reached when treating patients with IV infliximab with the currently approved dosing.

The dose selection for this study was based on achieving a C_{trough}, which exceeded a target threshold of 5 μg/mL and an $AUC_{8weeks,ss}$ that aligned as closely as possible to that achieved following 5 mg/kg of Remsima IV. Since IV administration leads to high C_{max} and low C_{trough}, compared to SC administration, aligning the AUC will inevitably lead to higher C_{trough} concentrations following SC administration. An inferior C_{trough} could have been achieved only if the AUC had been severely misaligned. While, a non-inferior C_{trough} can ensure comparable efficacy, it is not helpful in determining comparability of safety.

Efficacy was assessed in CD patients by CDAI score and endoscopic response. The most recent EMA Guideline on the development of new medicinal products for the treatment of Crohn's Disease (CPMP/EWP/2284/99 Rev. 2, revised June 2018) points out that both reliability and validity of the Crohn's Disease Activity Index (CDAI) has been questioned. However, this index has previously been used extensively in clinical trials in CD and it is used here to measure secondary endpoints in a descriptive manner, which is acceptable to the CHMP.

Colonoscopy investigation was to be conducted locally but evaluated and adjudicated centrally, which should have minimised the variability in assessment. The scale used to evaluate the grade of mucosal inflammation is validated and extensively used (SES-CD).

Assessment of efficacy in UC patients using Mayo score is in line with the EMA Guideline on the development of new medicinal products for the treatment of Ulcerative Colitis. According to this guideline, the total Mayo score including physician's global assessment is not of primary interest and the partial Mayo score is to be preferred.

Sample size and statistical methods

The sample size was targeted to provide sufficient power to demonstrate non-inferiority in terms of C_{trough} at week 22 (the primary objective of this trial). Randomisation was stratified and that was taken into account in the primary analysis, though the stratification cut-off value for weight was changed from 100kg to 80kg during the conduct of the trial (amendment 2, 09Jan2018). This amendment is in line with the amended dosing scheme, where the cut-off for increased dose was set at 80kg based on results from dose finding studies and was done prior to inclusion of first patient. This is therefore found acceptable to the CHMP.

The definition of the analysis populations follows conventions. The primary analysis was conducted in a subset of the PK population as full dose until Week 22 was required for a subject to be included in the analysis, which is acceptable in this setting where the primary endpoint is PK endpoint.

In the interpretation of the efficacy results, it should be taken into account that 'as observed' excludes subjects with incomplete data, thus assumes that the outcome of the discontinued subject would follow the response pattern of those who are compliant. This affects interpretation of the actual values of CDAI and Mayo scores. At the same time, the non-responder imputation has been applied to response-type of outcomes, and this method treats incomplete data more conservatively. In general, the applied statistical methods are acceptable to the CHMP for this type of trial.

Baseline data

Forty-five patients of 195 screened (23%) did not meet the inclusion criteria. However, the percentage is relatively small and the studied population is considered reasonably representative of a real life population of patients with IBD.

The proportions of patients who discontinued the study during the maintenance phase were 16.7% and 23.1% in the SC 120/240 mg and IV 5 mg/kg treatment arms, respectively. In this type of long-term maintenance study the discontinuation rate is acceptable to the CHMP. The reasons for discontinuation were broadly similar between the treatment arms and between CD and UC patients and discontinuation was more common in the IV arm, if anything, which supports non-inferiority of Remsima SC. Primary reasons for discontinuation during the maintenance phase was development of signs of disease progression 4 (6.1%) in the SC 120/240 mg treatment arm and 5 (7.7%) in the IV treatment arm. In addition, patients were also withdrawn by investigator's decision. Assessment of individual patient data revealed that all patients who were classified as "withdrawn from the study by investigator's decision" were withdrawn due to lack of efficacy or insufficient efficacy. All patients who discontinued were included in the safety and efficacy analyses and were classified as non-responders. Based on the reasons for discontinuation, this classification is endorsed by CHMP.

The baseline characteristics and prior treatment histories are representative for the studied diseases. The baseline demographics were similar between the SC and IV study groups. The use of concomitant immunomodulatory medication (AZA or MTX or hydroxychloroquine sulfate, cyclosporine and corticosteroids), was evenly distributed between treatment arms in both patient groups.

However, some differences in baseline characteristics were found. The total number of medical histories at screening was higher in the SC treatment arm (277 and 180 medical histories reported in the SC and IV 5 arms, respectively). The difference between treatment arms in terms of medical history at screening is mainly driven by the System Organ Classes (SOC) Gastrointestinal disorders and Blood and lymphatic system disorders. Patients in the SC arm also had more recordings of Infections and infestations at baseline. (See discussion regarding differences in safety outcome in section 2.5.1.)

In spite of identical induction phases and similar baseline CDAI scores, there was a slightly lower response rate at week 6 among CD patients in the SC arm compared to the IV arm. The initial weaker response in the SC arm was driven by the group of patients who received 240mg SC, i.e. patients with a body weight ≥80kg. These patients had a significantly higher baseline CDAI score than patients with a body weight <80kg (320.4 vs. 286.8 in SC treated patients; among IV patients ≥80kg baseline CDAI was 296.7).

Efficacy data and additional analyses

Efficacy in Patients with Active Crohn's Disease

At baseline both treatment arms had similar CDAI scores (301 and 303 in SC 120/240 mg and IV 5mg/kg treatment arms respectively). Both treatment arms improved during the identical induction phase (weeks 0-6), but the improvement was slightly greater in the IV arm at week 6 (-129 and -151 in SC and IV treatment arms respectively). By week 22, both treatment arms had similar actual CDAI scores and equal improvement from baseline. Clinical remission was reached by 16 (57.1%)and 15 (60.0%) of patients in the SC 120/240 mg and IV 5mg/kg treatment arms respectively by week 22; the corresponding figure for those receiving 120mg (proposed dose) was 13/20 (65%).

Overall, the mean CDAI score decreased steadily over time in both treatment arms over the whole treatment period of 54 weeks in a comparable manner. However, there were dropouts along the way and no imputation of missing values was done for continuous variables. Since the majority of discontinuations were due to lack of effect or progression of disease, the mean CDAI score only

represents the mean for those patients who were well enough not to terminate the study. Therefore, an ever decreasing mean value of absolute CDAI score cannot be interpreted as an ongoing clinical improvement. In fact, when looking at response rates, it seems that response increases up until week 22 in both treatment arms, where after a plateau is reached.

In the initial submission it was noticed that some patients had negative CDAI total scores. A common statement in scholarly articles on the CDAI score is that CDAI score should range from 0-600. In the original publication by Best et al. it is stated that "Each variable is coded in such a way that the expected value in a normal individual is zero, and progressively larger positive values are expected to reflect progressively greater activity of Crohn's disease." It does not follow from this statement that values less than zero reflect a better outcome, as zero is defined as normal. For example, negative values for the hematocrit component reflect a high haematocrit, implying dehydration, and cannot be interpreted as a positive sign in CD. The weight component of the CDAI is intended to detect weight loss and thus gives higher scores if the patient is underweight. While weight gain can be a sign of improvement in a seriously ill CD patient, a negative score in the weight component only represents overweight. Therefore, the inclusion of negative CDAI scores is not clinically justified and it is skewing the results toward a more positive outcome. Five patients in the SC group had negative scores and only one in the IV group. Thus, initially a potential for bias in the results was recognised. Upon request, the MAH adjusted all individual CDAI subscores to a minimum of zero and recalculated the relevant efficacy results. After adjustment of the CDAI scores, the mean actual CDAI scores, the CDAI-70 and CDAI-100 response rates and the remission rates were almost unchanged compared to the original results.

Colonoscopy was not performed on all patients. It is stated in the CSR that SES-CD score was assessed only in patients who had confirmed mucosal abnormalities from previous assessment. This approach is by design only able to detect a potential improvement while a disease progression in patients with no mucosal abnormality at baseline would go undetected. However, upon request, the MAH provided convincing evidence that the colonoscopy approach to exclude patients without confirmed mucosal abnormalities did not result in skewed efficacy results.

Based on the provided data, CT-P13 SC 120/240 mg is non-inferior to CT-P13 IV 5 mg/kg in terms of proportions of CD patients achieving clinical remission and endoscopic remission according to CDAI score (<150) and SES-CD score. In terms of CRP, the SC treatment arm achieved slightly better results than the IV arm. All secondary efficacy outcomes are aligned and support non-inferiority of CT-P13 SC.

Clinical response in the 120/240 arm according to CDAI-70 and CDAI-100 at week 22 did not fully support non-inferiority of Remsima SC. This finding seems to be sufficiently explained by the following chance finding: In spite of identical induction phases and similar baseline CDAI scores, there was a slightly lower response rate at week 6 among CD patients in the SC arm compared to the IV arm. Hence, CD patient in the SC arm could have been slower or weaker responders by chance selection. However, this did not translate into weaker response rates in the long run. By week 30, also the response rate, not only remission rate, was similar between treatment arms.

The initial weaker response in the SC arm was driven by the group of patients who received 240mg SC, i.e. patients with a body weight ≥80kg. Their response rates remained lower compared to <80kg SC patients and compared to average IV patients throughout the study. Based on these discrepancies in baseline data and asymmetrical response according to body weight, it seems that the somewhat weaker response in the SC 120/240 mg arm seen at week 22 was a chance finding.

Patients treated with the sought dose SC 120mg, who had a similar response at randomisation as those treated with IV 5mg/kg, showed comparable, or even slightly better, response and remission

rates throughout the study compared to the whole IV arm, at all time points after week 6. However, results between these two groups are not fully comparable because the SC 120 arm only contained patients with a body weight <80 kg, while the IV arm contained 7 patients ≥80kg. Therefore, the MAH was asked to provide subgroup analyses of response and remission results by body weight for the IV arm. In patients weighing ≥ 80 kg, the proportion of patients achieving clinical response according to CDAI-70 and CDAI-100 was clearly smaller in the SC arm than in the IV arm. However, this difference was seen already at week 6 when treatments were identical, and also remained at week 54 (identical treatments from week 30 to week 54). This indicates that the difference between treatment arms in patients weighing ≥ 80 kg is a chance finding and is not related to weaker efficacy of the SC formulation in heavy patients.

Pooled Efficacy Analysis of Study CT-P13 1.6 Part 1 and Part 2 in CD Patients

Study CT-P13 1.6 Part 1 and Part 2 shared the same inclusion/ exclusion criteria and the sub-studies are similar with regard to background therapy, study design, and assessment of the endpoints. However, in Part 2 dosage was weight based, while patients were randomised to different doses in Part 1. Therefore, interpretation of the pooled results is not straight forward. However, the results of the pooled analysis indicate that patients who first received Remsima IV 5mg/kg for 30 weeks and then switched to Remsima SC 120/240mg (Part 2) had slightly higher response rates by week 54 than patients who continued with the IV dosage (Part 1). The small numbers preclude any definitive conclusions.

Efficacy in Patients with Active Ulcerative Colitis

At Week 22, there was a slightly greater improvement in the SC 120/240 mg treatment arm in terms of both response and remission rates according to both total and partial Mayo scores.

The MAH states that the relatively lower proportion of patients achieving mucosal healing at Week 22 in the IV treatment arm is a reflection of greater missing rates in the IV arm.

The number of patients who discontinued from the study prior to Week 22 or missed endoscopy subscore at Week 22 in the SC 120/240 mg and IV 5 mg/kg treatment arms was 4 (10.5%) and 11 (28.2%) patients, respectively.

If a patient discontinued from the study prior to a visit or missed endoscopy subscore at a visit, the patient was considered as not having achieved mucosal healing at that visit. This approach is endorsed by CHMP since the major reason for discontinuation was lack of response.

Based on the provided data, Remsima SC 120/240 mg, as well as the proposed 120mg dose, is non-inferior to CT-P13 IV 5 mg/kg in UC patients in terms of response and remission rates according to both total and partial Mayo scores before switching of treatment at week 30 and after switching up to week 54. All efficacy outcomes are aligned and support non-inferiority of Remsima SC.

Subgroup analysis

All CD subjects had moderate disease severity (CDAI score between 220 and 450 points) and all but 3 UC patients had moderate disease severity (6-10 points on Mayo score). Hence, no subgroup analysis for disease severity was conducted.

In CD patients, there was no consistent trend for superiority or inferiority of either treatment in patients weighing <80 kg. In the subgroup of patients weighing ≥ 67 kg but < 80 kg the efficacy of Remsima SC was not inferior to that of Remsima IV, (slightly better if anything), despite a somewhat lower predicted drug exposure in terms of AUC.

In patients weighing ≥ 80 kg, the proportion of patients achieving clinical response according to CDAI-70 and CDAI-100 was clearly smaller in the SC arm than in the IV arm. However, this difference was seen already at week 6 when treatments were identical, and also remained at week 54 (identical treatments from week 30 to week 54). This indicates that the difference between treatment arms in patients weighing ≥ 80 kg is a chance finding and is not related to weaker efficacy of the SC formulation in heavy patients.

In UC patients, the subgroup analyses of clinical response and remission based on Partial Mayo Score showed no trends related to body weight in either of the treatment arms. No subgroup analysis was performed for efficacy according to use of methotrexate or other concomitant immunosuppressant medication. This is acceptable since the efficacy of Remsima SC with methotrexate has been established and the efficacy without concomitant immunosuppressant is not expected to be lesser, if anything, the exposure is expected to be higher, in this group, due to lower incidence of ADA.

Appropriateness of the proposed dosing

In study CT-P13 3.5 Part 2, Remsima SC 120 mg Q2W was shown to be non-inferior to Remsima IV 3 mg/kg Q8W in RA patients in terms of efficacy, to give rise to a comparable but slightly higher AUC and to give rise to a manifold higher C_{trough} compared to Remsima IV 3 mg/kg. When comparing Remsima SC 120 mg to Remsima IV 5 mg/kg in study CT-P13 1.6, the observed AUC was approximately 1.35-fold higher for dosing regimen 120 mg SC Q2W compared with dosing regimen 5 mg/kg IV Q8W. Although the predicted AUC over 8 weeks of Remsima SC 120 mg was slightly lower for some patients than that of Remsima IV 5 mg/kg, this was not translated into weaker efficacy for IBD patients in study CT-P13 1.6.

In study 1.6 Part 2, patients who received Remsima 120mg had consistently non-inferior and even slightly better results than patients in the IV arm. Patients with a body weight above 80kg received Remsima SC 240 mg Q2W. Among CD patients in this patient group, results were slightly less favourable in the SC arm than in the IV arm. However, this was explained by higher CDAI scores at randomisation. Among UC patients, the results were comparable between treatment arms in both weight/dose groups.

Population PK modelling showed that the target C_{trough} threshold for efficacy (> 5 µg/mL) would be met for even the heaviest weight groups following the 120 mg dosing. Of note, this threshold is often not met with the currently approved IV dosing and the chance of meeting the C_{trough} threshold for efficacy is larger with SC 120 mg dosing than with IV 5mg/kg dosing. Furthermore, PK-PD modelling data indicated that CDAI and partial Mayo score were similar between patients treated with Remsima IV 5 mg/kg and Remsima SC 120 mg and that Remsima SC 120mg was non-inferior even in the heaviest patients (up to 150 kg). C_{trough} is considered to be the main PK parameter predicting efficacy and the C_{trough} threshold for efficacy (> 1 µg/mL in RA and > 5 µg/mL in IBD) is supported by literature and was approved through SA.

In addition, in Study CT-P13 1.6 Part 1, there were 3 patients who weighed ≥ 80 kg at Week 6 and were assigned to Remsima SC 120 mg cohort. These 3 patients achieved both CDAI-70 and CDAI-100 responses and clinical remission at Weeks 30 and 54.

Clinical data from studies 3.5 and 1.6 suggest that efficacy of Remsima SC is non-inferior to Remsima IV even if C_{max} is clearly lower. Therefore, it can be concluded that C_{max} is not predictive of response and does not need to be comparable. Based on clinical findings from studies 1.6 and 3.5, on PK and PK-PD modelling and on the literature review provided by the MAH, maintaining a C_{trough} above > 5 µg/mL should be enough to ensure efficacy of Remsima SC 120mg in all patients. Hence, it is not considered necessary to increase the dose of Remsima SC to 240mg for patients ≥80kg.

Efficacy results after dose escalation in study CT-P13 1.6 Part 2

Five patients with CD and 9 patients with UC who were planned to receive CT-P13 SC 120 mg were administered an escalated dose of 240mg.

One CD patient and 3 UC patients were in the IV group and received the escalated dose already at week 30. Therefore, the improvement in drug concentration and/or efficacy seen in these patients cannot be attributed solely to the escalated dose as the switch from IV to SC might have had an equal impact due to higher drug concentrations. Data from these patients is relevant only when evaluating the safety of an escalated dose.

Among the remaining 4 CD patients, three achieved higher concentrations and concomitantly lower CDAI scores after dose increase, while one patient, achieved better CDAI score after dose escalation without an increase in drug concentration. All of these patients had C_{trough} concentrations well above the target of 5 µg/mL (range 8.9-29.6 µg/mL) immediately before loss of response. Hence, the loss of response was not driven by low concentrations.

Among UC patients, three patients showed improvement according to Mayo score after dose escalation. Three patients discontinued due to signs of disease progression, despite the double dose.

In all, 14 patients (n=5 CD, n=9 UC) received the escalated dose and 7 of these patients showed some sign of improvement, although the evidence for causality between improvement and dose increase is lacking. Moreover, the follow-up time was very limited and, therefore, the duration of the renewed response among patients who once lost response is very uncertain and so is the long term safety of such high doses.

Notably, for Remsima IV (and Remicade IV) it is stated in the SmPC that the dose could be increased to 7.5 mg/kg every 8 weeks in RA, or to 10mg/kg in Crohn's disease in those who initially responded but lost response. 89% in CD and 57% in fistulising CD responded to this dose increase. In the SmPC of Remicade/Remsima IV there is no possibility to increase the dose in other indications, including UC. The MAH applied initially for this dose increase not only for CD, but also for UC.

Overall, CHMP considered that there is not enough evidence to support a recommendation on dose escalation from CS-P13 SC 120mg to 240mg. Additional efficacy and sufficient safety of 240mg SC, especially for patients weighing <80 kg, have not been confirmed.

The MAH therefore withdrew the initial proposal for increased dosing from 120mg to 240mg in CD and UC.

Extrapolation of efficacy to patients with AS, PsA and Ps

Point for justification of extrapolation of efficacy and proposed dosing made by the MAH

- In IBD: C_{trough} threshold of 5 µg/mL is associated with clinical improvement (Ward et al., 2017; Adedokun et al., 2014; Cornillie et al., 2014; Gonczi et al., 2016)

- The trough levels for infliximab in psoriasis patients were positively associated with clinical response (Torii et al., 2012; Reich et al., 2005; Takahashi et al., 2012)

- A C_{trough} target of 3-7 µg/mL has also been reported for AS (De Vries et al., 2007), which aligns with CELLTRION data from Study CT-P13 1.1 in AS patients

- It is also interesting to note that Brandse et al. (2017) reported, following studying sera from 332 patients with IBD (253 Crohn's disease and 79 ulcerative colitis), that insufficient exposure below an infliximab plasma level of 3 µg/mL increased the risk of anti-infliximab antibodies by 4-fold.

- In view of the fact that the same dose is recommended for AS, PsA and Ps as for IBD, and in view of the data reported above, a C_{trough} threshold of 5 ug/mL should be achieved and should be adequate for these indications as well

- As like RA, the mode of action in AS, PsA and Ps involves neutralization of soluble TNFα and the dose correlates with that for IBD – it is reasonable to conclude that a dose of 120 mg should ensure a C_{trough} > 5 ug/mL which should ensure therapeutic effect in these indications.

Justification based on literature and previous Celltrion studies as summarised by the MAH

The CHMP concluded in scientific advice that clinical studies with Remsima SC would not be required in patients with AS, PsA and Ps to gain approval for SC formulation for all adult indications currently approved for IV formulation, if an appropriate review on association of PK parameters and clinical efficacy and safety in these three indications supports the posology. The review is summarized below.

Pharmacodynamic perspective: The efficacy of infliximab resides in its ability to generally modulate the immune system via binding of soluble TNFα, which is the predominant or sole mechanism of action in RA, AS, PsA and Ps while in the case of CD and UC binding to transmembrane TNFα is also important. The MAH considers it reasonable from the pharmacodynamic perspective to apply a C_{trough} threshold that is expected to provide optimal efficacy in both RA and IBD indications for AS, PsA and Ps, in which the mechanism of action is similar to RA and approved IV dose similar to IBD, i.e. 5 mg/kg Q8W.

Previous studies conducted by the MAH: Study CT-P13 1.1 was a randomized, double-blind, multicenter, multiple-dose, two-arm, parallel-group, efficacy, PK and safety study. Patients with AS (n=249) were treated with Remsima IV 5 mg/kg or Remicade IV 5 mg/kg. Subgroup analysis showed a clear trend in clinical response that correlated with C_{trough} levels: The median C_{trough} in the responders at Week 30 were 3.79 μg/mL and 3.49 μg/mL in the Remsima and Remicade treatment groups, respectively, whereas the median C_{trough} in the non-responders at Week 30 were 1.17 μg/mL and 1.45 μg/mL, respectively. The subgroup analysis by C_{trough} quartile also demonstrated the correlation between clinical response and C_{trough}.

Published scientific literature: As summarised in Table 35, trough levels for infliximab in AS, PsA and Ps patients have been positively associated with clinical response, although variability in the C_{trough} level associated with response is noted.

Table 35 Association between Infliximab C_{trough} levels and clinical outcomes in AS, PsA and PS

	Patient Type	Parameter	Infliximab C_{trough} µg/mL (patient number)	
			Responder	Non-responder
De Vries et al., 2007	AS (N=38)	ASAS-20 (Week 54)	8.2 [1] (21/38)	6.3 [1] (17/38)
Torii H et al., 2012	PsA & Ps (N=114)	PASI 90	≥2 [2]	< 1 [2] (at Week 30) < 0.1 [2] (at Week 46 onwards)
		PASI 90 (Week 50 or Week 70)	2.64 [2] (interquartile range: 1.12–3.82)	< 0.1 [1] (interquartile range: 0.1–1.40)
Reich et al., 2005	Ps (N=378)	PASI 75 (Week 50)	> 1 [2] (56/75)	< 1 [2] (19/75)
Takahashi H et al., 2013	Ps (N=20)	PASI 75	0.92 [1]	N/A
[1] Mean trough concentration of infliximab. [2] Median trough concentration of infliximab				

Passot et al (2016) investigated the influence of the underlying disease on infliximab PK parameters using a retrospective analysis of C_{trough} observations collected routinely at the University Hospital of Tours, France. Patients in whom ADA was detected during the follow-up were excluded from the analysis. Observations from 218 patients (91 with AS, 63 with CD, 16 with UC, 18 with RA (9 of whom co-treated with MTX), and 30 with PsA) were available. A one-compartment population PK model with first-order elimination rate described satisfactorily the observed data. The estimated PK parameters were similar for AS and PsA patients. Diagnosis of RA, CD, and UC was covariate on clearance with estimate 0.392, 0.384 and 0.472, respectively, i.e. clearance was increased compared with patients with AS and PsA. CD and UC were also covariates on volume of distribution with estimate 0.399 and 0.417. Clinical efficacy and safety were not investigated in the study.

The CHMP agreed with the analysis of study CT-P13 1.1 and the published literature indicating that infliximab trough concentrations are associated with clinical response in AS, PsA and Ps. Variability was observed in the mean or median C_{trough} in responders. This can be attributed to differences between patient populations (including baseline disease severity) and the outcome measure (e.g. PASI 90 vs PASI 75). In addition, older bioanalytical methods might not provide identical results compared with the most recent methods. In summary, it is difficult to estimate a specific target C_{trough}, but an average C_{trough} of approximately 5 µg/mL in patients with AS, PsA and Ps seems likely to be associated with clinical efficacy.

Passot et al. (2016) reported similar CL in patients with AS and PsA but higher CL in patients with RA. The authors suggested that this might be caused by higher TNF burden in RA patients. In patients with CD and UC both CL and V were higher than in AS (and PsA) patients. As both CL and V increased, the elimination half-life did not change markedly. A potential explanation for these results might be loss of infliximab in stools of patients with severe IBD (Brandse et al., 2015). Unlike Passot et al., results of the MAH's 2nd population PK analysis indicated similar clearance and volume parameter estimates for healthy volunteers and subjects with RA, AS, CD and UC. Differences between disease severity and the amount of post-dose PK samples may at least partly explain the differing results. If infliximab clearance in AS and PsA patients is lower than in CD and UC patients, exposure to infliximab would be increased.

With the proposed posology, the mean C_{trough} levels observed in both RA patients (study CT-P13 3.5 Part 2) and IBD patients (study CT-P13 1.6 Part 1 and Part 2) are well above the target levels in all weight bands. Based on the above, similar dosing in As and PsA as in IBD should give rise to similar or possibly

even slightly greater exposure.

Because it is known that the IV dose of 5mg/kg is efficacious in the sought indications, and C_{trough} has been shown to remain clearly higher with the 120mg SC dosing, even in patients without CIM and with positive NAb status, the CHMP agreed that it is expected that the proposed posology for the indications AS, PsA and Ps would results in a similar effect.

For discussion on extrapolation of safety and immunogenicity, see section 2.5 and the Benefit-Risk section.

2.4.4. Conclusions on the clinical efficacy

It is known that the IV infliximab dose of 5mg/kg is efficacious in the RA/ IBD/ AS/ PsA/ Ps-indications. It is also known that C_{trough}-levels above the threshold of 3-5 ug/mL correlate with efficacy in these indications. C_{trough} was shown to remain clearly higher than 5 ug/mL with the 120mg SC infliximab dosing in patients with RA (in the earlier line extension) and now in IBD, even in patients without CIM and with positive Nab status and also in the heaviest patients. Further, efficacy of SC infliximab was shown to be non-inferior to that of IV infliximab in RA in a properly powered randomized comparative trial.

The currently provided descriptive clinical efficacy data from a small, randomized, open label, mainly PK-study supports that Remsima SC 120mg is clinically non-inferior to Remsima IV 5mg/kg also in CD and UC patients. There is no clinical data in AS/ PsA/ Ps-patients treated with SC-infliximab. However, based on the above, it is expected that the proposed posology for AS, PsA, AS would result in similar C_{trough} levels and hence similar clinical effect as seen with IV-infliximab.

2.5. Clinical safety

Introduction

In all, safety data for Remsima SC have been collected in four clinical studies, consisting the overall clinical development programme for Remsima SC:

- Study CT-P13 1.5: Phase I, open-label, dose-escalating, single-dose study in which 38 healthy subjects were treated with CT-P13 IV or CT-P13 SC
- Study CT-P13 1.9: Phase I, open-label, single-dose PK and safety study in which 215 healthy subjects were treated with CT-P13 SC via auto-injector (AI) or CT-P13 SC via pre-filled syringe (PFS)
- Study CT-P13 3.5 Parts 1 and 2: Phase I/III, double-blind, randomised, multi-dose, parallel-group study in which 391 patients with RA (48 patients in Part 1 and 343 patients in Part 2) were treated with CT-P13 IV or CT-P13 SC
- Study CT-P13 1.6 Parts 1 and 2: Phase I, open-label, randomised, multi-dose, parallel-group study in which 175 patients with active Crohn's disease or active ulcerative colitis (CD or UC) (44 patients with CD in Part 1 and 131 patients with CD or UC in Part 2) were treated with CT-P13 IV or CT-P13 SC.

The complete safety data for studies CT-P13 1.5, CT-P13 1.9, CT-P13 3.5 Part 1 and Part 2 and Study CT-P13 1.6 Part 1 have been assessed in the line extension application (EMEA/H/C/002576/X/0062).

In the current application, new data was submitted, where clinical safety of Remsima SC was compared with Remsima IV, in subjects with CD and UC in study CT-P13 1.6. Part 2. Further details on the design and conduct of this study are found in the Clinical Efficacy-section of this AR.

Safety of Remsima SC was not studied in AS, Ps and PsA, which is in accordance with the CHMP scientific advice. Extrapolation of safety to these indications is discussed in the Extrapolation Section of this AR.

Patient exposure

The originator infliximab, Remicade IV, has been approved in the EU since 1999. The safety profile of infliximab has been well characterised by more than 20 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 IV has been approved in 80 countries, and launched in 60 countries worldwide. Thus, the overall total cumulative exposure with infliximab IV, including post-marketing exposure, is significant.

In all 819 subjects (391 RA patients, 97 CD patients, 78 UC patients and 253 healthy subjects) were exposed to at least one dose of CT-P13 IV or SC across four controlled clinical studies. 751 subjects (363 RA patients, 79 CD patients, 74 UC patients and 235 healthy subjects) have received at least one dose of CT-P13 SC, including those who switched to CT-P13 SC treatment at Week 30 (160 RA patients from Study CT-P13 3.5 Part 2 and 20 CD and 36 UC patients from Study CT-P13 1.6 Part 2). Overall, 654 subjects (221 HVs, 340 RA, 44 CD and 49 UC patients) received at least one dose of 120 mg of CT-P13 SC (Table 36).

In the study CT-P13 1.6 Part 2 a total of 136 patients were enrolled and 131 patients were randomly assigned to 1 of 2 treatment arms at Week 6; the safety population consisting of 66 (28 CD and 38 UC) patients in the SC 120/240 mg treatment arm and 65 (25 CD and 40 UC) patients in the IV 5 mg/kg treatment arm). From Week 6 to Week 54, 249 patients overall (172 RA, 44 CD and 33 UC patients) received CT-P13 SC and among them, 201 patients (155 RA, 24 CD and 22 UC patients) received 120 mg of CT-P13 SC.

The duration of the study for Part 2 was overall up to 62 weeks, which included screening (up to 6 weeks) and the last dose at 54 weeks plus the following 2 weeks off-dose period.

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

Table 36 Number of Subjects Exposed to CT-P13 SC in CT-P13 SC Studies

Study	Subjects	Dosage (CT-P13 SC)	Study Duration	Number of Patients Receiving			
				At Least 1 Dose of CT-P13 SC	CT-P13 SC Treatment from Weeks 6 to 30	CT-P13 SC Treatment from Weeks 6 to 54	CT-P13 SC Treatment from Weeks 6 to 64
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	328[1] (120 mg)	159[2] (120 mg)	146[2] (120 mg)	80 (120 mg)
Total in Rheumatoid Arthritis Patients				**363**	**192**	**172**	**80**
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
Study CT-P13 1.6 Part 2	CD	120 mg 240 mg	54 Weeks	33[3] (120 mg) 15[4] (240 mg)	17 (120 mg) 7 (240 mg)	15 (120 mg) 7 (240 mg)	N/A
Total in Crohn's Disease Patients				**79**	**50**	**44**	**N/A**
Study CT-P13 1.6 Part 2	UC	120 mg 240 mg	54 Weeks	49[5] (120 mg) 25[6] (240 mg)	22 (120 mg) 13 (240 mg)	22 (120 mg) 11 (240 mg)	N/A
Total in Ulcerative Colitis Patients				**74**	**35**	**33**	**N/A**
Total				**751**	**277**	**249**	**80**

Note: For the number of patients receiving CT-P13 SC from Weeks 6 to 30, 54 or 64, the number of patients who completed treatment up to the respective week (Weeks 30, 54 or 64) is counted regardless of doses skipped in between. [1] 168 patients in the SC arm and 160 patients in the IV arm who switched to CT-P13 SC treatment at Week 30. [2] Excluding Patient 3802-4002, who was randomised to the IV arm at Week 6, but was analysed in the SC arm for the safety population as the patient received CT-P13 SC 120 mg instead of placebo SC at Week 14 [3] 20 CD patients in the SC arm and 13 CD patients in the IV arm who switched to CT-P13 SC treatment at Week 30. [4] 8 CD patients in the SC arm and 7 CD patients in the IV arm who switched to CT-P13 SC treatment at Week 30. [5] 28 UC patients in the SC arm and 21 UC patients in the IV arm who switched to CT-P13 SC treatment at Week 30. [6] 10 UC patients in the SC arm and 15 UC patients in the IV arm who switched to CT-P13 SC treatment at Week 30. CD: Crohn's disease, HV: Healthy volunteers, IV: Intravenous, N/A: Not applicable, RA: Rheumatoid arthritis, SC: Subcutaneous, UC: Ulcerative colitis

Exposure by subject in Study CT-P13 1.6 Part 2

In the dose-loading phase, all randomized patients received two infusions of CT-P13 IV. The mean (SD) total administered doses were similar across the treatment arms (696.3 [141.38] and 724.3 [164.27] mg in the SC 120/240 mg and IV 5 mg/kg treatment arms, respectively).

The MAH has proposed a fixed maintenance dose 120 mg SC q2w. In the maintenance phase, the mean (SD) total administered dose was 3541.8 (1511.20) and 2818.0 (1292.90) mg in the SC 120/240 mg and IV 5 mg/kg treatment arms, respectively.

Table 37 Summary of Study Drug Exposure (Maintenance Phase): Safety Population

	SC 120/240 mg (N=66)	IV 5 mg/kg (N=65)
Maintenance Phase		
Total number of doses received		
n	66	65
Mean (SD)	22.6 (6.09)	13.2 (5.26)
Median (min, max)	25.0 (1, 25)	16.0 (1, 16)
Total administered dose (mg)		
n	66	65
Mean (SD)	3541.8 (1511.20)	2818.0 (1292.90)
Median (min, max)	3000.0 (120, 6000)	2547.5 (380, 4956)
Maintenance Phase (on or after Week 30)		
Total number of doses received		
n	59	56
Mean (SD)	12.6 (1.34)	12.0 (2.88)
Median (min, max)	13.0 (5, 13)	13.0 (1, 13)
Total administered dose (mg)		
n	59	56
Mean (SD)	2031.9 (733.96)	2046.4 (856.03)
Median (min, max)	1560.0 (600, 3120)	1560.0 (120, 3120)

Abbreviations: IV, intravenous; Max, maximum; Min, minimum; SC, subcutaneous; SD, standard deviation. Note: All patients who were continuing the study at Week 30 in the IV 5 mg/kg treatment arm were switched to receive CT-P13 SC treatment from Week 30.

The mean (SD) total number of SC and IV doses received during the maintenance phase was 22.6 (6.09) out of 25 doses and 13.2 (5.26) out of 16 doses in the SC 120/240 mg and IV 5 mg/kg treatment arms, respectively, indicating that the majority of patients nearly completed the treatment up to and including Week 54.

All patients who were ongoing with the study at Week 30 in the IV 5 mg/kg treatment arm switched to receive either 120 or 240 mg of CT-P13 SC treatment based on their body weight at Week 30. Among patients who were planned to receive SC 120 mg on or after Week 30, the number of patients with at least 1 escalated dose was similar between the 2 treatment arms (6/44 [13.6%] and 8/38 [21.1%] patients in the SC 120/240 mg and IV 5 mg/kg treatment arms, respectively).

In CD patients, the mean (SD) total administered dose in the dose-loading phase were similar across the two treatment arms (693.3 [130.46] and 707.9 [193.05] mg in the SC 120/240 mg and IV 5 mg/kg treatment arms, respectively). In the maintenance phase, the mean (SD) total administered dose was 3407.1 (1410.57) and 2630.1 (1435.03) mg in the SC 120/240 mg and IV 5 mg/kg treatment arms, respectively. The majority of the patients had completed the treatment up to and including Week 54.

In UC patients, the mean (SD) total administered dose in the dose-loading phase were similar across the two treatment arms (698.5 [150.62] and 734.6 [145.13] mg in the SC 120/240 mg and IV 5 mg/kg treatment arms, respectively). In the maintenance phase, the mean (SD) total administered dose was 3641.1 (1592.54) and 2935.5 (1199.59) mg in the SC 120/240 mg and IV 5 mg/kg treatment arms, respectively. The majority of the patients had completed the treatment up to and including Week 54.

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); 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 CT-P13 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), Systemic injection reactions (SIR) and delayed hypersensitivity reactions (DEL) and localised injection site reactions (ISR), intended to capture local injection site reactions; as well as infections (including TB), and malignancies.

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. Patient overall satisfaction were assessed by using 100-mm VAS as a tertiary endpoint.

Treatment Period
TEAEs during the treatment period (including dose-loading phase and a maintenance phase) are not presented here in detail for brevity. Overall 75.8% and 64.6% of patients in the SC and IV groups had at least one TEAE; 9.1% and 10.8% had at least one TESAE; 22.7% and 4.6% had localised ISR; and 36.4% and 30.8% had an infection.

TEAEs during the maintenance period from week 6 to less than week 30 are not presented here in detail for brevity (for data see section Analysis across studies). Overall 57.6% and 49.2% of patients

in the SC and IV groups had at least 1 TEAE; 3.0% and 6.2% had at least one TESAE; 16.7% and 1.5% had localised ISR; and 16.7% and 16.9% had an infection, respectively, with, overall, no unexpected findings or apparent differences or clear trends between the treatment arms, excluding the higher incidence of localised ISR in the SC arm, also seen in the entire maintenance phase of the study and in the pivotal RA study.

Maintenance Phase

An overall summary of TEAEs during the maintenance phase is presented for the safety population in the following table.

Table 38 Summary of Treatment-Emergent Adverse Events during the Maintenance Phase: Safety Population

	SC 120/240 mg (N=66)	IV 5 mg/kg (N=65)	Total (N=131)
Total number of TEAEs	**226**	**137**	**363**
Number (%) of patients with at least 1 TEAE	49 (74.2)	38 (58.5)	87 (66.4)
Related to the study drug	28 (42.4)	20 (30.8)	48 (36.6)
Unrelated to the study drug	41 (62.1)	32 (49.2)	73 (55.7)
Total number of TESAEs	**5**	**8**	**13**
Number (%) of patients with at least 1 TESAE	5 (7.6)	6 (9.2)	11 (8.4)
Related to the study drug	1 (1.5)	2 (3.1)	3 (2.3)
Unrelated to the study drug	4 (6.1)	5 (7.7)	9 (6.9)
Total number of TEAEs leading to study drug discontinuation	**1**	**3**	**4**
Number (%) of patients with at least 1 TEAE leading to study drug discontinuation	1 (1.5)	3 (4.6)	4 (3.1)
Related to the study drug	1 (1.5)	3 (4.6)	4 (3.1)
Unrelated to the study drug	0	0	0
Total number of TEAEs classified as IRR	**0**	**2**	**2**
Number (%) of patients with at least 1 TEAE classified as IRR	0	2 (3.1)	2 (1.5)
Total number of TEAEs classified as SIR	**1**	**0**	**1**
Number (%) of patients with at least 1 TEAE classified as SIR	1 (1.5)	0	1 (0.8)
Total number of TEAEs classified as delayed hypersensitivity	**2**	**0**	**2**
Number (%) of patients with at least 1 TEAE classified as delayed hypersensitivity	2 (3.0)	0	2 (1.5)
Total number of TEAEs classified as localized ISR	**50**	**14**	**64**
Number (%) of patients with at least 1 TEAE classified as localized ISR	15 (22.7)	3 (4.6)	18 (13.7)
Total number of TEAEs classified as infection	**31**	**24**	**55**
Number (%) of patients with at least 1 TEAE classified as infection	21 (31.8)	19 (29.2)	40 (30.5)
Total number of TEAEs classified as malignancy	**1**	**0**	**1**
Number (%) of patients with at least 1 TEAE classified as malignancy	1 (1.5)	0	1 (0.8)

Abbreviations: 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. Note: The total number of TEAEs included all-

patient events. At each level of summarization, 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".

On or after Week 30

An overall summary of TEAEs on or after Week 30 is presented for the safety population in Table 39.

Table 39 Summary of Treatment-Emergent Adverse Events on or after Week 30: Safety Population

	SC 120/240 mg (N=66)	IV 5 mg/kg (N=65)	Total (N=131)
Total number of TEAEs	**115**	**57**	**172**
Number (%) of patients with at least 1 TEAE	31 (47.0)	21 (32.3)	52 (39.7)
Related to the study drug	13 (19.7)	11 (16.9)	24 (18.3)
Unrelated to the study drug	26 (39.4)	13 (20.0)	39 (29.8)
Total number of TESAEs	**3**	**4**	**7**
Number (%) of patients with at least 1 TESAE	3 (4.5)	2 (3.1)	5 (3.8)
Related to the study drug	1 (1.5)	1 (1.5)	2 (1.5)
Unrelated to the study drug	2 (3.0)	2 (3.1)	4 (3.1)
Total number of TEAEs leading to study drug discontinuation	**1**	**0**	**1**
Number (%) of patients with at least 1 TEAE leading to study drug discontinuation	1 (1.5)	0	1 (0.8)
Related to the study drug	1 (1.5)	0	1 (0.8)
Unrelated to the study drug	0	0	0
Total number of TEAEs classified as SIR	**1**	**0**	**1**
Number (%) of patients with at least 1 TEAE classified as SIR	1 (1.5)	0	1 (0.8)
Total number of TEAEs classified as delayed hypersensitivity	**1**	**0**	**1**
Number (%) of patients with at least 1 TEAE classified as delayed hypersensitivity	1 (1.5)	0	1 (0.8)
Total number of TEAEs classified as localized ISR	**25**	**13**	**38**
Number (%) of patients with at least 1 TEAE classified as localized ISR	7 (10.6)	2 (3.1)	9 (6.9)
Total number of TEAEs classified as infection	**16**	**12**	**28**
Number (%) of patients with at least 1 TEAE classified as infection	12 (18.2)	9 (13.8)	21 (16.0)
Total number of TEAEs classified as malignancy	**1**	**0**	**1**
Number (%) of patients with at least 1 TEAE classified as malignancy	1 (1.5)	0	1 (0.8)

Abbreviations: ISR, injection site reaction; IV, intravenous; SC, subcutaneous; SIR, systemic injection reaction; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event. Note: The total number of TEAEs included all-patient events. At each level of summarization, 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". All patients who were continuing the study at Week 30 in the IV 5 mg/kg treatment arm were switched to receive CT-P13 SC treatment from Week 30. Treatment-emergent AEs occurred on or after Week 30 were summarized.

Display of Adverse Events

Treatment Period

All TEAEs during the treatment period that were reported for at least 5% of patients in any treatment arm: are summarized by SOC and PT for the safety population in Table 40.

Table 40 Treatment-Emergent Adverse Events Reported during the Treatment Period for at Least 5% of Patients in Any Treatment Arm by System Organ Class and Preferred Term: Safety Population

System Organ Class[1] Preferred Term[1]	SC 120/240 mg (N=66)	IV 5 mg/kg (N=65)	Total (N=131)
	Number (%) of patients		
Gastrointestinal disorders	**18 (27.3)**	**12 (18.5)**	**30 (22.9)**
Colitis ulcerative	5 (7.6)	8 (12.3)	13 (9.9)
Abdominal pain	6 (9.1)	2 (3.1)	8 (6.1)
Nausea	6 (9.1)	1 (1.5)	7 (5.3)
Diarrhoea	5 (7.6)	1 (1.5)	6 (4.6)
Vomiting	5 (7.6)	1 (1.5)	6 (4.6)
General disorders and administration site conditions	**15 (22.7)**	**3 (4.6)**	**18 (13.7)**
Localized injection site reaction[2]	15 (22.7)	3 (4.6)	18 (13.7)
Nervous system disorders	**5 (7.6)**	**8 (12.3)**	**13 (9.9)**
Headache	5 (7.6)	8 (12.3)	13 (9.9)
Blood and lymphatic system disorders	**7 (10.6)**	**3 (4.6)**	**10 (7.6)**
Neutropenia	5 (7.6)	3 (4.6)	8 (6.1)
Leukopenia	4 (6.1)	2 (3.1)	6 (4.6)
Infections and infestations	**8 (12.1)**	**2 (3.1)**	**10 (7.6)**
Nasopharyngitis	4 (6.1)	2 (3.1)	6 (4.6)
Oral herpes	4 (6.1)	0	4 (3.1)
Skin and subcutaneous tissue disorders	**5 (7.6)**	**5 (7.7)**	**10 (7.6)**
Rash	5 (7.6)	5 (7.7)	10 (7.6)
Musculoskeletal and connective tissue disorders	**5 (7.6)**	**4 (6.2)**	**9 (6.9)**
Arthralgia	5 (7.6)	4 (6.2)	9 (6.9)

Abbreviations: IV, intravenous; SC, subcutaneous; TEAE, treatment-emergent adverse event. Note: At each level of summarization, patients were counted once if they reported 1 or more events. Only the most severe event was counted. 1 From MedDRA, Version 20.1. 2Preferred term reported as "injection site reaction".

Maintenance Phase

All TEAEs during the maintenance phase that were reported for at least 5% of patients in any treatment arm are summarized by SOC and PT for the safety population in Table 41.

Table 41 Treatment-Emergent Adverse Events Reported during the Maintenance Phase for at Least 5% of Patients in Any Treatment Arm by System Organ Class and Preferred Term: Safety Population

System Organ Class[1] Preferred Term[1]	SC 120/240 mg (N=66)	IV 5 mg/kg (N=65)	Total (N=131)
	Number (%) of patients		
Gastrointestinal disorders	**14 (21.2)**	**11 (16.9)**	**25 (19.1)**
Colitis ulcerative	3 (4.5)	8 (12.3)	11 (8.4)
Abdominal pain	5 (7.6)	1 (1.5)	6 (4.6)
Nausea	5 (7.6)	1 (1.5)	6 (4.6)
Diarrhoea	4 (6.1)	1 (1.5)	5 (3.8)
General disorders and administration site conditions	**15 (22.7)**	**3 (4.6)**	**18 (13.7)**
Localized injection site reaction[2]	15 (22.7)	3 (4.6)	18 (13.7)
Blood and lymphatic system disorders	**7 (10.6)**	**3 (4.6)**	**10 (7.6)**
Neutropenia	5 (7.6)	3 (4.6)	8 (6.1)
Leukopenia	4 (6.1)	1 (1.5)	5 (3.8)
Skin and subcutaneous tissue disorders	**4 (6.1)**	**4 (6.2)**	**8 (6.1)**
Rash	4 (6.1)	4 (6.2)	8 (6.1)
Nervous system disorders	**4 (6.1)**	**3 (4.6)**	**7 (5.3)**
Headache	4 (6.1)	3 (4.6)	7 (5.3)
Infections and infestations	**4 (6.1)**	**2 (3.1)**	**6 (4.6)**
Nasopharyngitis	4 (6.1)	2 (3.1)	6 (4.6)
Musculoskeletal and connective tissue disorders	**2 (3.0)**	**4 (6.2)**	**6 (4.6)**
Arthralgia	2 (3.0)	4 (6.2)	6 (4.6)

Abbreviations: IV, intravenous; SC, subcutaneous; TEAE, treatment-emergent adverse event. Note: At each level of summarization, patients were counted once if they reported 1 or more events. Only the most severe event was counted. 1 From MedDRA, Version 20.1.2 Preferred term reported as "injection site reaction".

In CD patients, the proportion of patients who experienced at least 1 TEAE during the maintenance phase was higher in the SC 120/240 mg treatment arm (23 [82.1%] and 14 [56.0%] patients for the SC 120/240 mg and IV 5 mg/kg treatment arms, respectively); the difference in the incidence of TEAEs between the 2 treatment arms could be attributed to the higher proportion of patients who experienced at least 1 TEAE classified as gastrointestinal disorders in the SC 120/240 mg treatment arm. However, the proportion of the patients with the medical history of gastrointestinal disorders was higher in the SC 120/240 mg treatment arm at baseline as well.

In UC patients, the proportion of patients who experienced at least 1 TEAE during the maintenance phase was similar between the 2 treatment arms (26 [68.4%] and 24 [60.0%] patients for the SC 120/240 mg and IV 5 mg/kg treatment arms, respectively).

On or after Week 30

 All TEAEs on or after Week 30 that were reported for at least 5% of patients in any treatment arm are summarized by SOC and PT for the safety population in Table 42.

Table 42 Treatment-Emergent Adverse Events Reported on or after Week 30 for at Least 5% of Patients in Any Treatment Arm by System Organ Class and Preferred Term: Safety Population

System Organ Class[1] Preferred Term[1]	SC 120/240 mg (N=66)	IV 5 mg/kg (N=65)	Total (N=131)
	Number (%) of patients		
General disorders and administration site conditions	**7 (10.6)**	**2 (3.1)**	**9 (6.9)**
Localized injection site reaction[2]	7 (10.6)	2 (3.1)	9 (6.9)
Gastrointestinal disorders	**4 (6.1)**	**0**	**4 (3.1)**
Abdominal pain	4 (6.1)	0	4 (3.1)

Abbreviations: IV, intravenous; SC, subcutaneous; TEAE, treatment-emergent adverse event. Note: At each level of summarization, patients were counted once if they reported 1 or more events. Only the most severe event was counted. All patients who were continuing the study at Week 30 in the IV 5 mg/kg treatment arm were switched to receive CT-P13 SC treatment from Week 30. Treatment-emergent AEs occurred on or after Week 30 were summarized.1. From MedDRA, Version 20.1. 2. Preferred term reported as "injection site reaction".

In CD patients, the proportion of patients who experienced at least 1 TEAE on or after Week 30 was higher in the SC 120/240 mg treatment arm (14 [50.0%] and 8 [32.0%] patients for the SC 120/240 mg and IV 5 mg/kg treatment arms, respectively); the difference in the incidence of TEAEs between the 2 treatment arms could be attributed to the higher proportion of patients who experienced at least 1 TEAE classified as gastrointestinal disorders in the SC 120/240 mg treatment arm. However, the proportion of the patients with the medical history of gastrointestinal disorders was higher in the SC 120/240 mg treatment arm at baseline as well.

In UC patients, the proportion of patients who experienced at least 1 TEAE on or after Week 30 was slightly higher in the SC 120/240 mg treatment arm (17 [44.7%] and 13 [32.5%] patients for the SC 120/240 mg and IV 5 mg/kg treatment arms, respectively).

Treatment-Emergent Adverse Events Considered by the Investigator to be Related to the Study Drug Treatment Period

Maintenance Phase

The proportion of patients who experienced at least 1 TEAE considered by the investigator to be related to study drug during the maintenance phase was slightly higher in SC 120/240 mg treatment arm (28 [42.4%] and 20 [30.8%] patients for the SC 120/240 mg and IV 5 mg/kg treatment arms, respectively).

The most frequently reported related TEAE was localised ISR (14 [21.2%] patients) in the SC 120/240 mg treatment arm, an expected trend based on the route of administration; and for patients in the IV 5 mg/kg treatment arm, localised ISR and rash, but reported in only 3 (4.6%) patients each.

On or after Week 30

The proportion of patients who experienced at least 1 TEAE considered by the investigator to be related to study drug on or after Week 30 was similar between the 2 treatment arms after switching to SC 120/240 mg in IV 5 mg/kg treatment arm at Week 30 (13 [19.7%] and 11 [16.9%] patients for the SC 120/240 mg and IV 5 mg/kg treatment arms, respectively).

The most frequently reported TEAE considered by the investigator to be related to study drug on or after Week 30 was localised ISR (7 [10.6%] patients) in the SC treatment arm; and localised ISR (2 [3.1%] patients) and neutropenia (2 [3.1%] patients) in the IV 5 mg/kg treatment arm.

Treatment-Emergent Adverse Events by Intensity

Maintenance Phase

The majority of TEAEs reported during the maintenance phase were CTCAE grade 1 or 2 in intensity.

The number of patients who experienced at least 1 grade 3 TEAE considered by the investigator to be related to the study drug was 8 (6.1%) patients (2 [3.0%] and 6 [9.2%] patients in the SC 120/240 mg and IV 5 mg/kg treatment arms, respectively).

Three grade 4 TEAEs during the maintenance phase were reported for 3 (2.3%) patients (2 [3.0%] and 1 [1.5%] patients in the SC 120/240 mg and IV 5 mg/kg treatment arms, respectively). Of these, grade 4 TEAE of neutropenia was reported in 1 patient each the SC 120/240 mg and IV 5 mg/kg treatment arms, and grade 4 TEAE of appendicitis was reported in 1 patient the SC 120/240 mg treatment arm. All grade 4 TEAEs were considered by the investigator to be unrelated to the study drug. Of these, only appendicitis was reported as TESAE.

On or after Week 30

The majority of TEAEs on or after Week 30 were grade 1 or 2 in intensity. In terms of grade 3 or higher TEAEs, there were no notable differences between the 2 treatment arms after switching to SC 120/240 mg in the IV 5 mg/kg treatment arm at Week 30.

Serious adverse event/deaths/other significant events

Deaths

No deaths were reported during the study CT-P13 1.6 part 2.

Maintenance Phase

The number of patients who experienced at least 1 TESAE during the maintenance phase are given in Table 43.

In CD patients, the proportion of patients who experienced at least 1 TESAE during the maintenance phase were 3 (10.7%) and 2 (8.0%) patients for the SC 120/240 mg and IV 5 mg/kg treatment arms, respectively. In UC patients, the proportion of patients who experienced at least 1 TESAE during the maintenance phase were 2 (5.3%) and 4 (10.0%) patients for the SC 120/240 mg and IV 5 mg/kg treatment arms, respectively.

There were no notable differences between the 2 treatment arms in proportion of patients who experienced at least 1 TESAE after switching to SC 120/240 mg in IV 5 mg/kg treatment arm at Week 30.

Table 43 Treatment-Emergent Serious Adverse Events during the Maintenance phase by System Organ Class and Preferred Term: Safety Population

System Organ Class[1] Preferred Term[1]	SC 120/240 mg (N=66)	IV 5 mg/kg (N=65)	Total (N=131)
	Number (%) of patients		
Total number of TESAEs	**5**	**9**	**14**
Number (%) of patients with at least 1 TESAE	**5 (7.6)**	**7 (10.8)**	**12 (9.2)**
Related	1 (1.5)	3 (4.6)	4 (3.1)
Unrelated	4 (6.1)	5 (7.7)	9 (6.9)
Infections and infestations	**2 (3.0)**	**4 (6.2)**	**6 (4.6)**
Anal abscess – Grade 3, unrelated	1 (1.5)	0	1 (0.8)
Appendicitis – Grade 4, unrelated	1 (1.5)	0	1 (0.8)
Bronchitis – Grade 3, related	0	1 (1.5)	1 (0.8)
Disseminated tuberculosis – Grade 3, related	0	1 (1.5)	1 (0.8)
Pneumonia – Grade 3, related	0	1 (1.5)	1 (0.8)
Pneumonia legionella – Grade 3, unrelated	0	1 (1.5)	1 (0.8)
Viral infection – Grade 3, unrelated	0	1 (1.5)	1 (0.8)
Gastrointestinal disorders	**0**	**2 (3.1)**	**2 (1.5)**
Diarrhoea – Grade 3, unrelated	0	1 (1.5)	1 (0.8)
Irritable bowel syndrome – Grade 3, unrelated	0	1 (1.5)	1 (0.8)
Blood and lymphatic system disorders	**1 (1.5)**	**0**	**1 (0.8)**
Anaemia – Grade 3, unrelated	1 (1.5)	0	1 (0.8)
Injury, poisoning and procedural complications	**0**	**1 (1.5)**	**1 (0.8)**
Contusion – Grade 3, unrelated	0	1 (1.5)	1 (0.8)
Neoplasms benign, malignant and unspecified (incl. cysts and polys)	**1 (1.5)**	**0**	**1 (0.8)**
Non-small cell lung cancer – Grade 3, related	1 (1.5)	0	1 (0.8)
Pregnancy, puerperium and perinatal conditions	**0**	**1 (1.5)**	**1(0.8)**
Abortion spontaneous – Grade 3, related	0	1 (1.5)	1(0.8)
Renal and urinary disorders	**1 (1.5)**	**0**	**1 (0.8)**
Nephrolithiasis – Grade 3, unrelated	1 (1.5)	0	1 (0.8)

Abbreviations: IV, intravenous; SC, subcutaneous; TESAE, treatment-emergent serious adverse event. Note: At each level of summarization, 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 20.1.

Other Significant Adverse Events

Discontinuation due to adverse events

Maintenance Phase

The TEAEs leading to permanent discontinuation of study drug during the maintenance phase were reported for 1 (1.5%) and 3 (4.6%) patients in the SC 120/240 mg and IV 5 mg/kg treatment arms, respectively (Table 44).

Table 44 Treatment-Emergent Adverse Events Leading to Permanent Discontinuation of Study Drug Reported during the Maintenance phase by System Organ Class and Preferred Term: Safety population

System Organ Class[1] Preferred Term[1]	SC 120/240 mg (N=66)	IV 5 mg/kg (N=65)	Total (N=131)
	Number (%) of patients		
Total number of TEAEs leading to permanent discontinuation of study drug	1	3	4
Number (%) of patients with at least 1 TEAE leading to permanent discontinuation of study drug	1 (1.5)	3 (4.6)	4 (3.1)
Related	1 (1.5)	3 (4.6)	4 (3.1)
Infections and infestations	0	1 (1.5)	1 (0.8)
Disseminated tuberculosis – Grade 3	0	1 (1.5)	1 (0.8)
Injury, poisoning and procedural complications	0	1 (1.5)	1 (0.8)
Infusion related reaction[2] – Grade 2	0	1 (1.5)	1 (0.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.5)	0	1 (0.8)
Non-small cell lung cancer – Grade 3	1 (1.5)	0	1 (0.8)
Skin and subcutaneous tissue disorders	0	1 (1.5)	1 (0.8)
Psoriasis – Grade 3	0	1 (1.5)	1 (0.8)

Abbreviations: IV, intravenous; PT, preferred term; SC, subcutaneous; TEAE, treatment-emergent adverse event. Note: At each level of summarization, 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 20.1. [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.

Infusion Reaction, Systemic Injection Reaction or Delayed Hypersensitivity

Maintenance Phase

The TEAEs classified as IRR (AEs checked as ARR in the eCRF and occurred between start of administration and 24 hours from the end of IV infusion) during the maintenance phase was reported for 2 (3.1%) patients in the IV 5 mg/kg treatment arm, one patient was withdrawn from the study at Week 14 due to this event. Both were ADA and NAb positive when IRRs occurred and both events were grade 2 in intensity. The reported sign and symptom was dyspnea. The patients recovered without treatment within a day.

The TEAEs classified as grade 1 SIR (AEs checked as ARR in the eCRF and occurred between start of administration and 24 hours from the SC injection) during the maintenance phase was reported for 1 (1.5%) CD patient, at week 52, in SC 120/240 mg treatment arm only. This patient's ADA and NAb results were all negative over the study period. The reported signs and symptoms were nausea and dizziness. The patient recovered without treatment within a day.

The TEAEs classified as delayed hypersensitivity (AEs checked as ARR in the eCRF and that occurred after 24 hours from the study drug administration) were reported for 2 (3.0%) patients in SC 120/240 mg treatment arm only.

One UC patient experienced TEAE classified as delayed hypersensitivity 2 days after the study drug administration at Week 6 with sign and symptom of vascular headache. The patient's ADA and NAb results were negative when the event occurred. The patient recovered without treatment within a day.

Another CD patient experienced TEAE classified as delayed hypersensitivity 1 day after the study drug administration at Week 52 with signs and symptoms of edema and flushing. Patient's ADA results performed on Week 46 and Week 54 were positive while the NAb results were negative. The patient recovered without treatment 3 days after onset. Complement tests were not provided for either of these events.

There were no notable differences between the two treatment arms in proportion of patients with TEAEs classified as SIR or delayed hypersensitivity on or after Week 30.

Localised Injection Site Reaction

Maintenance Phase

As expected for the SC route of administration, the proportion of patients who experienced at least 1 TEAE classified as localised ISR during the maintenance phase was higher in the SC 120/240 mg treatment arm compared to the IV 5 mg/kg treatment arm (15 [22.7%] and 3 [4.6%] patients in the SC 120/240 mg and IV 5 mg/kg treatment arms, respectively).

The most frequently reported signs and symptoms of localised ISR in all patients during the maintenance phase were injection site erythema; they were of grade 1 or 2 in intensity and majority of the patients recovered without any treatments.

No serious localised ISRs were reported.

The TEAEs classified as localised ISR on or after Week 30 were reported, in all, in 9 (6.9%) patients, (7 [10.6%] and 2 [3.1%] patients in the SC 120/240 mg and IV 5 mg/kg treatment arms, respectively). Of these, 3 out of the 7 patients in the SC 120/240 mg treatment arm had reported localised ISR before Week 30.

Table 45 Treatment-Emergent Adverse Events Classified as Localized Injection Site Reaction during the Maintenance Phase by SOC and PT: Safety Population

System Organ Class[1] Preferred Term[1]	SC 120/240 mg (N=66)	IV 5 mg/kg (N=65)	Total (N=131)
	Number (%) of patients		
Total number of TEAEs classified as localized ISR	50	14	64
Number (%) of patients with at least 1 TEAE classified as localized ISR	15 (22.7)	3 (4.6)	18 (13.7)
General disorders and administration site conditions	15 (22.7)	3 (4.6)	18 (13.7)
Localized injection site reaction[2]	15 (22.7)	3 (4.6)	18 (13.7)
Related	14 (21.2)	3 (4.6)	17 (13.0)
Grade 1	11 (16.7)	1 (1.5)	12 (9.2)
Grade 2	3 (4.5)	2 (3.1)	5 (3.8)
Unrelated	1 (1.5)	0	1 (0.8)
Grade 1	1 (1.5)	0	1 (0.8)

Abbreviations: ISR, injection site reaction; IV, intravenous; PT, preferred term; SC, subcutaneous; TEAE, treatment-emergent adverse event. Note: At each level of summarization, 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. From MedDRA, Version 20.1.Preferred term reported as "injection site reaction".

Infections

Maintenance Phase

The proportion of patients who experienced at least 1 TEAE classified as infection during the maintenance phase was similar between the 2 treatment arms (21 [31.8%] and 19 [29.2%] patients in the SC 120/240 mg and IV 5 mg/kg treatment arms, respectively).

The most frequently reported TEAEs classified as infection during the maintenance phase were nasopharyngitis reported in 4 (6.1%) patients for the SC 120/240 mg treatment arm and nasopharyngitis, bronchitis, latent TB and sinusitis reported in 2 (3.1%) patients each for the IV 5 mg/kg treatment arm; majority were grade 1 or 2 in intensity.

In CD patients, the proportion of patients who experienced at least 1 TEAE classified as infection during the maintenance phase was slightly higher in the SC arm (11 [39.3%] and 7 [28.0%] patients for the SC and IV arms, respectively). Of these, 2 out of 11 patients in the SC 120/240 mg treatment arm had a medical history of infection, which was directly related to the TEAE classified as infection. Furthermore, 7 out of 11 patients in SC 120/240 mg treatment arm and 4 out of 7 patients in the IV arm used long-term immunosuppressants as prior and/or concomitant medications, until the events occurred.

In UC patients, the proportion of patients who experienced at least 1 TEAE classified as infection during the maintenance phase was similar in the 2 treatment arms (10 [26.3%] and 12 [30%] patients for the SC 120/240 mg and IV 5 mg/kg treatment arms, respectively).

Malignancy

Maintenance Phase

The TEAE classified as malignancy during the maintenance phase was reported for 1 (1.5%) patient in SC 120/240 mg treatment arm only. The patient (CD) was a 67-year-old white female who received the first dose of study drug on 04 July 2018 and experienced grade 3 NSCLC 1 day after Week 50 drug administration. As a result, the patient was hospitalised and received left upper lobectomy and

chemotherapy. The investigator reported the causal relationship of the event to study drug as possibly related and the patient discontinued the study due to this event. The event was considered resolved with the sequelae of left upper lobectomy.

Laboratory findings

Over time, the changes from baseline in all clinical chemistry, urinalysis, and hematology laboratory parameters were generally small, and there were no notable differences between the 2 treatment arms (for CRP and ESR see PD section of this AR).

Individual Clinically Significant Abnormalities

The majority of patients had no CTCAE grade or CTCAE grade 1 (mild) for each laboratory parameter and each subsequent time point. The majority of the abnormal laboratory results with CTCAE grade 3 (severe) or higher were reported during the maintenance phase (Table 46).

Table 46 Summary of Most Severe CTCAE Grading during the Maintenance Phase (CTCAE Grade 3 or Higher): Safety Population

Laboratory Category CTCAE Term CTCAE Grade	SC 120/240 mg (N=66)	IV 5 mg/kg (N=65)	Total (N=131)
	Number (%) of patients		
Clinical Chemistry			
Alanine aminotransferase increased			
Grade 3 (Severe)	0	1 (1.5)	1 (0.8)
CPK increased			
Grade 4 (Life-Threatening)	2 (3.0)	0	2 (1.5)
GGT increased			
Grade 3 (Severe)	1 (1.5)	0	1 (0.8)
Hypertriglyceridemia			
Grade 3 (Severe)	2 (3.0)	0	2 (1.5)
Hematology			
Anemia			
Grade 3 (Severe)	1 (1.5)	0	1 (0.8)
Lymphocyte count decreased			
Grade 3 (Severe)	2 (3.0)	0	2 (1.5)
Neutrophil count decreased			
Grade 3 (Severe)	3 (4.5)	4 (6.2)	7 (5.3)
Grade 4 (Life-Threatening)	1 (1.5)	1 (1.5)	2 (1.5)
Platelet count decreased			
Grade 3 (Severe)	1 (1.5)	0	1 (0.8)
White blood cell decreased			
Grade 3 (Severe)	0	2 (3.1)	2 (1.5)

Abbreviations: CPK, creatine phosphokinase; CTCAE, Common Terminology Criteria for Adverse Events; GGT, gamma glutamyl transferase; IV, intravenous; SC, subcutaneous. Note: The summary included only the most severe case during scheduled visit, unscheduled visit, or EOS visit. Percentages were calculated by using the number of patients in the safety population as the denominator. At each level of summarization, only the most severe case was counted. The results after study drug administration at Week 6 were included.

Complement (C3, C4) and Total Hemolytic Complement

Complement tests (C3, C4, and total hemolytic complement) were assessed at Week 0 for all patients in each treatment arm and when a patient experienced a delayed hypersensitivity reaction to determine serum sickness. Two cases of delayed hypersensitivity, occurring after 24 hours of study drug administration, were observed in the SC 120/240 mg arm. These two cases were both considered minor event and they resolved without requiring treatment. No confirmed cases of serum sickness were observed in the study.

Vital Sign Measurements, Hypersensitivity Monitoring, and Other Observations Related to Safety

Vital Signs, Weight, and Body Mass Index

Mean changes from baseline in vital sign, during hypersensitivity monitoring and weight values were small, and there were no notable differences between the 2 treatment arms at any time point. In both treatment arms, the most commonly reported clinically notable vital sign results during hypersensitivity monitoring were high diastolic blood pressure.

Electrocardiogram Patients with normal or abnormal, not clinically significant ECG results at baseline did not have clinically significant ECG result at post-baseline scheduled visits, except for 3 (2.3%) patients (2 patients in the SC 120/240 mg and 1 patient in the IV 5 mg/kg treatment arm).

Physical examination The majority of patients generally had normal baseline physical examination findings, which remained normal at each post-baseline visit excluding EOS and unscheduled visit.

Tuberculosis A single patient with UC in the IV 5 mg/kg treatment arm was withdrawn due to reported grade 3 TESAE of disseminated TB after Week 14.

Local Site Pain Higher level of mean VAS of local site pain was observed in the SC arm at logical time points, as at the first time of SC injection and at treatment switch.

Safety in special populations

Adverse Events by Age

Overall, no consistent trend between the subgroups of different ages was observed in both treatment arms (Table 47).

Table 47 Summary of Safety by Age for Patients in CT-P13 1.6 Part 2 up to Week 54 Maintenance Phase): Safety Population

Subgroup (Age [Years])	CT-P13 IV 5 mg/kg		CT-P13 SC 120/240 mg	
	< 65	≥ 65	< 65	≥ 65
N	59	6	62	4
TEAE	33 (55.9)	5 (83.3)	45 (72.6)	4 (100.0)
TESAE	5 (8.5)	1 (16.7)	4 (6.5)	1 (25.0)
IRR	2 (3.4)	0	0	0
SIR	0	0	1 (1.6)	0
Localised ISR	3 (5.1)	0	14 (22.6)	1 (25.0)
Infection	17 (28.8)	2 (33.3)	20 (32.3)	1 (25.0)
Serious Infection	3 (5.1)	1 (16.7)	2 (3.2)	0

Note: Patients in the IV 5 mg/kg arm switched to CT-P13 SC treatment at Week 30. IV: Intravenous, IRR: Infusion related reaction, ISR: Injection site reaction, SC: Subcutaneous, SIR: Systemic injection reaction, TEAE: Treatment-emergent adverse event, TESAE: Treatment-emergent serious adverse event.

Adverse Events by Gender

For TEAE, the incidence rate of TEAE was higher in the female patients (83.3%) than male patients (66.7%) in the SC 120/240 mg arm. However, this was likely driven by the higher rate of localised ISR, which were all Grade 1 or 2 in severity.

Adverse Events by Infliximab Serum Concentration Level

Key safety features were analysed by serum concentration level for the patients of the SC 120/240 mg arm in Study CT-P13 1.6 Part 2, and are summarised in Table 48. The patients were categorised using 33rd and 67th percentile of mean pre-dose serum concentration at Weeks 22, 30, 38, 46 and 54. Overall, there was no apparent correlation between the incidence of the events and mean pre-dose serum concentration level in patients administered with CT-P13 SC.

Table 48 Summary of Key Safety Features by Mean Concentration Level in the CT-P13 SC Arm in Study CT-P13 1.6 Part 2 (Maintenance Phase) up to week 54: Safety Population

C_{trough} (ng/mL)	Con ≤ 17880 (N=20)	17880 < Con ≤ 24820 (N=20)	Con > 24820 (N=19)
TEAE	16 (80.0)	16 (80.0)	12 (63.2)
Grade 3 TEAE	3 (15.0)	4 (20.0)	4 (21.1)
TESAE	0	3 (15.0)	2 (10.5)
TEAE leading to discontinuation	0	1 (5.0)	0
SIR	0	1 (5.0)	0
Localised ISR	4 (20.0)	5 (25.0)	5 (26.3)
Infection	5 (25.0)	9 (45.0)	5 (26.3)
Serious infection	0	1 (5.0)	1 (5.3)

Note: The patients were categorised using 33 and 67 percentile of mean concentration of predose at Weeks 22, 30, 38, 46 and 54 in the Safety Population. Seven patients were recorded as "missing" due to missing serum concentration levels.
Con: Concentration, ISR: Injection site reaction, SC: Subcutaneous, SIR: Systemic injection reaction, TEAE: Treatment-emergent adverse event, TESAE: Treatment-emergent serious adverse event

Adverse Events by Weight (<80 kg; > 80 kg)

A requested subgroup analysis by body weight of < 80 kg and ≥ 80 kg showed (acknowledging the low numbers in some of the weight subgroups) no apparent correlation between body weight and the safety profiles of either the CT-P13 IV or SC treatment arms.

Immunological events and Immunogenicity

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.

Immunogenicity

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). Results from studies CT-P13 1.5, CT-P13 1.9 and CT-P13 3.5 and preliminary results from Study CT-P13 1.6 Part 1 have been assessed in the line extension application (EMEA/H/C/2576/X/62). Briefly, the results were as follows:

- In healthy volunteers (HV), the proportion of anti-drug antibodies (ADA) and neutralising antibodies (NAb) positive patients were higher in the CT-P13 SC cohorts compared to the CT-P13 IV cohort (Study CT-P13 1.5).

- In contrast to what was observed in healthy volunteers, in both inflammatory bowel disease (IBD) and RA patients, the ADA results showed a trend to comparable proportions of patients with positive ADA response between the CT-P13 IV and CT-P13 SC arms (Studies CT-P13 1.6 and CT-P13 3.5).

- ADA presence was associated with reduced drug exposure, while the degree of impact of the ADA status on the drug exposure was similar between the CT-P13 IV and CT-P13 SC arms (Study CT-P13 3.5 Part 2)

- Higher ADA titre was associated with slightly reduced efficacy. Nonetheless, there was no evidence that the presence of ADAs is associated with clinical deterioration or with an increased safety risk (Study CT-P13 3.5 Part 2)

Taking into consideration the potential for drug interference due to the relatively high drug serum concentrations observed in samples taken from patients receiving CT-P13 SC, the MAH has developed a new ADA assay method based on an ECL platform. Therefore, immunogenicity samples in Study CT-P13 1.6 Part 1 and Part 2 and Study CT-P13 3.5 Part 1 and Part 2 were re-analysed.

Sampling

Table 49 Immunogenicity Sampling Time point in Studies CT-P13 1.6 and 3.5

Clinical Study	Sampling Time point
Study CT-P13 1.6 Part 1 and 2 (RD, CD, UC)	Weeks 0, 6, 14, 22, 30, 38, 46, 54 and EOS [1] visit
Study CT-P13 3.5 Part 1 and 2 (RD, RA)	Weeks 0, 6, 14, 22, 30, 38, 46, 54 and EOS [1] visit

[1] In Studies CT-P13 1.6 Part 1 and CT-P13 3.5 Part 1, all EOS assessments were completed 8 weeks after the last study drug administration. In Study CT-P13 1.6 Part 2, all EOS assessments were completed 2 weeks after the last study drug administration. For patients with early discontinuation before switching to CT-P13 SC at Week 30 in the CT-P13 IV 5 mg/kg arm or before randomisation at Week 6 in the CT-P13 SC 120/ 240 mg arm, the EOS visit occurred 8 weeks after the last dose of CT-P13 IV was received. In Study CT-P13 3.5 Part 2, the EOS assessments were completed 2 weeks after the last dose of CT-P13 SC was received. For patients who discontinued the study early, before Week 30, all EOS assessments were completed 8 weeks after the last CT-P13 IV or placebo IV was received (Weeks 0, 2, 6, 14, and 22). For patients who discontinued the study early, on or after Week 30, EOS assessments were completed 2 weeks after the last CT-P13 SC was received. In Korea, all EOS assessments were completed 8 weeks after the last study drug administration. CD: Crohn's disease, EOS: End-of-study, RA: Rheumatoid arthritis, RD: Repeat dose, UC: Ulcerative colitis

Results

ADA/NAb Incidence and Titre in IBD Patients

Study CT-P13 1.6 Part 1:

Table 50 Frequency of ADA and NAb in Study CT-P13 1.6 Part 1: Safety Population

Visit Result	ADA ELISA & NAb ECL bead Methods				New ADA ECL ACE & NAb ECL ACE Methods			
	CT-P13 IV 5 mg/kg (N=13)	CT-P13 SC 120 mg (N=11)	CT-P13 SC 180 mg (N=12)	CT-P13 SC 240 mg (N=8)	CT-P13 IV 5 mg/kg (N=13)	CT-P13 SC 120 mg (N=11)	CT-P13 SC 180 mg (N=12)	CT-P13 SC 240 mg (N=8)
Post-treatment (including EOS and unscheduled visits) [1], n (%)								
ADA Positive	8 (61.5)	2 (18.2)	4 (33.3)	3 (37.5)	9 (69.2)	5 (45.5)	9 (75.0)	5 (62.5)
NAb Positive (as % of ADA positive)	8 (100.0)	0	3 (75.0)	3 (100.0)	7 (77.8)	1 (20.0)	3 (33.3)	3 (60.0)

Table 51 ADA Titre Results in Study CT-P13 1.6 Part 1 (New ADA ECL ACE method): Safety Population

Visit Statistic		CT-P13 IV 5 mg/kg (N=13)	CT-P13 SC 120 mg (N=11)	CT-P13 SC 180 mg (N=12)	CT-P13 SC 240 mg (N=8)
Week 54	n	6	1	4	2
	Mean (± SD)	41.0 (± 32.35)	27.0 (N/A)	10.0 (± 11.83)	1094.0 (± 1545.74)
	Median (Min, Max)	27 (3, 81)	27 (27, 27)	6 (1, 27)	1094 (1, 2187)

Study CT-P13 1.6 Part 2:

The proportion of patients who had post-treatment ADA positive results up to Week 30 was slightly higher in the CT-P13 IV 5 mg/kg arm than the CT-P13 SC 120/ 240 mg arm: 42 (64.6%) and 33 (50.0%) patients, respectively. Among the patients who had post-treatment positive ADA results, 24 (57.1%) and 9 (27.3%) patients, respectively, had NAb positive responses.

After switching to SC 120/ 240 mg for all patients, the proportion of patients who had post-treatment ADA positive results up to Week 54 including all available results at EOS and unscheduled visits were

comparable between the 2 arms: 44 (67.7%) and 48 (72.7%) patients in the CT-P13 IV 5 mg/kg and CT-P13 SC 120/ 240 mg arms, respectively. Among the patients who had post-treatment positive ADA results, 24 (54.5%) and 12 (25.0%) patients, respectively, had NAb positive responses (Table 52).

Table 52 Frequency of ADA and NAb in Study CT-P13 1.6 Part 2: Safety Population

Visit Result	ADA ELISA & NAb ECL bead Methods		New ADA ECL ACE & NAb ECL ACE Methods	
	CT-P13 IV 5 mg/kg (N=65)	CT-P13 SC 120/ 240 mg (N=66)	CT-P13 IV 5 mg/kg (N=65)	CT-P13 SC 120/ 240 mg (N=66)
Week 0 (Pre-dose), n (%)				
ADA Positive	2 (3.1)	0	2 (3.1)	0
NAb Positive (as % of ADA positive)	1 (50.0)	0	0	0
Week 6, n (%)				
ADA Positive	3 (4.6)	0	7 (10.8)	3 (4.5)
NAb Positive (as % of ADA positive)	1 (33.3)	0	1 (14.3)	1 (33.3)
Week 14, n (%)				
ADA Positive	10 (15.4)	1 (1.5)	19 (29.2)	14 (21.2)
NAb Positive (as % of ADA positive)	4 (40.0)	1 (100.0)	9 (47.4)	7 (50.0)
Week 22, n (%)				
ADA Positive	18 (27.7)	2 (3.0)	32 (49.2)	21 (31.8)
NAb Positive (as % of ADA positive)	8 (44.4)	2 (100.0)	12 (37.5)	4 (19.0)
Week 30, n (%)				
ADA Positive	27 (41.5)	4 (6.1)	35 (53.8)	25 (37.9)
NAb Positive (as % of ADA positive)	10 (37.0)	1 (25.0)	19 (54.3)	2 (8.0)
Week 38, n (%)				
ADA Positive	N/A[1]		27 (41.5)	29 (43.9)
NAb Positive (as % of ADA positive)			10 (37.0)	4 (13.8)
Week 46, n (%)				
ADA Positive			23 (35.4)	32 (48.5)
NAb Positive (as % of ADA positive)			9 (39.1)	5 (15.6)
Week 54, n (%)				
ADA Positive			25 (38.5)	31 (47.0)
NAb Positive (as % of ADA positive)			9 (36.0)	4 (12.9)
Post-treatment (up to Week 30), n (%)				
ADA Positive	29 (44.6)	5 (7.6)	42 (64.6)	33 (50.0)
NAb Positive (as % of ADA positive)	12 (41.4)	3 (60.0)	24 (57.1)	9 (27.3)
Post-treatment (including EOS and unscheduled visit)[2], n (%)				
ADA Positive	N/A[1]		44 (67.7)	48 (72.7)
NAb Positive (as % of ADA positive)			24 (54.5)	12 (25.0)

[1] Immunogenicity results up to Week 30 were analysed using the ADA ELISA and NAb ECL bead methods. [2] Patients who had at least 1 "positive" ADA or NAb result at post-dose visits up to Week 30 (for ADA ELISA & NAb ECL bead methods) or Week 54 (for new ADA ECL ACE & NAb ECL ACE methods) including all available results at EOS and unscheduled visits regardless of their ADA or NAb status at baseline. In Study CT-P13 1.6 Part 2, all EOS assessments were completed 2 weeks after the last study drug administration. For patients with early discontinuation before switching to CT-P13 SC at Week 30 in the CT-P13 IV 5 mg/kg arm or before randomisation at Week 6 in the CT-P13 SC 120/ 240 mg arm, the EOS visit occurred 8 weeks after the last dose of CT-P13 IV

In study 1.6 Part 2 the mean and the median of ADA titres were generally comparable between the 2 arms up to Week 54 with overlapping confidence intervals at all sampling time points. According to the summary of NAb titres depicted in the CSR of CT-P13 1.6 Part 2, also the NAb titres between the 2 arms were generally comparable.

ADA/NAb Incidence and Titre in RA Patients

Study CT-P13 3.5 Part 1:

Table 53 Frequency of ADA and NAb in Study CT-P13 3.5 Part 1: Safety Population

Visit Result	ADA ELISA & NAb ECL bead Methods				New ADA ECL ACE & NAb ECL ACE Methods			
	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=13)	CT-P13 SC 90 mg (N=11)	CT-P13 SC 120 mg (N=12)	CT-P13 SC 180 mg (N=12)
Post-treatment (including EOS and unscheduled visits) [1], n (%)								
ADA Positive	11 (84.6)	9 (81.8)	6 (50.0)	7 (58.3)	10 (76.9)	10 (90.9)	5 (41.7)	6 (50.0)
NAb Positive (as % of ADA positive)	7 (63.6)	4 (44.4)	2 (33.3)	3 (42.9)	9 (90.0)	6 (60.0)	4 (80.0)	4 (66.7)

Study CT-P13 3.5 Part 2:

Analysed with the new ADA assay, the proportion of post-treatment ADA positive patients up to Week 30 were slightly higher in the CT-P13 IV 3 mg/kg arm than in the CT-P13 SC 120 mg arm: 123 (70.3%) and 99 (58.9%) patients in the CT-P13 IV 3 mg/kg and CT-P13 SC 120 mg arms, respectively. Among the patients who had post-treatment positive ADA results, 106 (86.2%) and 64 (64.6%) patients, respectively showed NAb positive response.

After switching to CT-P13 SC administration at Week 30 in the CT-P13 IV 3 mg/kg arm, the proportion of patients who had ADA positive results were comparable between the 2 arms up to Week 54. This analysis further supports that switching the maintenance therapy from CT-P13 IV and CT-P13 SC did not lead to an increased ADA incidence.

Table 54 Frequency of ADA and NAb in Study CT-P13 3.5 Part 2: Safety Population

Visit Result	ADA ELISA & NAb ECL bead Methods		New ADA ECL ACE & NAb ECL ACE Methods	
	CT-P13 IV 3 mg/kg (N=175)	CT-P13 SC 120 mg (N=168)	CT-P13 IV 3 mg/kg (N=175)	CT-P13 SC 120 mg (N=168)
Week 0 (Pre-dose), n (%)				
ADA Positive	8 (4.6)	5 (3.0)	7 (4.0)	4 (2.4)
NAb Positive (as % of ADA positive)	2 (25.0)	0	2 (28.6)	0 (0)
Week 6, n (%)				
ADA Positive	18 (10.3)	21 (12.5)	14 (8.0)	17 (10.1)
NAb Positive (as % of ADA positive)	12 (66.7)	15 (71.4)	9 (64.3)	9 (52.9)
Week 14, n (%)				
ADA Positive	70 (40.0)	36 (21.4)	64 (36.6)	52 (31.0)
NAb Positive (as % of ADA positive)	56 (80.0)	31 (86.1)	59 (92.2)	41 (78.8)
Week 22, n (%)				
ADA Positive	104 (59.4)	53 (31.5)	104 (59.4)	82 (48.8)
NAb Positive (as % of ADA positive)	69 (66.3)	37 (69.8)	89 (85.6)	57 (69.5)
Week 30, n (%)				
ADA Positive	107 (61.1)	49 (29.2)	100 (57.1)	82 (48.8)
NAb Positive (as % of ADA positive)	65 (60.7)	34 (69.4)	84 (84.0)	45 (54.9)

Week 38, n (%)				
ADA Positive	68 (38.9)	51 (30.4)	95 (54.3)	83 (49.4)
NAb Positive (as % of ADA positive)	55 (80.9)	40 (78.4)	74 (77.9)	52 (62.7)
Week 46, n (%)				
ADA Positive	60 (34.3)	44 (26.2)	87 (49.7)	75 (44.6)
NAb Positive (as % of ADA positive)	50 (83.3)	34 (77.3)	70 (80.5)	51 (68.0)
Week 54, n (%)				
ADA Positive	64 (36.6)	48 (28.6)	79 (45.1)	70 (41.7)
NAb Positive (as % of ADA positive)	43 (67.2)	36 (75.0)	64 (81.0)	47 (67.1)
Post-treatment (up to Week 30), n (%)				
ADA Positive	124 (70.9)	65 (38.7)	123 (70.3)	99 (58.9)
NAb Positive (as % of ADA positive)	82 (66.1)	49 (75.4)	106 (86.2)	64 (64.6)
Post-treatment (including EOS and unscheduled visits)[1], n (%)				
ADA Positive	126 (72.0)	83 (49.4)	129 (73.7)	114 (67.9)
NAb Positive (as % of ADA positive)	93 (73.8)	67 (80.7)	112 (86.8)	85 (74.6)

[1] Patients who had at least 1 "positive" ADA or NAb result at post-dose visits up to Week 54 including EOS and unscheduled visits regardless of their ADA or NAb status at baseline. In Study CT-P13 3.5 Part 2, the EOS assessments were completed 2 weeks after the last dose of CT-P13 SC was received. For patients who discontinued the study early, before Week 30, all EOS assessments were completed 8 weeks after the last CT-P13 IV or placebo IV was received (Weeks 0, 2, 6, 14, and 22). For patients who discontinued the study early, on or after Week 30, EOS assessments were completed 2 weeks after the last CT-P13 SC was received. In Korea, all EOS assessments were completed 8 weeks after the last study drug administration. Immunogenicity at unscheduled visit was defined as immunogenicity results of samples collected at non-scheduled immunogenicity testing visit or those of samples collected due to delayed hypersensitivity reaction.

Note: The proportion of ADA positive patients was calculated using the number of patients in Safety population per treatment arm as the denominator. The proportion of NAb positive patients was re-calculated using ADA positive patients as a denominator.

All analyses were conducted by excluding the data of patients from the significant GCP non-compliance site (site 2840 in Russia). ACE: Affinity capture elution, ADA: Anti-drug antibody, ECL: Electrochemiluminescent, ELISA: Enzyme-linked immunosorbent assay, EOS: End-of-study, GCP: Good Clinical Practice, IV: Intravenous, n: Number of patients with the event, N: Number of patients in each arm in Safety population, NAb: Neutralising antibody, SC: Subcutaneous

The mean and the median of ADA titres were generally comparable between the two administration routes up to Week 54.

Effect of ADA on PK and efficacy in Study CT-P13 1.6 Part 2 (CD and UC Patients)

In Study 1.6 Part 2 (CD and UC patients) the presence of ADA in serum resulted in an overall decrease in drug levels. The mean pre-dose serum concentrations tended to be slightly lower in the ADA positive subgroup both in the CT-P13 IV 5 mg/kg and the CT-P13 SC 120/ 240 mg arms up to Week 54, but the ADA positive patients of the CT-P13 SC 120/ 240 mg arm still showed higher drug levels compared to both ADA positive and ADA negative patients in the CT-P13 IV 5 mg/kg arm.

Table 55 PK Parameters (observed pre-dose concentration and predicted AUC_{ss8W}) by Visit-based ADA Status in Study CT-P13 1.6 Part 2 (New ADA ECL ACE Method): Pharmacokinetic Population

Visit	Statistic	CT-P13 IV 5 mg/kg (N=64)		CT-P13 SC 120/ 240 mg (N=63)	
		ADA Positive	ADA Negative	ADA Positive	ADA Negative
Pre-dose concentration (μ g/mL)					
Week 22	n	32	24	21	36
	Mean (± SD)	1.9808 (± 2.04596)	3.9397 (± 2.62980)	16.6352 (± 7.10486)	24.3969 (± 10.21209)
	95% CI	(1.24317, 2.71846)	(2.82924, 5.05018)	(13.40115, 19.86933)	(20.94167, 27.85222)
AUC_{ss8w} * (hr*μ g/mL)					
Week 22	n	35	21	24	30
	Mean (± SD)	25411.1 (± 9292.59)	33104.8 (± 10429.26)	31683.3 (± 10892.11)	36523.3 (± 8606.36)
	95% CI	(22219.03, 28603.26)	(28357.42, 37852.10)	(27084.00, 36282.67)	(33309.67, 39737.00)

In CD and UC patients, there was no specific trend in the proportion of patient achieving clinical remission in relation to ADA status between the two treatment arms according to CDAI or Mayo scores (Table 56, Table 57)

Table 56 Proportion of CD Patients Achieving Clinical Remission (Based on CDAI) at Week 30 by Visit-based ADA/NAb Status (ACE) in Study 1.6 Part 2

Visit Subgroup	SC 120mg (N=20)	SC 240mg (N=8)	SC 120/240mg (N=28)	IV 5mg/kg (N=25)
Week 30				
ADA Positive	5/7 (71.4%)	3/3 (100%)	8/10 (80%)	6/8 (75%)
Exact 95% CI for Proportion (%)	(29.04, 96.33)	(29.24, 100.00)	(44.39, 97.48)	(34.91, 96.81)
NAb Positive	N/A	N/A	N/A	5/6 (83.3%)
Exact 95% CI for Proportion (%)	N/A	N/A	N/A	(35.88, 99.58)
NAb Negative	5/7 (71.4%)	3/3 (100%)	8/10 (80%)	1/2 (50%)
Exact 95% CI for Proportion (%)	(29.04, 96.33)	(29.24, 100.00)	(44.39, 97.48)	(1.26, 98.74)
ADA Negative	9/12 (75%)	1/2 (50%)	10/14 (71.4%)	8/12 (66.7%)
Exact 95% CI for Proportion (%)	(42.81, 94.51)	(1.26, 98.74)	(41.90, 91.61)	(34.89, 90.08)
ADA Negative & NAb Negative	14/19 (73.7%)	4/5 (80%)	18/24 (75%)	9/14 (64.3%)
Exact 95% CI for Proportion (%)	(48.80, 90.85)	(28.36, 99.49)	(53.29, 90.23)	(35.14, 87.24)
Missing	0/1	0/3	0/4	0/5
Exact 95% CI for Proportion (%)	(0.00, 97.50)	(0.00, 70.76)	(0.00, 60.24)	(0.00, 52.18)

Table 57 Proportion of UC Patients Achieving Clinical Remission (Based on Mayo Scoring System) at Week 22 by Visit-based ADA/NAb Status (ACE) in Study 1.6 Part 2

Parameter Visit Subgroup	SC 120mg (N=28)	SC 240mg (N=10)	SC 120/240mg (N=38)	IV 5mg/kg (N=39)
Total Mayo Score				
Week 22				
ADA Positive	6/11 (54.5%)	1/2 (50%)	7/13 (53.8%)	7/26 (26.9%)
Exact 95% CI for Proportion (%)	(23.38, 83.25)	(1.26, 98.74)	(25.13, 80.78)	(11.57, 47.79)
NAb Positive	1/3 (33.3%)	0/1	1/4 (25%)	3/11 (27.3%)
Exact 95% CI for Proportion (%)	(0.84, 90.57)	(0.00, 97.50)	(0.63, 80.59)	(6.02, 60.97)
NAb Negative	5/8 (62.5%)	1/1 (100%)	6/9 (66.7%)	4/15 (26.7%)
Exact 95% CI for Proportion (%)	(24.49, 91.48)	(2.50, 100.00)	(29.93, 92.51)	(7.79, 55.10)
ADA Negative	6/13 (46.2%)	6/8 (75%)	12/21 (57.1%)	2/9 (22.2%)
Exact 95% CI for Proportion (%)	(19.22, 74.87)	(34.91, 96.81)	(34.02, 78.18)	(2.81, 60.01)
ADA Negative & NAb Negative	11/21 (52.4%)	7/9 (77.8%)	18/30 (60%)	6/24 (25%)
Exact 95% CI for Proportion (%)	(29.78, 74.29)	(39.99, 97.19)	(40.60, 77.34)	(9.77, 46.71)
Missing	1/4 (25%)	N/A	1/4 (25%)	1/4 (25%)
Exact 95% CI for Proportion (%)	(0.63, 80.59)	N/A	(0.63, 80.59)	(0.63, 80.59)

Effect of ADA on safety in Study CT-P13 1.6 Part 2 (CD and UC Patients)

During the Maintenance Phase up to Week 54 of Study CT-P13 1.6 Part 2, a subgroup analysis on incidences of infection and immune-mediated adverse events (infusion related reaction [IRR; IV only], systemic injection reaction [SIR; SC only], delayed hypersensitivity and localised injection site reaction [ISR]) as well as treatment-emergent adverse events (TEAE) and treatment-emergent serious AE (TESAE) by post-treatment ADA status was conducted.

The results demonstrated that there was overall no apparent correlation between the immune-mediated AEs, TEAE, TESAE or infection rates and ADA presence. In the SC 120/ 240 mg arm, the incidences of localised ISR were slightly higher in the post-treatment ADA negative subgroup than in the post- treatment ADA positive subgroup: 7/18 (38.9%) and 8/48 (16.7%) patients, respectively (Table 58). However, the reported localised ISRs were all non-serious AEs with grade 1 or 2. Most patients recovered within a few days. The analysis of the results of incidences of AEs stratified by ADA titre tertile at Week 54 also showed that there was no specific pattern in incidences of AEs and ADA titres across tertiles.

Table 58 Summary of Adverse Events during the Maintenance Phase up to Week 54 by Post-Treatment ADA Status in Study CT-P13 1.6 Part 2 (ADA ECL ACE Method): Safety Population

Adverse Event	CT-P13 IV 5 mg/kg [3] (N=65)		CT-P13 SC 120/ 240 mg (N=66)	
	ADA Positive [1] (N'=44)	ADA Negative [2] (N'=21)	ADA Positive [1] (N'=48)	ADA Negative [2] (N'=18)
TEAE	25 (56.8%)	13 (61.9%)	36 (75%)	13 (72.2%)
TESAE	3 (6.8%)	3 (14.3%)	3 (6.3%)	2 (11.1%)
Infection	11 (25.0%)	8 (38.1%)	15 (31.3%)	6 (33.3%)
Infusion related reaction	2 (4.5%)	0	0	0

Systemic injection reaction [3]	0	0	0	1 (5.6%)
Delayed hypersensitivity	0	0	2 (4.2%)	0
Localised injection site reaction	1 (2.3%)	2 (9.5%)	8 (16.7%)	7 (38.9%)

[1] Patients who had at least 1 "positive" ADA result at post-dose visits up to Week 54 including EOS and unscheduled visits regardless of their ADA status at baseline. [2] Patients who had all "negative" ADA result at post-dose visits up to Week 54 including EOS and unscheduled visits regardless of their ADA status at baseline. [3] CT-P13 IV was switched to CT-P13 SC after Week 30. Note: Only TEAEs occurred during the Maintenance Phase up to Week 54 are included. Percentage was calculated using the number of patients (N') in each subgroup as denominator. All immunogenicity results (including EOS and unscheduled visits) after study drug administration were considered. In Study CT-P13 1.6 Part 2, all EOS assessments were completed 2 weeks after the last study drug administration. For patients with early discontinuation before switching to CT-P13 SC at Week 30 in the CT-P13 IV 5 mg/kg arm or before randomisation at Week 6 in the CT-P13 SC 120/ 240 mg arm, the EOS visit occurred 8 weeks after the last dose of CT-P13 IV was received. Immunogenicity at unscheduled visit was defined as immunogenicity results of samples collected at non-scheduled immunogenicity testing visit or those of samples collected due to delayed hypersensitivity reaction. Infusion Related Reaction: AEs checked as ARR in the eCRF and occurred between IV infusion start and after 24 hours of IV infusion end. Systemic Injection Reaction: AEs checked as ARR in the eCRF and occurred between SC injection start and after 24 hours of SC injection start. Delayed Hypersensitivity: AEs checked as ARR in the eCRF and that occurred after 24 hours of IV infusion end or of SC injection start. Localized Injection Site Reaction: AEs classified as injection site reaction in the eCRF was included. ACE: Affinity capture elution, ADA: Anti-drug antibody, ARR: Administration-related reaction, ECL: Electrochemiluminescent, EOS: End-of-study, IV: Intravenous, N: Number of patients in each cohort in Safety population, N': N: Number of patients in each subgroup, SC: Subcutaneous, TEAE: Treatment-emergent adverse event, TESAE: Treatment-emergent serious adverse event

<u>Effect of ADA on Safety in Study CT-P13 3.5 Part 2 (RA Patients) - new ADA and NAb ECL ACE methods</u>

Similar analyses were conducted with data from Study CT-P13 3.5 Part 2 in a post-hoc manner to assess potential impact of ADA on safety. The results demonstrated that there was overall no apparent correlation between the rate of immune-mediated AEs and ADA presence. The incidence rates of SIR, localised ISR and delayed hypersensitivity and AEs were similar between the post-treatment ADA positive and negative subgroups for both arms. However, opposite trends were observed for TESAE between the 2 arms; the incidence rate of TESAE for post-treatment ADA positive and negative subgroups were 8.5% and 4.3%, respectively in the CT-P13 IV arm, and 2.6% and 5.6%, respectively in the CT-P13 SC arm) (Table 59). Moreover, the incidence of infection/immune-mediated AEs, TEAE and TESAE by ADA titre quartile showed no apparent correlation between ADA titre and AE incidences.

Table 59 Summary of Adverse Events during the Maintenance Phase up to Week 64 by Post-Treatment ADA Status in Study CT-P13 3.5 Part 2 (New ADA ECL ACE Method): Safety Population

Adverse Event	CT-P13 IV 3 mg/kg (N=175)		CT-P13 SC 120 mg (N=168)	
	ADA Positive [1] (N'=129)	ADA Negative [2] (N'=46)	ADA Positive [1] (N'=129)	ADA Negative [2] (N'=46)
TEAE	80 (62.0%)	37 (80.4%)	58 (50.9%)	34 (63.0%)
TESAE	11 (8.5%)	2 (4.3%)	3 (2.6%)	3 (5.6%)
Infection	43 (33.3%)	17 (37.0%)	32 (28.1%)	17 (31.5%)
Infusion related reaction	6 (4.7%)	1 (2.2%)	0	0
Systemic injection reaction[3]	3 (2.3%)	0	0	2 (3.7%)
Delayed hypersensitivity	0	0	1 (0.9%)	3 (5.6%)
Localised Injection site reaction	12 (9.3%)	10 (21.7%)	23 (20.2%)	7 (13.0%)

[1] Patients who had at least 1 "positive" ADA result at post-dose visits up to Week 54 including EOS and unscheduled visits regardless of their ADA status at baseline. [2] Patients who had all "negative" ADA result at post-dose visits up to Week 54 including EOS and unscheduled visits regardless of their ADA status at baseline. [3] The 2 systemic injection reaction cases in the CT-P13 IV arm occurred after switching to CT-P13 SC at Week 30. Note: Only TEAEs occurred during the Maintenance Phase up to Week 64 were included. Percentage was calculated using the number of patients (N') in each subgroup as denominator. All immunogenicity results (including EOS and unscheduled visit) after study drug administration were considered. For Study CT-P13 3.5 Part 2, the EOS assessments were completed 2 weeks after the last dose of CT-P13 SC was received. For patients who discontinued the study early, before Week 30, all EOS assessments were completed 8 weeks after the last CT-P13 IV or placebo IV was received (Weeks 0, 2, 6, 14, and 22). For patients who discontinued the study early, on or after Week 30, EOS assessments were completed 2 weeks after the last CT-P13 SC was received. In Korea, all EOS assessments were completed 8 weeks after the last study drug administration. All analyses were conducted by excluding the data of patients from the significant GCP non-compliance site (site 2840 in Russia). ACE: Affinity capture elution, ADA: Anti-drug antibody, ECL: Electrochemiluminescent, EOS: End-of-study, GCP: Good Clinical Practice, IV:

Intravenous, N: Number of patients in each arm in Safety population, N': Number of patients in each subgroup, SC: Subcutaneous, TEAE: Treatment-emergent adverse event, TESAE: Treatment-emergent serious adverse event

Impact of Immunosuppressive Therapies on Immunogenicity

To support extrapolation of immunogenicity data collected from RA and IBD patients to AS, PsA and Ps indications, the MAH has investigated the impact of concomitant immunosuppressants on ADA based on the data from historical literature as well as CT-P13 IV and SC studies.

In Study CT-P13 1.6 Part 2 up to Week 30 with CD and UC patients, immunosuppressants (such as AZA, 6-MP and MTX) were allowed. The proportion of patients who used immunosuppressants up to Week 30 was 58/131 (44.3%).

Consistent with the result in previous studies, the patients who received immunosuppressants showed reduced ADA incidence compared to the patients who did not receive immunosuppressants. A total of 16/58 (27.6%) patients receiving concomitant immunosuppressants were ADA positive while 44/73 (60.3%) patients without immunosuppressant were ADA positive. The impact of immunosuppressant on ADA presence was comparable between the CT-P13 IV 5 mg/kg and CT-P13 SC 120/ 240 mg arms (Table 60).

Table 60 Summary of ADA and NAb Incidence at Week 30 by Use of Immunosuppressant (AZA, 6-MP or MTX) in Study CT-P13 1.6 Part 2 (New ADA ECL ACE Method)

Subgroup ADA Status NAb Status	CT-P13 IV 5 mg/kg (N=65)	CT-P13 SC 120/ 240 mg (N=66)	Total (N=131)
With Immunosuppressant Treatment			
ADA Positive	10/29 (34.5%)	6/29 (20.7%)	16/58 (27.6%)
NAb Positive (as % of ADA positive)	4/10 (40.0%)	1/6 (16.7%)	5/16 (31.3%)
Without Immunosuppressant Treatment			
ADA Positive	25/36 (69.4%)	19/37 (51.4%)	44/73 (60.3%)
NAb Positive (as % of ADA positive)	15/25 (60.0%)	1/19 (5.3%)	16/44 (36.4%)

6-MP: 6-Mercaptopurine, ACE: Affinity capture elution, ADA: Anti-drug antibody, AZA: Azathioprine, ECL: Electrochemiluminescent, EOS: End-of-study, MTX: Methotrexate, NAb: Neutralising antibody

The impact of immunosuppressant on the incidence of ARRs (including IRR, SIR and Delayed Hypersensitivity) and localized ISR was comparable between the CT-P13 IV 5 mg/kg and CT-P13 SC 120/ 240 mg arms (Table 61).

Table 61 Summary of ARR and Localized ISR Incidence up to Week 30 by current use of treatment with AZA, 6-MP or MTX (Maintenance Phase)

Current Use of AZA, 6-MP or MTX	CT-P13 IV 5 mg/kg (N=65)	CT-P13 SC 120/240 mg (N=66)	Total (N=131)
USED			
Administration Related Reaction (ARR)	0	1/29 (3.4)	1/58 (1.7)
Localized ISR	1/29 (3.4)	5/29 (17.2)	6/58 (10.3)
NOT-USED			
Administration Related Reaction (ARR)	2/36 (5.6)	0	2/73 (2.7)
Localized ISR	1/36 (2.8)	6/37 (16.2)	7/73 (9.6)

Safety related to drug-drug interactions and other interactions

No interaction studies have been performed with CT-P13 SC.

Post marketing experience

CT-P13 SC has been authorised for marketing in the EU for the adult RA indication only; however, up to the date of submission for this Type II variation, it has not been marketed in the EU or any country worldwide.

2.5.1. Discussion on clinical safety

Summary of the clinical safety database

The originator infliximab, Remicade IV, has been approved in the EU since 1999. The safety profile of infliximab has been well characterised by more than 20 years of clinical use. Thus, the overall total cumulative exposure with infliximab IV, including also the post-marketing exposure, is significant.

Remsima SC is the very first SC formulation for infliximab, and is considered as such a 'stand-alone application'. The complete safety data for Remsima SC studies CT-P13 1.5, CT-P13 1.9, CT-P13 3.5 Part 1 and Part 2 and Study CT-P13 1.6 Part 1 in CD patients have been assessed in the line extension application (EMEA/H/C/002576/X/0062).

In the current application, new data was submitted on the clinical safety (week 54) of Remsima SC compared to Remsima IV, in IBD subjects, with CD and UC, in study CT-P13 1.6 Part 2. This completes the MAH's current Remsima SC development database.

The safety of Remsima SC has not been studied in AS, Ps and PsA, which is in accordance with the CHMP scientific advice. The aim is to extend the Remsima SC indication from the source population (RA and IBD) to these target patient populations (AS, Ps and PsA).

Overall exposure

In this application the overall planned Remsima SC development programme, including patient exposure data and overall safety data, have been complemented and completed by the week 54 data of the study CT-P13 1.6 Part 2. The safety population consisted of all patients who received at least 1 dose of study drug at Week 6 or thereafter.

In all, 819 subjects (391 RA patients, 97 CD patients, 78 UC patients and 253 healthy subjects) have been exposed to at least 1 dose of CT-P13 IV or SC across four controlled clinical studies. A total of 751 subjects (363 RA patients, 79 CD patients, 74 UC patients and 235 healthy subjects) have received at least 1 dose of CT-P13 SC, including 160 RA patients from Study CT-P13 3.5 Part 2 and 20 CD and 36 UC patients from Study CT-P13 1.6 Part 2, who switched to CT-P13 SC treatment at Week 30. From Week 6 to Week 54, 249 patients overall (172 RA, 44 CD and 33 UC patients) received CT-P13 SC and among them, 201 patients (155 RA, 24 CD and 22 UC patients) received 120 mg of CT-P13 SC. It is acknowledged that the overall exposure, in terms of patient numbers, to Remsima SC, in all the clinical studies of the entire MAH SC development programme appears not extensive, especially considering the numerous indications applied for.

Overall, with respect to the mean (SD) values of total administered doses up to and including Week 54, both in the loading and maintenance phases, and between the two UC and CD patient groups of the SC 120 mg treatment arm, were largely similar to that of IV 5 mg/kg treatment arm. In addition, the total number of doses received were broadly similar.

The number of patients with at least 1 escalated dose was also similar between the 2 treatment arms. The majority of patients in each treatment arm were continuing the study at Week 54. During the maintenance phase, 11 (16.7%) patients in the SC 120/240 mg arm and 15 (23.1%) patients in the IV 5 mg/kg treatment arm discontinued the study, which is an acceptable attrition rate for this type of study.

However, of note is that after SC administration, AUC-levels were higher and C_{trough} concentrations were up to ten-fold higher in comparison to IV administration. This is a safety concern, especially in long-term, beyond the currently available 54 weeks exposure, as data on effects of this on patient safety, particularly concerning serious infections (including TB and other opportunistic infections) is still scarce, and data on cancer is still unknown. So far, in short term and up to week 54, no clinically relevant, unexpected safety signals have been identified. Also, the vast experience on infliximab in general needs to be taken into account here. In addition, the MAH is proposing a robust post-approval programme to further characterise the safety of SC Remsima. Thus, the size of the safety database and duration of exposure is considered appropriate for the evaluation of the general safety profile of SC Remsima and, overall, could be sufficient also for the intended extrapolation purposes, considering the existence of the company robust post marketing plan, pending the RSI.

Safety in study CT-P13 1.6 Part 2

Adverse events

The selection of the variables for the safety assessment is considered adequate by the CHMP.

Safety data has been presented for three different study periods: treatment period, which consisted of the dose-loading phase (all patients receiving IV Remsima) and the maintenance phase (one arm receiving SC and one IV Remsima); the maintenance phase and the On-or-after-Week 30 phase, where IV-patients were switched to SC administration. The focus is on the maintenance phase, allowing direct comparison of SC and IV safety data. It is, however, noted that the 'treatment period' reflects best how the product will be used in real-world situation. However, as the focus is on the comparison of safety data between IV Remsima and SC Remsima, result mainly for the most sensitive period for comparing these two products, the maintenance phase, is reported in more detail.

In the entire treatment period (including both the loading and the maintenance phases) the proportions of patients with at least one TEAE, TESAE, TEAE leading to discontinuation of study drug, TEAE classified as IRR, SIR and delayed hypersensitivity reactions, were no higher in the SC group compared to the IV group. The respective numbers for infections were also similar between the groups, 24 (36.4%) in the SC and 20 (30.8%) in the IV treatment arm. The proportion of patients that reported localised injection site reactions (ISR) was notably higher in the SC group (for details see under dedicated heading below).

In the maintenance phase, the number and pattern of events were similar and comparable between the treatment groups. The rates for infections were also similar in the two arms, 21 (31.8%) in the SC and 19 (29.2%) in the IV arms and comparable to those found in the pivotal RA study, 29.2% and 34.3%, respectively. The localised ISRs were again clearly more common in the SC group 22.7% than in the IV group 4.6%. Overall, however, there were slightly more TEAEs in the SC arm (74.2% vs 58.5%), which seemed to be due to the increased number of localised ISRs.

Switching treatments appeared not to have a clear effect on safety, as in the period on and after week 30, the number and patter of events were alike between the treatment arms and did not differ markedly or rates were slightly lower than those of the maintenance phase (for example infections were seen in 18.2% vs 13.8% in SC and IV groups). Overall, again, there were slightly more TEAEs in the SC arm (47.0% vs 32.3%), again, probably driven by the higher incidence of localised ISR.

Thus, when analysing the number of patients that reported adverse events and the type of events recorded, the data did not reveal any unexpected findings, and the safety profile of Remsima SC no worse than that of Remsima IV and the known overall safety profile of infliximab. The single notable finding among otherwise comparable safety data, between two treatment arms, was the higher proportion of patients that reported localised ISR in the SC group. Bearing in mind that the SC formulation was administered every two weeks and the IV formulation every 8 weeks, these local reactions would be expected to be even higher in the SC group. The overall safety profile of the patients treated with SC was no worse compared to the IV in the incidence of AE, even after switching.

The incidence rates were slightly different, when analysing the safety data for TEAE reported for at least 5% of patients. In the maintenance phase (most sensitive evaluation period to compare SC and IV formulations), the following incidence rates were recorded: gastrointestinal disorders 14 (21.2%) and 11 (16.9%), localised ISR 15 (22.7%) and 3 (4.6%) and infections and infestations (namely nasopharyngitis) 4 (6.1%) and 2 (3.1%) and blood and lymphatic system disorders 7 (10.6%) and 3 (4.6%) in the SC and IV treatment arms, respectively. Association with switching appeared unlikely, with the trend less evident after switching for localised ISR and the single PT of abdominal pain, remaining. Otherwise, there were no obvious differences, including the event of headache.

The proportion of patients who experienced at least 1 TEAE considered to be related to study drug during the maintenance phase was slightly higher in the SC 120/240 mg treatment arm (28 [42.4%] vs 20 [30.8%] in the IV 5 mg/kg treatment arm). The most frequently reported were localised ISR (and rash for the IV arm) with again the number higher for the SC route 14 (21.2%) and only 3 (4.6%) for the IV route, which appears not unexpected. The pattern was less evident after switching and the rates slightly lower (7 [10.6%] patients) in the SC and (2 [3.1%]) in the IV treatment arm.

The majority of TEAEs reported during the maintenance phase were CTCAE grade 1 or 2 in intensity. Significant differences were not evident in events of grade 3 and higher, between the two treatment arms, even after switching.

Thus, overall, when analysing the number of patients that reported adverse events and the type of events recorded, the data did not reveal any unexpected findings, and the safety profile of Remsima SC was no worse than that of Remsima IV and the known overall safety profile of infliximab. The single notable, but not unexpected finding (considering the SC route of administration) among otherwise comparable safety data, between two treatment arms, was the higher proportion of patients that reported localised ISR in the SC group (see below for details).

Serious adverse events and deaths

The TESAEs considered by the investigator to be related to study drug were rare, solitary cases reported for 1 (1.5%) patient (NSCLC) in the SC 120/240 mg and 2 (3.1%) patients (bronchitis, pneumonia, disseminated tuberculosis) in the IV 5 mg/kg treatment arm, respectively. No differences were evident between CD and UC patients or when switching formulations. No deaths were reported during the study.

Discontinuation due to adverse events

The TEAEs leading to permanent discontinuation of study drug during the maintenance phase were reported for 1 (1.5%) and 3 (4.6%) patients in the SC 120/240 mg (NSCLC) and IV 5 mg/kg treatment arms (IRR, psoriasis and disseminated TB), respectively. All four events were considered related to the study drug, were rare, solitary cases, of grade 2 or 3, no more numerous in patients treated with the SC formulation. The nature of the SAE did not differ from previously reported. Switching of treatment appeared not to associate with them.

TEAE of special interest

Infusion Related Reaction, Systemic Injection Reaction or Delayed Hypersensitivity Treatment Period

The TEAEs classified as IRR (grade 2) reported for two (3.1%) patients in the IV 5 mg/kg treatment arm. The TEAEs classified as SIR was reported for one (1.5%) patient in SC 120/240 mg treatment arm only. The TEAEs classified as delayed hypersensitivity were reported (one at week 6 and one at week 52; vascular headache, and edema and flushing) for two (3.0%) patients in SC 120/240 mg treatment arm. Complement tests were not done. One patient was negative and one positive for ADA, the latter negative for NAbs. Both patients recovered within 1-3 days without treatment.

The ARR rates in IBD patients were low, incidences rare, and with no differences between the mode of administration, SC or IV. This was in spite of the more common use of corticosteroids for systemic use in the IV arm. Further, ARR were no more numerous in comparison to those reported in the pivotal RA study 1 (0.6%) in SC and 8 (4.5%) in IV arms, respectively (see effects Table of this AR). This is, in all, of importance, as infliximab is known to be very immunogenic (with 30% murine variable region amino acid sequence), a trait that is likely to be influenced by both use of immunosuppressants and mode of administration (the subcutaneous route often being the more immunogenic one). This could have consequences for clinical safety (as well as efficacy), but so far, this appears not to be the case for SC Remsima. Moreover, this should be considered acknowledging that the IV infliximab is administered in a controlled clinical (hospital) setting, whereas SC Remsima will be used at home.

Localised injection site reactions

The proportion of patients who experienced at least 1 TEAE classified as localised ISR during the maintenance phase was higher in the SC 120/240 mg treatment arm compared to the IV 5 mg/kg treatment arm, 15 (22.7%) and 3 (4.6%) patients in the SC and IV treatment arms, respectively.

Among these patients, two in the IV 5 mg/kg treatment arm experienced TEAEs classified as localised ISR on or after Week 30 that is after switching.

The most frequently reported signs and symptoms of localised ISR in all patients were injection site erythema (10 [15.2%] and 2 [3.1%] patients in the SC 120/240 mg and IV 5 mg/kg treatment arms, respectively). All events were of grade 1 or 2 in intensity and the majority of the patients recovered without any treatments. No serious localised ISRs were reported.

The TEAEs classified as localised ISR on or after Week 30 were reported, in all, in 9 (6.9%) patients; 7 (10.6%) and 2 (3.1%) patients in the SC 120/240 mg and IV 5 mg/kg treatment arms, respectively. Of these, three out of the seven patients in the SC 120/240 mg treatment arm had reported localised ISR before Week 30.

In conclusion, a notable finding among the TEAEs was the higher incidence of grade 1 and 2 localised ISR in patients treated with the SC formulation, 15 (22.7%) SC and 3 (4.6%) IV, which appeared not to associate with switching. This was comparable to the results, 30 (17.9%) SC and 22 (12.6%) IV, of the pivotal RA study (see effects Table of this assessment report). The finding is not unexpected and similar rates have been shown to be comparable to rates for other licenced SC **TNFα-inhibitors,** also used in the home-administration setting. It should also be kept in mind that not all localised ISRs are immune-mediated, such as haemorrhage and pain. Section 4.8 of SmPC is updated to report the higher incidence of localised ISR after SC injection from the phase 1 study in patients with CD and UC.

Infections

The number of patients in total (31 and 24) and the number (%) with at least 1 TEAE classified as infection during the maintenance phase were similar between the 2 treatment arms 21 (31.8%) and 19 (29.2%) with the patients in the SC 120/240 mg and IV 5 mg/kg treatment arms, respectively. Most of the events were of grade 1 or 2 in intensity.

Findings were, overall, similar between the subgroups of CD and UC patients, although in CD patients slight imbalance was seen (39.3% and 28% in SC and IV arms). However, the numbers were small, so no firm conclusions can be drawn.

A single patient with UC in the IV 5 mg/kg treatment arm was withdrawn due to grade 3 TESAE of disseminated TB after Week 14.

In conclusion, infections were no more numerous in the SC than in the IV treatment arm, in the overall IBD study population. The pattern and numbers were largely comparable to that in the pivotal RA population (see effects Table of this AR). Serious infections were rare in both treatment arms and similar to previously reported. Further post-marketing studies are included in the RMP to follow also infections in patients receiving SC Remsima.

Malignancy

A single malignancy was reported in the study for 1 (1.5%) patient with CD in the SC 120/240 mg treatment arm (NSCLC, after week 50) judged possibly related to the treatment. The follow-up is too short for any conclusions.

Laboratory findings

Over time, the changes from baseline in all clinical chemistry, urinalysis, and hematology laboratory parameters were generally small, and there were no notable differences between the two treatment arms, most patients having no or of mild grade derangement. Most of the laboratory findings, graded as severe or life threatening, were low in numbers (1 to 2 cases), with no differences between the treatment arms. They included a case of elevated liver enzyme in the IV arm and two patients with elevated CPK, one each GGT and triglycerides in the SC arm and anemia and decreased lymphocyte and platelet counts in the SC arm and WBC in the IV arm. Neutropenia was, however, reported more often, grade 3 in 3 (4.5) and in 4 (6.2) patients and a case of grade 4 each, in the SC and IV respectively. Overall the numbers were small, and no clear trends were seen. These laboratory finding appear not unexpected and are comparable to findings inherent to this IBD patient group and to the treatment.

Safety in special populations

The incidence of serious infections in infliximab-treated patients 65 years and older has been reported to be greater than that of under 65 years of age (Remsima SmPC, 2019). The current data presented for Remsima IV, Remicade IV, and Remsima SC in the RA and IBD indications appears discrepant and varied and the data should be interpreted with caution, as the numbers of patients in some subgroup were small. Analysis of AE by age were hampered by the small numbers of patients in the subgroup of >65 year olds.

A requested subgroup analysis by body weight of < 80 kg and ≥ 80 kg showed (acknowledging the low numbers in some of the weight subgroups) that there was no apparent correlation between body weight and the safety profiles in either of the CT-P13 IV or SC treatment arms.

Gender appeared not to have effect in the incidence of the safety variables.

There was no apparent correlation or trends evident, between the incidence of the events and mean pre-dose serum concentration level in patients administered with CT-P13 SC. Previous literature search by the MAH on this issue has yielded conflicting results. However, after SC administration C_{trough} concentrations were up to ten-fold higher in comparison to IV route. This is a safety concern, also in the elderly, especially in long-term, as data on effects of this on patient safety is still scarce or even unknown beyond the 54 weeks follow-up. So far, in short term and up to week 54, it appears that no clinically relevant, unexpected safety signals have been identified.

No interaction studies have been performed with CT-P13 SC.

Immunogenicity

The overall program, including the sampling schedules and duration of follow-up, was approved by CHMP through scientific advice and is adequate for demonstrating comparability of immunogenicity of SC and IV formulations in RA, CD and UC patients. Extrapolation of the results to As, PsA and Ps are discussed in the benefit risk section.

In light of the observed drug concentrations in studies 3.5 and 1.6, the drug tolerance of the new ADA assay is acceptable.

Antibody levels as low as 100 ng/mL have been proposed to be clinically significant, but the level with clinical significance is dependent on concentrations of the therapeutic drug. In light of the observed drug concentrations in studies 3.5 and 1.6, the drug tolerance of the new Nab assay is acceptable in terms of detecting clinically significant NAb levels. However, for comparability of results between IV and SC arms, the drug tolerance is not optimal. Because of different drug concentrations in the two treatment arms, comparison of the incidence of detected NAb may be misleading.

Results

ADA/NAb incidence and titre

The detected ADA and NAb incidences increased when the new methods were applied. The drug tolerance was sufficient for ADA detection as drug concentration levels were below 120.0 μg/mL for all samples in the ADA negative samples.

In study 1.6 Part 1 the incidence of ADA was comparable between IV and SC treatments. The incidence of clinically relevant levels of NAb was not higher in the SC arms. The mean and the median of ADA titres were generally comparable between the two administration routes up to Week 54.

In study 1.6 Part 2 the incidence of ADA was comparable between IV and SC treatments. During the maintenance phase 44 (67.7%) and 48 (72.7%) patients in the CT-P13 IV 5 mg/kg and CT-P13 SC 120/ 240 mg arms, respectively were ADA positive. After switching to SC administration at Week 30, the ADA positive rates were slightly lower in the IV arm up to Week 54. The post-treatment measurements, including EOS for discontinued patients and unscheduled visits, were comparable up to week 30 and up to week 54 with overlapping confidence intervals. Switching therapy from IV to SC administration did not result in increased immunogenicity.

In study 3.5 Part 1 and Part 2 the incidence of ADA was not higher in the SC arm than in the IV arm. The incidence of clinically relevant levels of NAb was not higher in the SC arms. The mean and the median of ADA titres were generally comparable between the two administration routes up to Week 54. Switching the maintenance therapy from IV to SC at week 30 did not lead to an increased ADA incidence in the original IV arm.

Effect of ADA on PK, efficacy and safety

The presence of ADA in serum resulted in an overall decrease in drug levels, but the SC treatment remained non-inferior in terms of drug exposure (C_{trough} and AUC) even among ADA positive patients throughout the study.

In study 1.6 Part 2, the impact of the ADA status on the proportion of remitters is counterintuitive, as the remission rates are slightly lower among ADA negative patients than among ADA positive patients. However, the number of patients in the subgroups are very small, and preclude any definitive conclusions. The proportion of patients reaching clinical remission among ADA positive patients was numerically slightly greater in the SC arm compared to the IV arm in both CD and UC patients.

Overall, there was no apparent correlation between the immune-mediated AEs, TEAE, TESAE or infection rates and ADA presence and there was no specific pattern in incidences of AEs and ADA titres across tertiles. The results were similar in RA patients (study CT-P13 3.5). Overall, numbers were small in some comparisons, thus firm conclusions cannot be drawn.

<u>Impact of Immunosuppressive Therapies on Immunogenicity</u>

Overall, based on the historical literature and immunogenicity data from CT-P13 IV/SC trials in RA and IBD patients, the results show that the concomitant use of immunosuppressant medication is correlated with a reduced ADA incidence rate.

However, the use of concomitant immunosuppressive medication (CIM) did not shift the relative immunogenicity between formulations. Among patients who did not use CIM 19/37 (51.4%) in the SC arm and 25/36 (69.4%) in the IV arm were ADA positive at week 30. The results from Study 1.6 Part 2 were in line with previous results and confirmed that the SC formulation is not more immunogenic in either users or non-users of CIM.

The impact of immunosuppressant on the incidence of ARRs (including IRR, SIR and Delayed Hypersensitivity) and localised ISR was comparable between the CT-P13 IV 5 mg/kg and CT-P13 SC 120/ 240 mg arms.

<u>Home-administration</u>
Infliximab is known to be very immunogenic (with 30% murine variable region amino acid sequence), a trait that is likely to be influenced by both use of immunosuppressants and mode of administration (subcutaneous route often being the more immunogenic, although almost the opposite has been shown for the SC Remsima). Importantly, IV infliximab has been administered in controlled clinical (hospital) setting, whereas, SC Remsima will be used at home.

According to the earlier knowledge on the IV infliximab (reflected also in the IV-infliximab SmPC), patients who discontinue immunosuppressants prior to or during infliximab treatment are at greater risk of developing antibodies and thus, at risk of immune-related reactions. This is of importance, as unlike in the earlier approved SC RA indication, in the currently sought SC indications, infliximab may be given also without a concomitant immunosuppressant. Further, according to the IV SmPC, delayed hypersensitivity reactions occurred earlier in the treatment course, apparently especially in the IV psoriasis studies. Available data also suggest an increased risk for delayed hypersensitivity, with increasing infliximab-free interval.

However, while the present data on patients treated without CIM is limited, and only on a few CD/UC-patients, the results do not raise concerns regarding immunogenicity and safety in patients without concomitant methotrexate or other immunosuppressive medication. This is because the rate of ADA positivity was comparable (or even lower) in the SC arm than in the IV arm, ADA titres were comparable and the frequency of NAb was no higher in the SC arm, in spite of the new, more sensitive methodology. In addition, no apparent differences in the clinical consequences of ADA-formation were evident between the IV and SC groups. Based on a previous analysis performed by the MAH, the incidence of localised injection site reactions was comparable to other licensed SC **TNFα-inhibitors,** used in the home-administration setting.

Also, the proposed SmPC and PL clearly warn about allergic reactions/ delayed hypersensitivity. Importantly, Remsima SC treatment is to be initiated and supervised by qualified physicians, and suitability of the patient for subcutaneous home use should be assessed and patients should be advised to inform their healthcare professional if they experience symptoms of an allergic reaction before administering the next dose. Premedication is recommended in the loading phase. Thus, the SmPC and PL include sufficient warnings and instructions for home-use.

<u>Conclusion on immunogenicity</u>

Since the rate of ADA positivity was comparable or even numerically slightly lower in the SC arm than in the IV arm, ADA titres were comparable between the treatment arms and the frequency of NAb was not higher in the SC arm, it can be concluded that Remsima SC is non-inferior to Remsima IV in terms of immunogenicity.

While the present data on patients treated without CIM is limited, the results do not raise concerns regarding immunogenicity and safety in patients without concomitant methotrexate or other immunosuppressive medication. Further data will be accrued in the post-approval pharmacovigilance programme. Thus, the use of Remsima SC, in all the sought indications, is acceptable also in the home-setting.

This overall supports the validity of extrapolation of the data to the indications where the use of CIM is less common than in RA.

Post marketing experience

Thus far, no post-marketing experience on the treatment of patient with the SC formulation exists.

The overall conclusion is that in the IBD study sample (adult patients with moderately active CU or moderate to severe UC) of study CT-P13 1.6 part 2, the overall safety in patients treated with Remsima SC 120/240 mg appears comparable to the safety of treatment with Remsima IV 5 mg/kg, excepting a higher incidence of localised ISR. The results did not raise concerns regarding immunogenicity and safety in patients with or without concomitant immunosuppressive medication. The SC formulation did not appear to be more immunogenic. In all, the safety profile of Remsima SC appears to be quite consistently similar to the previously described safety profile of SC infliximab in the SC development program (including the safety data on RA patients of the pivotal study) and also similar with the extensive safety data, including the post marketing safety data, available for the infliximab IV formulation.

Analysis performed across trials

Integrated Safety Analysis of Study CT-P13 1.6 Part 1 and Part 2 in IBD (CD and UC) Patients

Table 62 Overview of Adverse Events in Study CT-P13 1.6 Part 2 and Parts 1/2 Pooled (Maintenance Phase): Safety Population

	Study CT-P13 1.6 Part 2 (Crohn's Disease + Ulcerative Colitis)				Study CT-P13 1.6 Parts 1 and 2 Pooled	
	Week 6 to < Week 30		Week 6 to Week 54		Week 6 to Week 54	
	CT-P13 IV 5 mg/kg (N=65)	CT-P13 SC 120/240 mg (N=66)	CT-P13 IV 5 mg/kg[1] (N=65)	CT-P13 SC 120/240 mg (N=66)	Pooled CT-P13 IV[1] (N=78)	Pooled CT-P13 SC (N=97)
Total number of TEAEs	80	111	137	226	173	304
Number (%) of patients with ≥ 1 TEAE	32 (49.2)	38 (57.6)	38 (58.5)	49 (74.2)	48 (61.5)	72 (74.2)
Related	15 (23.1)	22 (33.3)	20 (30.8)	28 (42.4)	23 (29.5)	39 (40.2)
Unrelated	27 (41.5)	26 (39.4)	32 (49.2)	41 (62.1)	42 (53.8)	61 (62.9)
Number (%) of patients with ≥ 1 TEAE leading to death	0	0	0	0	1 (1.3)	1 (1.0)
Related	0	0	0	0	0	0
Unrelated	0	0	0	0	1 (1.3)	1 (1.0)
Number (%) of patients with ≥ 1 TESAE	4 (6.2)	2 (3.0)	6 (9.2)	5 (7.6)	10 (12.8)	11 (11.3)

Related	1 (1.5)	0	2 (3.1)	1 (1.5)	2 (2.6)	1 (1.0)
Unrelated	3 (4.6)	2 (3.0)	5 (7.7)	4 (6.1)	9 (11.5)	10 (10.3)
Number (%) of patients with ≥ 1 TEAE leading to study drug discontinuation	3 (4.6)	0	3 (4.6)	1 (1.5)	6 (7.7)	5 (5.2)
Related	3 (4.6)	0	3 (4.6)	1 (1.5)	4 (5.1)	2 (2.1)
Unrelated	0	0	0	0	2 (2.6)	3 (3.1)
Number (%) of patients with ≥ 1 TEAE classified as IRR/ SIR/delayed hypersensitivity[2]	2 (3.1)	1 (1.5)	2 (3.1)	3 (4.5)	3 (3.8)	4 (4.1)
Related	2 (3.1)	1 (1.5)	2 (3.1)	3 (4.5)	3 (3.8)	4 (4.1)
Unrelated	0	0	0	0	0	0
Number (%) of patients with ≥ 1 TEAE classified as localised ISR[3]	1 (1.5)	11 (16.7)	3 (4.6)	15 (22.7)	3 (3.8)	20 (20.6)
Related	1 (1.5)	10 (15.2)	3 (4.6)	14 (21.2)	3 (3.8)	18 (18.6)
Unrelated	0	1 (1.5)	0	1 (1.5)	0	2 (2.1)
Number (%) of patients with ≥ 1 TEAE classified as infection	11 (16.9)	11 (16.7)	19 (29.2)	21 (31.8)	22 (28.2)	34 (35.1)
Related	4 (6.2)	6 (9.1)	6 (9.2)	9 (13.6)	7 (9.0)	16 (16.5)
Unrelated	7 (10.8)	7 (10.6)	15 (23.1)	14 (21.2)	17 (21.8)	21 (21.6)
Number (%) of patients with ≥ 1 TEAE classified as malignancy	0	0	0	1 (1.5)	1 (1.3)	1 (1.0)
Related	0	0	0	1 (1.5)	0	1 (1.0)
Unrelated	0	0	0	0	1 (1.3)	0

[1] In Study CT-P13 1.6 Part 2, patients in the IV 5 mg/kg arm switched to CT-P13 SC treatment at Week 30. [2] In Study CT-P13 1.6 Part 1, IRR/SIR/delayed hypersensitivity was reported as infusion-related reaction in the eCRF and in Part 2, IRR/SIR/delayed hypersensitivity was reported as administration-related reaction in the eCRF. [3] In Study CT-P13 1.6 Part 1 and Part 2, 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. Columns with Part 1 data deleted for brevity.

Table 63 TEAEs Reported for at Least 2% of Patients Overall by SOC and PT in Study CT-P13 1.6 Part 2 (Maintenance Phase): Safety Population

System Organ Class Preferred Term	Week 6 to < Week 30			Week 6 to Week 54		
	CT-P13 IV 5 mg/kg (N=65)	CT-P13 SC 120/240 mg (N=66)	Total (N=131)	CT-P13 IV 5 mg/kg[1] (N=65)	CT-P13 SC 120/240 mg (N=66)	Total (N=131)
Number (%) of patients with at least 1 TEAE	**32 (49.2)**	**38 (57.6)**	**70 (53.4)**	**38 (58.5)**	**49 (74.2)**	**87 (66.4)**
Blood and lymphatic system disorders	**2 (3.1)**	**5 (7.6)**	**7 (5.3)**	**5 (7.7)**	**9 (13.6)**	**14 (10.7)**
Anaemia	0	1 (1.5)	1 (0.8)	1 (1.5)	2 (3.0)	3 (2.3)
Leukopenia	0	3 (4.5)	3 (2.3)	1 (1.5)	4 (6.1)	5 (3.8)
Neutropenia	1 (1.5)	2 (3.0)	3 (2.3)	3 (4.6)	5 (7.6)	8 (6.1)
Gastrointestinal disorders	**10 (15.4)**	**15 (22.7)**	**25 (19.1)**	**14 (21.5)**	**22 (33.3)**	**36 (27.5)**
Abdominal pain	1 (1.5)	2 (3.0)	3 (2.3)	1 (1.5)	5 (7.6)	6 (4.6)
(Aggravation of) Colitis ulcerative	5 (7.7)	2 (3.0)	7 (5.3)	8 (12.3)	3 (4.5)	11 (8.4)
(Aggravation of) Crohn's disease	0	1 (1.5)	1 (0.8)	1 (1.5)	3 (4.5)	4 (3.1)
Diarrhoea	1 (1.5)	3 (4.5)	4 (3.1)	1 (1.5)	4 (6.1)	5 (3.8)
Nausea	1 (1.5)	3 (4.5)	4 (3.1)	1 (1.5)	5 (7.6)	6 (4.6)
Vomiting	0	2 (3.0)	2 (1.5)	0	3 (4.5)	3 (2.3)
General disorders and administration site conditions	**5 (7.7)**	**13 (19.7)**	**18 (13.7)**	**7 (10.8)**	**18 (27.3)**	**25 (19.1)**
Asthenia	3 (4.6)	0	3 (2.3)	3 (4.6)	0	3 (2.3)
Localised injection site reaction[2]	1 (1.5)	11 (16.7)	12 (9.2)	3 (4.6)	15 (22.7)	18 (13.7)
Infections and infestations	**11 (16.9)**	**11 (16.7)**	**22 (16.8)**	**19 (29.2)**	**21 (31.8)**	**40 (30.5)**
Bronchitis	0	0	0	2 (3.1)	2 (3.0)	4 (3.1)
Latent Tuberculosis	0	0	0	2 (3.1)	1 (1.5)	3 (2.3)
Nasopharyngitis	2 (3.1)	4 (6.1)	6 (4.6)	2 (3.1)	4 (6.1)	6 (4.6)
Oral herpes	0	2 (3.0)	2 (1.5)	0	3 (4.5)	3 (2.3)
Pharyngitis	1 (1.5)	0	1 (0.8)	1 (1.5)	2 (3.0)	3 (2.3)
Sinusitis	1 (1.5)	0	1 (0.8)	2 (3.1)	1 (1.5)	3 (2.3)
Injury, poisoning and procedural complications	**3 (4.6)**	**1 (1.5)**	**4 (3.1)**	**4 (6.2)**	**3 (4.5)**	**7 (5.3)**
Infusion-related reaction/systemic injection reaction/delayed hypersensitivity[3]	2 (3.1)	1 (1.5)	3 (2.3)	2 (3.1)	3 (4.5)	5 (3.8)

Musculoskeletal and connective tissue disorders	**7 (10.8)**	**1 (1.5)**	**8 (6.1)**	**10 (15.4)**	**3 (4.5)**	**13 (9.9)**
Arthralgia	2 (3.1)	1 (1.5)	3 (2.3)	4 (6.2)	2 (3.0)	6 (4.6)
Arthritis	2 (3.1)	0	2 (1.5)	3 (4.6)	0	3 (2.3)
Nervous system disorders	**5 (7.7)**	**3 (4.5)**	**8 (6.1)**	**6 (9.2)**	**5 (7.6)**	**11 (8.4)**
Dizziness	2 (3.1)	1 (1.5)	3 (2.3)	2 (3.1)	2 (3.0)	4 (3.1)
Headache	3 (4.6)	2 (3.0)	5 (3.8)	3 (4.6)	4 (6.1)	7 (5.3)
Skin and subcutaneous tissue disorders	**11 (16.9)**	**8 (12.1)**	**19 (14.5)**	**13 (20.0)**	**10 (15.2)**	**23 (17.6)**
Dry skin	1 (1.5)	2 (3.0)	3 (2.3)	1 (1.5)	2 (3.0)	3 (2.3)
Pruritus	1 (1.5)	2 (3.0)	3 (2.3)	1 (1.5)	2 (3.0)	3 (2.3)
Rash	3 (4.6)	2 (3.0)	5 (3.8)	4 (6.2)	4 (6.1)	8 (6.1)
Vascular disorders	**1 (1.5)**	**2 (3.0)**	**3 (2.3)**	**1 (1.5)**	**2 (3.0)**	**3 (2.3)**
Hypertension	1 (1.5)	2 (3.0)	3 (2.3)	1 (1.5)	2 (3.0)	3 (2.3)

[1] Patients in the IV 5 mg/kg arm switched to CT-P13 SC treatment at Week 30. [2] Localised ISR was reported as injection site reaction in the eCRF.

[3] IRR/SIR/delayed hypersensitivity was reported as administration-related reaction in the eCRF. eCRF: Electronic case report form, IRR: Infusion-related reaction, ISR: Injection site reaction, IV: Intravenous, PT: Preferred term, SC: Subcutaneous, SIR: Systemic n class, TEAE: Treatment-emergent adverse event

Extrapolation of safety from RA and IBD to AS, PsA, Ps indications

In the previous CHMP Scientific Advice, it was underlined that the expected safety database was to be sufficiently large to provide for a meaningful comparison of safety and immunogenicity, especially for the SC route of administration, provided that no new safety concerns arise, for example, a dramatic increase in the immunogenicity of CT-P13 by SC route.

It is acknowledged that the overall SC database is not extensive, especially considering that several indications without any clinical data (AS, PsA, Ps) are applied for. In all, 819 subjects (391 RA patients, 97 CD patients, 78 UC patients and 253 healthy subjects) have been exposed to at least 1 dose of CT-P13 IV or SC across four controlled clinical studies. A total of 751 subjects (363 RA patients, 79 CD patients, 74 UC patients and 235 healthy subjects) have received at least one dose of CT-P13 SC and of them 249 have been treated for up to week 54, that is, for up to a year and a further 277 patients for a shorter duration of time; among them 201 patients (155 RA, 24 CD and 22 UC patients) receiving the sought dose of 120 mg of CT-P13 SC for up to a year (for full details see Table 36 of this AR).

The total numbers exposed would, for example, only just fulfill the ICH E1 guideline data requirements for long-term, and for overall data, for medicines of long-term use. However, the vast experience (over two decades) of treatment with IV infliximab, in general, needs to be taken into account here. Also, in this extrapolation setting, considering the strength of prior safety data, overall the quality of data, similarity and consistency of the Remsima SC safety findings, over indications and between the two formulations (excluding the elevated incidence of localised ISRs), the current Remsima SC safety database, even with its limitations, could be sufficient for the current extrapolation, with a prerequisite of an adequate and sufficiently robust post-marketing strategy (including dedicated post authorisation safety studies). The currently proposed post-marketing plan, including two placebo-controlled long-term maintenance studies (one in CD-patients and one in UC-patients), as well as an observational study in AS, PsA and Ps-patients, together with the already agreed upon observational RA-study, are considered sufficient (see RMP section of this AR) and provided that the protocol is agreed on with the PRAC.

In this application, in the study CT-P13 1.6 part 2 a dose regimen of Remsima SC 120 mg Q2W as maintenance therapy is proposed as the optimal dosing regimen for all indications regardless of body weight.

In this study, the overall safety of adult patients with moderately active CD or moderate to severe UC treated with Remsima SC infliximab appeared comparable to the safety of treatment with the Remsima IV formulation, excepting a higher incidence of localised ISR. Apart from this one exception, the safety profile was also consistent with the previously described safety profile of SC infliximab in the SC development program and the also with extensive safety data available for the infliximab IV formulation.

Some inherent limitations to the overall SC safety data, however, remain. Concerning the rationale for extrapolation, it was noted that the baseline characteristics of the source populations (RA, IBD), are not fully representative for the intended target indications (AS, Ps and PsA); these patients are generally younger and do not receive concomitant immunosuppressant medication and existing data on use of SC infliximab without the concomitant immunosuppressive therapy is relatively scarce. In addition, the higher, up to ten-fold, C_{trough} levels achieved, compared to IV, when on the proposed Remsima SC 120mg Q2W posology is, in longer term, a safety concern, although so far, in short term and up to week 54, no clinically relevant unexpected safety signals have been identified.

In conclusion, in the study CT-P13 1.6 part 2 the overall safety of the IBD study sample (adult patients with moderately active CD or moderate to severe UC) treated with the proposed posology for Remsima

SC infliximab, appears comparable to the overall safety of infliximab IV, excepting a higher incidence of localised ISR. While the present data on patients treated without CIM is limited, the results do not raise concerns regarding immunogenicity and safety in patients without concomitant methotrexate or other immunosuppressive medication. This supports the validity of extrapolation of the safety data to the indications, where use of CIM is less common than in RA.

Considering the strength of the prior safety data, overall the quality of data, similarity and consistency of the Remsima SC safety findings, over indications and between the two formulations (excluding the elevated incidence of localised ISRs), the accrued Remsima SC safety data supports, from the safety point of view, the extrapolation of the safety to the AS, PsA, Ps indications.

2.5.2. Conclusions on clinical safety

In the study CT-P13 1.6 part 2 the overall safety of the IBD study sample (adult patients with moderately active CD or moderate to severe UC) treated with Remsima SC was largely comparable to the safety of treatment with the IV formulation, excepting a higher incidence of localised ISR and referring also to the RSI. This finding was expected with SC administration. Apart from this, the safety profile appeared consistent with the previously described safety profile of Remsima SC and with available extensive safety data for the infliximab IV formulation.

Some uncertainties, also relevant for the extrapolation, of the Remsima SC safety data remain. They include:

- the higher C_{trough} levels achieved with the proposed Remsima SC posology is in long-term a safety concern.

- although the exposure could be estimated to be adequate and sufficient for the present extrapolation purposes, it is acknowledged that the overall patient exposure to the SC formulation is not extensive, even for the current extrapolation. A total of 751 subjects (363 RA patients, 79 CD patients, 74 UC patients and 235 healthy subjects) have received at least one dose of CT-P13 SC and of them 249 have been treated for up to week 54, that is, for up to a year, and a further 277 patients for a shorter duration of time; among them 201 patients (155 RA, 24 CD and 22 UC patients) receiving the sought dose of 120 mg of CT-P13 SC for up to a year (for full details see Table 36 of this AR).

- longer-term safety of Remsima SC beyond the 54 weeks remains yet unknown

- scarcity of data on treatment with SC formulation in the absence of immunosuppressive co-medication

In this setting a robust post marketing plan is a prerequisite. The post-marketing plan including two placebo-controlled long-term maintenance studies (one in CD-patients and one in UC-patients), as well as an observational study in AS, PsA and Ps-patients, together with the already agreed observational RA-study, is considered sufficient (see RMP part of this AR) to address these uncertainties, provided that the protocol is agreed with the PRAC. Overall, considering the strength of the prior safety data, overall the quality of data, similarity and consistency of the Remsima SC safety findings, over indications and between the two formulations (excluding the elevated incidence of localised ISRs), the accrued Remsima SC safety data is considered to be adequate and sufficient and supports the currently proposed extrapolation.

2.5.3. PSUR cycle

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.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP endorsed the Risk Management Plan version 12.2 with the following content:

Safety concerns

Important identified risks	Serious infections including sepsis BCG breakthrough infection and agranulocytosis in infants with *in utero* exposure to infliximab Demyelinating disorders Malignancy
Important potential risks	Colon carcinoma/dysplasia (in paediatric ulcerative colitis)
Missing information	Long term treatment with SC infliximab (SC only)

Pharmacovigilance plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
Registry CT-P13 4.2: An Observational, Prospective Cohort Study to Evaluate Safety and Efficacy of Remsima in Patients with Rheumatoid Arthritis	To assess the long-term safety of Remsima in RA patients by evaluation of ESI up to 5 years for each patient.	Long-term safety in RA with emphasis on TB and other serious infection	Protocol finalised	27 February 2014
			FPFV	17 December 2013
			Annual Safety and Efficacy Interim Analysis	The annual report submitted after 2019 will be replaced by the final report

			LPLV	2Q 2020
(EU) Status: Ongoing			Final report available	2Q 2021
Registry CT-P13 4.3: An observational, prospective cohort study to evaluate the safety and efficacy of Remsima in patients with Crohn's disease (CD) or Ulcerative Colitis (UC) (EU and Korea) Status: Ongoing	To assess the safety of Remsima by evaluation of ESI in IBD patients, who have active CD, fistulising CD or UC for up to 5 years for each patient.	Long-term safety in IBD with emphasis on TB and other serious infection	Protocol finalised	19 June 2014
			FPFV	22 April 2014
			Annual Safety and Efficacy Interim Analysis	The annual report to be submitted will be replaced by the final report
			LPLV	2Q 2020
			Final report available	2Q 2021
Registry CT-P13 4.4: An Observational, Prospective Cohort Study to Evaluate Safety and Efficacy of Remsima in Patients with Ankylosing Spondylitis (EU) Status: Ongoing	To assess the safety of Remsima in AS patientsby evaluation of ESI for up to 5 years from the first visit of each patient.	Long-term safety in AS with emphasis on TB and other serious infection	Protocol finalised	19 June 2014
			FPFV	13 August 2014
			LPLV	2Q 2020
			Final report available	2Q 2021
British Society for Rheumatology Biologics Register – Rheumatoid Arthritis (BSRBR-RA): A longitudinal observational study of patients with rheumatoid arthritis treated with biologic and other new advanced targeted therapies (UK) (Sponsor: Celltrion Inc.) Status: Ongoing	To test the hypothesis that any new biologic or other new advanced targeted therapy in patients with RA is associated with a similar risk of developing serious infections compared to patients with similar disease activity receiving established anti-TNF drugs.	Long-term safety in RA with emphasis on TB and other serious infection	Protocol finalised	March 2014
			FPFV	2Q 2015
			LPLV	4Q 2019
			Final report available	2Q 2021
Rheumatoid Arthritis Observation of Biologic Therapy	To study the long-term safety of biologic agents. This includes	Long-term safety in RA with emphasis on TB	Protocol finalised	01 July 2012

(RABBIT): Long-term Observation of Treatment with Biologics in Rheumatoid Arthritis (Germany) (Sponsor: Celltrion Inc.) Status: Ongoing	the observation of all adverse events (serious and non-serious) in order to assess the overall safety profile. Specific emphasis will be laid on "events of interest."	and other serious infection	FPFV	2Q 2015
			LPLV	4Q 2019
			Final report available	2Q 2021
British Society for Rheumatology Biologics Register – Rheumatoid Arthritis (BSRBR-RA): A longitudinal observational study of patients with rheumatoid arthritis treated with biologic and other new advanced targeted therapies (UK) (Sponsor: Pfizer Inc.) Status: Ongoing	To test the hypothesis that any new biologic or other new advanced targeted therapy in patients with RA is associated with a similar risk of developing serious infections compared to patients with similar disease activity receiving established anti-TNF drugs.	Long-term safety in RA with emphasis on TB and other serious infection	Protocol finalised	March 2014
			FPFV	2Q 2015
			LPLV	4Q 2019
			Final report available	2Q 2021
Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT): Long-term Observation of Treatment with Biologics in Rheumatoid Arthritis (Germany) (Sponsor: Pfizer Inc.) Status: Ongoing	To assess the long-term safety of Remsima in Rheumatoid Arthritis patients in comparison with patients receiving other TNF inhibitors and non-biological DMARDs.	Long-term safety in RA with emphasis on TB and other serious infection	Protocol finalised	01 July 2012
			FPFV	1Q 2015
			LPLV	4Q 2019
			Final report available	2Q 2021
CT-P13 SC 1.6 An Open-label, Randomized, Parallel Group, Phase I Study in Patients with Active Crohn's	To evaluate PK, PD, Efficacy and Safety between CT-P13 SC and CT-P13 IV in Patients with Active CD and Active UC	Safety in patients with CD (Part 1 & 2) and UC (Part 2 only) with the administration	Protocol finalised	09 January 2018

disease (CD) and Active Ulcerative Colitis (UC)

Status: Ongoing | | of SC formulation | FPFV | 20 October 2016 |
| | | | LPLV | 02 October 2019 |
| | | | Final report available | 2Q 2020 |
| CT-P13 SC 4.8
An observational, prospective cohort study to evaluate safety of CT-P13 Subcutaneous in patients with Rheumatoid Arthritis

Status: Planned | To evaluate additional safety of CT-P13 SC in RA patients | Long-term safety in patients with RA | Protocol finalised | November 2019 |
			FPFV	April 2021
			3-year report	April 2024
			LPLV	June 2025
			Final report available	December 2025
CT-P13 SC 3.8
A Randomized, Placebo-Controlled, Double-Blind, Phase 3 Study to Evaluate the Efficacy and Safety of the Subcutaneous Injection of CT-P13 (CT-P13 SC) as Maintenance Therapy in Patients with Moderately to Severely Active Crohn's Disease.

Status: Ongoing | To evaluate efficacy, PK, PD, usability, and overall safety including immunogenicity | Long-term safety in patients with CD | Protocol finalised | 17 May 2019 |
			FPFV	28 October 2019
			LPLV	July 2023
			Final report available	December 2023

CT-P13 SC 4.9 An Observational, Prospective Cohort Study to Evaluate Safety of Remsima® Subcutaneous in Patients with Ankylosing Spondylitis, Psoriatic Arthritis and Psoriasis Status: Planned	To assess the safety of Remsima® subcutaneous (SC) in Ankylosing Spondylitis (AS), Psoriatic Arthritis (PsA) and Psoriasis (Ps) patients by evaluation of adverse events of special interest (AESI)	Long-term safety in patients with AS, PsA and Ps	Protocol finalised	November 2020
			FPFV	September 2021
			3-year report*	September 2024
			LPLV	July 2026
			Final report available	January 2027
CT-P13 SC 3.7 A Randomized, Placebo Controlled, Double-Blind, Phase 3 Study to Evaluate the Efficacy and Safety of the Subcutaneous Injection of CT-P13 (CT-P13 SC) as Maintenance Therapy in Patients with Moderately to Severely Active Ulcerative Colitis Status: Planned	To evaluate additional efficacy, pharmacokinetics (PK), pharmacodynamics (PD), and overall safety including immunogenicity	Long-term safety in patients with UC	Protocol finalised	31 October 2019
			FPFV	To be determined
			LPLV	To be determined
			Final report available	To be determined

The following studies have been added to the pharmacovigilance plan as part of this procedure:

- Study CT-P13 SC 3.8: A Randomized, Placebo-Controlled, Double-Blind, Phase 3 Study to Evaluate the Efficacy and Safety of the Subcutaneous Injection of CT-P13 (CT-P13 SC) as Maintenance Therapy in Patients with Moderately to Severely Active Crohn's Disease.

- Study CT-P13 SC 4.9: An Observational, Prospective Cohort Study to Evaluate Safety of CT-P13 Subcutaneous in Patients with Ankylosing Spondylitis, Psoriatic Arthritis and Psoriasis

- Study CT-P13 SC 3.7: A Randomized, Placebo Controlled, Double-Blind, Phase 3 Study to Evaluate the Efficacy and Safety of the Subcutaneous Injection of CT-P13 (CT-P13 SC) as Maintenance Therapy in Patients with Moderately to Severely Active Ulcerative Colitis

Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk: Serious infections including sepsis	Routine risk minimisation measures: *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.* *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.* *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.* *SmPC section 4.4 where warning is given that the suppression of TNF-α may mask symptoms of infection such as fever.* *Severe infections such as sepsis is listed as a contraindication in SmPC section 4.3.* *Serious infections including sepsis is listed as special warnings and precautions for use in SmPC section 4.4.* *Serious infections including sepsis is listed as an adverse reaction in SmPC section 4.8.* *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 common before you are given Remsima/Inflectra.* *Serious infection is listed as contraindication and warning and precautions in PL section 2.* *Legal status: Medicinal product subject to restricted medical prescription.* Additional risk minimisation measures: *Patient reminder card.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None.* Additional pharmacovigilance activities: *CT-P13 4.2* *CT-P13 4.3* *CT-P13 4.4* *BSRBR-RA (Sponsor: Celltrion Inc.)* *RABBIT (Sponsor: Celltrion Inc.)* *BSRBR-RA (Sponsor: Pfizer Inc.)* *RABBIT (Sponsor: Pfizer Inc.)* *CT-P13 SC 1.6* *CT-P13 SC 3.7* *CT-P13 SC 3.8* *CT-P13 SC 4.8* *CT-P13 SC 4.9*
Important identified risk: BCG breakthrough infection and agranulocytosis in infants	Routine risk minimisation measures: *SmPC section 4.2 where advice is given that patients treated with Remsima/Inflectra should be given the*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Safety concern	Risk minimisation measures	Pharmacovigilance activities
with in utero exposure to infliximab	*package leaflet and the patient reminder card.* *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.* *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.* *Agranulocytosis is listed as an adverse reaction in SmPC section 4.8.* *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).* *Legal status: Medicinal product subject to restricted medical prescription.* Additional risk minimisation measures: *Patient reminder card.*	None. Additional pharmacovigilance activities: None.
Important identified risk: Demyelinating disorders	Routine risk minimisation measures: *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.* *SmPC section 4.4 where guidance is given that the in patients with 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.* *Demyelinating disorders is listed as an adverse reaction in SmPC section 4.8.* *Legal status: Medicinal product subject to restricted medical prescription.* Additional risk minimisation measures: *None.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None.* Additional pharmacovigilance activities: *CT-P13 4.2* *CT-P13 4.3* *CT-P13 4.4* *BSRBR-RA (Sponsor: Celltrion Inc.)* *BSRBR-RA (Sponsor: Pfizer Inc.)* *RABBIT (Sponsor: Celltrion Inc.)* *RABBIT (Sponsor: Pfizer Inc.)* *CT-P13 SC 1.6* *CT-P13 SC 3.7* *CT-P13 SC 3.8* *CT-P13 SC 4.8* *CT-P13 SC 4.9*

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk: Malignancy	Routine risk minimisation measures: *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.* *Malignancy is listed in SmPC section 4.8.* *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.* *Cancer in children and adults is listed in PL section 4.* *Legal status: Medicinal product subject to restricted medical prescription.* Additional risk minimisation measures: *None.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None.* Additional pharmacovigilance activities: *CT-P13 4.2* *CT-P13 4.3* *CT-P13 4.4* *BSRBR-RA (Sponsor: Celltrion Inc.)* *BSRBR-RA (Sponsor: Pfizer Inc.)* *RABBIT (Sponsor: Celltrion Inc.)* *RABBIT (Sponsor: Pfizer Inc.)* *CT-P13 SC 1.6* *CT-P13 SC 3.7* *CT-P13 SC 3.8* *CT-P13 SC 4.8* *CT-P13 SC 4.9*
Important potential risk: Colon carcinoma/dysplasia (in paediatric ulcerative colitis)	Routine risk minimisation measures (not applicable for SC): *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.* *SmPC section 4.4 where guidance is given that this evaluation should include colonoscopy and biopsies per local recommendations. Current data do not indicate that Remsima/Inflectra treatment influences the risk for developing dysplasia or colon cancer.* *Abnormal tissue swelling or growth is listed in PL section 4.* *Legal status: Medicinal product subject to restricted medical prescription.* Additional risk minimisation measures: *None.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None.* Additional pharmacovigilance activities: *CT-P13 4.3*
Missing Information:	Routine risk minimisation measures:	Routine pharmacovigilance activities beyond adverse

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Long term treatment with SC infliximab (SC only)	*Legal status: Medicinal product subject to restricted medical prescription.* Additional risk minimisation measures: *None.*	reactions reporting and signal detection: *None.* Additional pharmacovigilance activities: *CT-P13 SC 3.7* *CT-P13 SC 3.8* *CT-P13 SC 4.8* *CT-P13 SC 4.9*

2.7. Update of the Product information

Extension of indication of the subcutaneous formulation of Remsima, to add treatment of adult patients with Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and psoriasis in line with the adult indications of the IV formulation; consequently, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC and relevant sections of the Package leaflet are updated. An updated RMP (version 12.2) has also been submitted.

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2.7.1. User consultation

The MAH conducted a bridging analysis and a separate focus test to confirm the readability of Remsima 120 mg solution for injection in pre-filled syringe PL including new therapeutic indications (AS, PsA, Ps, CD, and UC). Since the readability of the PFS-S PL with RA indication has already been established in 2019 (EMEA/H/C/002576/X0062), the MAH conducted a focus test targeting the adapted parts of the leaflet only. The focus test included 4 questions and altogether 20 respondents (aged 18-65) took part in two testing rounds. In the first test round, all four questions met the predefined success criteria on finding and understanding. The second test round confirmed the positive results of the first test round and thus, no amendments were made in the Remsima PL.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

The current approved indication in the EU for Remsima SC is for adult RA patients as follows:

Remsima, following an initial dose of two intravenous infusions of infliximab, is indicated for the following conditions:

<u>Rheumatoid arthritis</u>

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.

With this Type II variation application, the MAH seeks to extend the use of the SC formulation of Remsima to the treatment of adult patients with CD, UC, AS, PsA and Ps as follows:

<u>Adult Crohn's disease</u>

Remsima is indicated for:

- treatment of moderately to severely active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.

- treatment of fistulising, active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy).

<u>Adult Ulcerative colitis</u>

Remsima is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

<u>Ankylosing spondylitis</u>

Remsima is indicated for treatment of severe, active ankylosing spondylitis, in adult patients who have responded inadequately to conventional therapy.

<u>Psoriatic arthritis</u>

Remsima is indicated for treatment of active and progressive psoriatic arthritis in adult patients when the response to previous DMARD therapy has been inadequate.

Remsima should be administered in combination with methotrexate or alone in patients who show intolerance to methotrexate or for whom methotrexate is contraindicated.

<u>Psoriasis</u>

Remsima is indicated for treatment of moderate to severe plaque psoriasis in adult patients who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or psoralen ultra-violet A (PUVA).

No paediatric indications are proposed for CT-P13 SC in this application. The proposed indications are all approved for Remsima IV.

3.1.2. Available therapies and unmet medical need

There are several medicinal products containing infliximab for intravenous infusion on the market. However, the subcutaneously administered infliximab is so far available only for RA patients. Several other TNFα inhibitors are available in SC formulation for the sought indications. Thus, this application does not address any 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 also optimisation of medical resources.

3.1.3. Main clinical studies

Patient studies:

a) In RA patients (already an approved indication); 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 of the study was open label, Part 2 was double-blinded.

Part 1 was conducted to determine the optimal dose of CT-P13 SC in 48 RA patients based on PK-data, whereas Part 2 was performed to establish therapeutic non-inferiority (based on clinical efficacy) of CT-P13 SC compared with CT-P13 IV in 348 RA patients.

Part 1 of study CT-P13 3.5 was 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. Efficacy results from this open label study showed non-inferior efficacy for all dose levels compared to Remsima IV 3mg/kg up to week 54.

Part 2 of study CT-P13 3.5 was the pivotal clinical study in RA patients. 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 CT-P13 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). 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. 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.

b) In IBD patients (sought indication): Study CT-P13 1.6:

This was a multi-dose, randomised, controlled, parallel group, 54-week study to evaluate PK, efficacy and safety of CT-P13 SC in IBD patients. Both parts of the study were open-label.

Part 1 was conducted to find the optimal dose of CT-P13 SC in 44 CD patients (no UC patients included) based on PK-data, while Part 2 was designed to demonstrate non-inferiority for PK of CT-P13 SC compared to CT-P13 IV in 130 patients.

Part 1 of study CT-P13 1.6 was the IBD dose finding study. The study was an open-label phase I study that compared CT-P13 SC (in three different dose-levels; 120 mg, 180 mg, and 240 mg at week 6 and then every 2 weeks) and CT-P13 IV (5 mg/kg at week 6 and then every eight weeks, dose escalation to 10 mg/kg allowed) 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. The selected SC posology did not perform consistently weaker than the approved IV dose.

In Part 2 of study CT-P13 1.6 the primary objective was to demonstrate that CT-P13 SC 120mg Q2W is non-inferior to CT-P13 IV 5 mg/kg Q8W in terms of PK, as determined by the $C_{trough, week\ 22}$ (pre-dose level at Week 22) in IBD patients. The study included 53 CD patients with moderate disease activity (CDAI score between 220 to 450 points; fistulising CD patients were not included) who had not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or were intolerant to or had medical contraindications for such therapies, and 78 UC patients with moderate or severe disease activity (total Mayo score between 6 and 12 points with endoscopic evidence of active UC as indicated by endoscopic subscore of ≥ 2 points) who had not responded despite conventional therapy including corticosteroids alone or in combination with 6-MP or AZA and medications containing 5-ASA, or who were intolerant to or had medical contraindications for such therapies. All enrolled patients initially received Remsima IV 3mg/kg infusion at Weeks 0 and 2.

c) <u>AS, Ps, PsA (sought indications)</u>

The application does not include any clinical data from patients with AS, Ps or PsA. Approval is sought based on extrapolation.

<u>Studies in healthy volunteers</u>

Two studies in Healthy volunteers (CT-P13 1.5 and CT-P13 1.9) contribute with supportive safety and immunogenicity data.

3.2. Favourable effects

The efficacy of Remsima IV was initially established in September 2013 as it was approved as a biosimilar product to Remicade (EMEA/H/C/002576). Following a line extension application (EMEA/H/C/002576/X/0062), the subcutaneous formulation (Remsima SC) was approved for treatment of RA. Notably, the originator Remicade does not have SC-formulation.

Favourable effects in RA patients (Study CT-P13 3.5 Part 2)

In summary, in RA patients 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. 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 (in favour of SC) is neither clinically nor statistically significant. Hence, Remsima SC 120 mg is non-inferior to Remsima IV 3 mg/kg in RA-patients with concomitant methotrexate use.

Favourable effects in IBD patients (Study CT-P13 1.6 Part 2)

In patients with active non-fistulating, moderate CD or moderate to severe UC, not adequately responding to conventional treatment, the following favourable effects were seen:

The primary endpoint of Study CT-P13 1.6 Part 2 was the observed serum infliximab pre-dose level at Week 22 ($C_{trough,week22}$). The geometric LS means of observed $C_{trough,week22}$ were 20.9844 and 1.8181 μg/mL in the SC 120/240 mg and IV 5 mg/kg treatment arms, respectively. The lower bound 90% CI for the ratio of the geometric LS means was 786.37%, which was greater than 80%, indicating non-inferiority of Remsima SC 120/240 mg compared to Remsima IV 5 mg/kg.

Clinical efficacy in CD patients was similar between the studied treatment arms. CDAI-70 response was reached in 22 (78.6%) and 21 (84.0%) patients in the SC 120/240 mg and IV 5 mg/kg treatment arms, respectively by week 22 and in 19 (67.9%) and 17 (68.0%) patients, respectively, by week 30.

Clinical remission (defined as an absolute CDAI score < 150 points) was reached in 57.1% and 60.0% in the SC and IV treatment arms, respectively by week 22.

Among patients who received the sought 120 mg dose of Remsima SC, response rate according to CDAI-70 at week 22 was 90% (n=18) and clinical remission was reached by 13/20 (65%) patients at week 22. Response remained comparable between treatment arms up to week 54, also after switching all patients to SC treatment at week 30.

All results on the secondary efficacy outcomes, as well as data from the small dose finding study 1.6 Part 1, are in line and support the non-inferiority of CT-P13 SC.

The number of UC patients achieving clinical response by week 22 according to Partial Mayo score was 32 (84.2%) and 30 (76.9%)in the SC 120/240 mg and IV 5 mg/kg treatment arms, respectively. Among patients who received the sought 120 mg dose of Remsima SC, 22 (78.6%) achieved clinical response by week 22.

After switching to Remsima SC at Week 30 in the IV treatment arm, the response rates according to Partial Mayo score persisted and were similar between the two studied treatment arms at Week 54 (31 [81.6%] and 28 [71.8%] in the SC and IV treatment arms, respectively). At week 54, response was reached by 22 (78.6%) among those UC patients who received the sought dose of 120 mg Remsima SC.

Since the need for concomitant corticosteroids was not imputed in the outcome estimands, this can be considered as an independent indicator of treatment response. At baseline, CD patients in the SC arm were similar to those in the IV arm in terms of disease activity and corticosteroid use. During the study, the use of corticosteroids increased in both treatment arms (probably due to intensified care, because of participation in the study), but during the maintenance phase the use of corticosteroids for systemic use was more common in the IV arm.

Also, UC patients were similar at baseline in terms of disease activity and medication. The use of antidiarrheal, intestinal anti-inflammatory/anti-infective agents increased in a similar manner in both treatment arms. However, during the maintenance phase, the use of concomitant corticosteroids for systemic use was significantly more common among IV patients, while the use of corticosteroids was reduced in the SC arm.

The reduced need for corticosteroids and other anti-inflammatory medication in the SC arm compared to the IV arm during the maintenance phase supports the conclusion of non-inferior efficacy for Remsima SC.

The provided data supports non-inferiority of Remsima SC 120/240 mg and 120mg compared to Remsima IV 5 mg/kg in CD and UC patients in terms of response and remission rates, before switching of treatment at week 30 and after switching up to week 54.

The proposed posology in IBD indications is 120 mg SC Q2W for all patients regardless of body weight; therefore, C_{trough} in subjects with body weight ≥80 kg will be lower than that observed in study 1.6 Part 2 but still several folds higher than with the approved Remsima IV posology. Simulations using the PPK model indicated that infliximab $C_{trough,ss}$ of infliximab 120 mg SC Q2W was 2.63~10.62-fold higher than the $C_{trough,ss}$ of infliximab 5 mg/kg IV Q8W over weight from 50 kg to 150 kg, the difference decreasing with high body weights. As it is believed that C_{trough} is the most important parameter in relation to effect, maintaining a C_{trough} above > 5 μg/mL (and above the concentration seen with approved posology of Remsima IV) should be enough to ensure efficacy of Remsima SC 120mg in all IBD patients. The relatively lower $AUC_{8W,ss}$ observed in heavier patients receiving Remsima SC 120 mg did not impact efficacy outcomes. Hence, the proposed posology of 120 mg regardless of body weight is considered appropriate by CHMP.

3.3. Uncertainties and limitations about favourable effects

The efficacy of Remsima SC was not studied in As, PsA and Ps indications. Hence, the assessment of efficacy in these indications is based on extrapolation.

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), haematologic reactions, systemic lupus erythematosus/lupus like 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 in RA patients (Study CT-P13 3.5 Part 2). Indication already approved.

In summary, during the Maintenance Phase of the pivotal RA study, TEAEs were, in all, reported for 117 (66.9%) and 92 (54.8%) IV and SC patients, respectively. The most common TEAE being localised ISR (IV 3 mg/kg: 12.6% vs. SC 120 mg: 17.9%). The majority of the events in both treatment arms were grade 1 or 2 in severity; number of grade 3 or higher TEAEs being alike in the 2 treatment arms. SAE were reported for 13 (7.4%) and 6 (3.6%) and TEAEs leading to study drug discontinuation, for 14 (8.0%) and 6 (3.6%) patients in the IV 3 mg/kg and SC 120 mg arms, respectively. 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. No increased safety concerns related to higher drug concentrations in SC patients were seen. The MAH conducted a comprehensive investigation on all five death cases and found no trend in regard to the PK parameters or immunogenicity and the incidence rate of death was within the range of reported rates from historical study. Overall, the safety profile of Remsima SC, in the proposed dose range, in RA patients, did not appear consistently worse than Remsima IV, with one notable exception: the proportion of patients that reported a TEAE classified as localised ISR, was generally higher in the SC group.

Unfavourable effects in IBD patients (Study CT-P13 1.6 Part 2) - the current application

According to the safety results of the study CT-P13 1.6 part 2, the proportions of patients with at least one TEAE, TESAE, TEAE leading to discontinuation of study drug or TEAE classified as ARR (IRR, SIR and delayed hypersensitivity reactions) were no higher in the SC group compared to the IV group. The respective numbers for infections were also similar between the groups, 24 (36.4%) in the SC and 20 (30.8%) in the treatment arms. The proportion of patients that reported localised injection site reaction (ISR) was notably higher in the SC group 15 (22.7%) vs 3 (4.6). This was the single notable finding among otherwise comparable safety data between treatment arms was the higher proportion of patients that reported localised ISR in the SC group. This pattern was also seen in the pivotal data on RA patients.

When analysing the safety data for TEAEs reported for at least 5% of patients, the incidence rates were slightly different. However, the MAH clarified acceptably that infections, anaemia, neutropenia and gastrointestinal disorders are recognised TEAEs reported in clinical trials with infliximab and that these disparate findings can be explained by previous medical history or could even be regarded as

chance findings. It was concluded that the findings did not indicate new safety signals or issues for the SC formulation of CT-P13 SC.

The requested analysis of the main safety data by body weight stratas (≥ 80 kg and < 80 kg) for both treatment arms showed (acknowledging the small numbers in some of the subgroups) no apparent correlation between body weight and the safety profiles, in either of the CT-P13 IV or SC treatment arms.

Concerning SAE, there were no differences in the number of patients who experienced at least 1 TESAE, 5 (7.6%) and 6 (9.2%) patients in the SC 120/240 mg and IV 5 mg/kg treatment arms, respectively. The TESAEs considered to be related to study drug were rare, solitary cases reported for 1 (1.5%) patient (NSCLC) in the SC 120/240 mg and 2 (3.1%) patients (disseminated TB and bronchitis with cardiac decompensation) in the IV 5 mg/kg treatment arm, respectively. No differences were evident between the two CD and UC patient groups or when switching formulations. No deaths were reported during the study.

The TEAEs leading to permanent discontinuation of study drug during the maintenance phase were reported for 1 (1.5%) and 3 (4.6%) patients in the SC 120/240 mg (NSCC) and IV 5 mg/kg treatment arms (NSCLC and IRR, psoriasis and disseminated TB), respectively, all considered related to the study drug. They were rare, solitary cases, of grade 2 or 3, no more numerous in patients treated with the SC, than with the IV formulations or those reported for the RA patients. Switching of treatment appeared not to associate with any of the discontinuations.

The number of patients in total and the number with at least 1 TEAE classified as infection was similar between the 2 treatment arms 21 (31.8%) and 19 (29.2%) with the patients in the SC 120/240 mg and IV 5 mg/kg treatment arms, respectively. The most frequently reported were nasopharyngitis reported in 4 (6.1%) patients and 2 (3.1%) patients for the SC and IV arms, respectively. Infection considered by the investigator to be related to study drug were overall reported in 15 (11.5%) patients, and were largely not more numerous in the SC 9 (13.6%) than in the IV treatment arm 6 (9.2%). Most of the events were of grade 1 or 2 in intensity. Findings were similar between the subgroups of CD and UC patients. Thus, infections were no more numerous in the SC than in the IV treatment arm, which is in line with the IV data.

A single malignancy was reported in the study for one (1.5%) patient with CD in the SC 120/240 mg treatment arm (NSCLC, after week 50) judged possibly related to the treatment, but the current follow-up is too short for any conclusions.

Over time, the changes from baseline in all clinical chemistry, urinalysis, and haematology laboratory parameters were generally small, and there were no notable differences between the two treatment arms.

The SC formulation was not more immunogenic among patients who did not use concomitant immunosuppressive medication [19/37 (51.4%) in the SC arm and 25/36 (69.4%) in the IV arm were ADA positive at week 30]. Among patients who used concomitant immunosuppressive medication, the results from Study 1.6 Part 2 were in line with previous RA results and supported the notion that SC Remsima is not more immunogenic than IV Remsima.

Infliximab is known to be very immunogenic (with 30% murine variable region amino acid sequence); a trait that is likely to be influenced by both use of immunosuppressants and the mode of administration (subcutaneous route often being more immunogenic) and it could have consequences for clinical safety, as well as efficacy. This, however, was not apparent in the IBD or RA patients on Remsima SC treatment. Overall ARR were rare. Moreover, this should be considered, acknowledging that the IV infliximab is administered in controlled clinical (hospital) setting, whereas, SC Remsima will

be used at home. However, while the present data on patients treated without CIM is limited, and only on a few CD/UC-patients, the results do not raise concerns regarding immunogenicity and safety in patients without concomitant methotrexate or other immunosuppressive medication. This is, because the rate of ADA positivity was comparable (or even lower) in the SC arm than in the IV arm, and ADA titres were comparable and the frequency of NAb was no higher in the SC arm, in spite of the new, more sensitive methodology. In addition, no apparent differences in the clinical consequences of ADA-formation were evident between the IV and SC groups. Furthermore, the similar incidences of localized injection site reactions were comparable to those of other licensed SC TNFα-inhibitors, which are also used in the home-administration setting. Further data will be accrued in the post-approval pharmacovigilance programme. Thus, the use of Remsima SC also in the home-setting is considered acceptable.

The impact of immunosuppressant on the incidence of ARRs (including IRR, SIR and Delayed Hypersensitivity) and localised ISR was comparable between the Remsima IV 5 mg/kg and Remsima SC 120/ 240 mg arms.

Using the new ADA ECL ACE and NAb ECL ACE methods the immunogenicity results showed (study CT-P13 1.6 Part 2) no clear associations of ADA status or titers and the rate of immune-mediated AEs (IRR, SIR, delayed hypersensitivity and localised ISR), TEAEs or TESAEs. The results were similar in RA patients (study CT-P13 3.5 Part 2). Overall, numbers were small and discrepant in some comparisons, thus firm conclusions cannot be drawn.

Hence, the present data, while limited, does not raise concerns regarding immunogenicity and safety in patients without concomitant methotrexate or other immunosuppressive medication. This supports the possibility of extrapolation of the data to the indications where patients use less MTX.

Overall, no unexpected findings were seen and the overall safety profile of the patients treated with SC was no worse compared to the IV arm, even after switching, and was overall comparable with the known safety profile of infliximab. The single notable finding among otherwise comparable safety data between treatment arms was the higher proportion of patients that reported localised ISR in the SC group.

3.5. Uncertainties and limitations about unfavourable effects

Thus far, no post-marketing experience on the treatment of patient with the SC formulation exists.

Up to tenfold higher C_{trough} levels, compared to IV, are achieved when on the proposed Remsima SC 120 mg Q2W posology. This is a safety concern, especially in long-term, beyond the current 54 week. Data on effects of this on patient safety, particularly concerning serious infections (including TB and other opportunistic infections) is still scarce, and as data on cancer is still unknown. So far, in short term and up to week 54, it appears that no clinically relevant, unexpected safety signals have been identified.

The overall exposure of the entire Remsima SC database is not extensive, especially considering the various indications applied for. A total of 751 subjects (363 RA patients, 79 CD patients, 74 UC patients and 235 healthy subjects) have received at least one dose of CT-P13 SC and of them 249 have been treated for up to week 54, that is, for up to a year and a further 277 patients for a shorter duration of time; among them 201 patients (155 RA, 24 CD and 22 UC patients) receiving the sought dose of 120 mg of CT-P13 SC for up to a year (for full details see Table 36 of this AR). However, it is considered adequate and sufficient for the current extrapolation purposes, with the sufficiently robust post marketing strategy being a prerequisite.

Especially, data on treatment with the Remsima SC without immunosuppressive co-medication appears scarce, and thus calls for post-approval safety data. The MAH has, indeed, proposed to further evaluate the safety of Remsima SC in addition to patients with RA, also in patients with Ankylosing Spondylitis, Psoriatic Arthritis and Psoriasis. The planned post-authorisation safety study CT-P13 4.9 is an observational, prospective cohort study, planned to include 576 patients (288 patients in each treatment group of Remsima IV and SC) who will be followed up for 24 months. In addition, two other placebo-controlled long-term maintenance studies, one in CD and one in UC patients have been planned. Overall, this post-approval PhV-programme is robust enough, also from the safety point of view. The final PhV-programme is agreed on with the PRAC.

The results of the analysis of the relationship between ADA-status and clinical safety outcome in study CT-P13 1.6 Part 2 up to week 54 showed no associations of ADA-status with the AE rates, including those of infections or hypersensitivity reactions. However, numbers in some comparisons were too small for firm conclusions.

To summarize, the uncertainties with regards to the unfavourable effects pertain mainly to the fact that there is still relatively limited safety data, especially considering the several applied for indications without any clinical data, and to the sufficiency of the overall data for current extrapolation purposes. To address these uncertainties, a robust post approval strategy has been proposed which is considered adequate by CHMP.

3.6. Effects Table

Table 64 Effects Table for Subcutaneous Remsima and Intravenous Remsima in Patients with Active Crohn's Disease (CD) and Active Ulcerative Colitis (UC) (Study CT-P13 1.6 Part 2) (Database lock: 25 October 2019).

Effect	Description	Unit	SC 120 mg	IV 5mg/kg	Uncertainties / Strength of evidence
Favourable Effects in CD patients					
CDAI-70 (Clinical response)	decrease in CDAI score of ≥ 70 points from the baseline value at week 22	N (%)	18 (90%)	21 (84.0%)	
Clinical remission	defined as an absolute CDAI score of < 150 points at week 22	N (%)	13 (65%)	15 (60.0%)	
Favourable Effects in UC patients					
Clinical response by partial Mayo score	defined as a decrease in partial Mayo score from baseline of at least 2 points, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point, or an absolute subscore for rectal bleeding of 0 or 1 point at week 22	N (%)	22 (78.6%)	30 (76.9%)	
Clinical remission by partial Mayo score	defined as a partial Mayo score of ≤ 1 point at week 22	N (%)	14 (50%)	15 (38.5%)	
Unfavourable Effects up to week 54 (CD and UC patients combined) *					
Infections	Infections	N (%)	21 (31.8%)	19 (29.2%)	
Localised ISR	Local acute reactions related to SC dosing	N (%)	15 (22.7%)	3 (4.6%)	
ARR	Systemic reactions related to infusion and injection of infliximab (IRR+SIR+delayed hypersensitivity)	N (%)	3 (4.5%)	2 (3.1%)	
ADA	ADA-positive patients up to week 54 (EOS)	N (%)	48 (72.7%)	44 (67.7%)	Post-treatment ADA frequencies up to W30 (i.e. the most sensitive comparison) were 33 (50.0%) in the SC arm and 42 (64.6%) in the IV arm.

Abbreviations: ISR: injection site reactions, ARR: Systemic Administration related reactions (including IRR: infusion-related reactions, SIR: systemic injection reactions and DEL: delayed hypersensitivity reactions). ADA: anti-drug antibodies. EOS: end of study.

Note: The IV 5 mg/kg treatment arm included 7 CD and 13 UC patients with a body weight ≥ 80kg, while all patients in the SC 120mg treatment arm were < 80kg. The efficacy of Remsima SC 120mg in patients weighing ≥ 80kg was estimated to be non-inferior to the efficacy of Remsima IV 5mg/kg based on PK and extrapolation exercise.

* Infection, localised ISR, ARR and ADA results of SC 120 mg also includes the data from SC 240 mg.

Table 65 Effects Table for Remsima SC 120mg in the treatment of rheumatoid arthritis - indication already approved (Study CT-P13 3.5 Part 2) (Database lock: 27 May 2019)

Effect	Description	Unit	SC 120mg	IV 3mg/kg	Uncertainties/ Strength of evidence	References
Favourable Effects						
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 at week 30	N (%)	142 (86.1%)	133 (76.4%)		Study CT-P13 3.5 Part 2
Unfavourable Effects up to EOS						
Infections*	Infections	N (%)	49 (29.2%)	60 (34.3%)		Study CT-P13 3.5 Part 2
Localised ISR*	Local injection site reactions	N (%)	30 (17.9%)	22 (12.6%)		Study CT-P13 3.5 Part 2
ARR*	Systemic reactions related to infusion and injection of infliximab (IRR+SIR+delayed hypersensitivity)	N (%)	5 (3.0%)	10 (5.7%)		Study CT-P13 3.5. Part 2
ADA	ADA-positive patients up to week 54 (EOS visit))	N (%)	114 (67.9%)	129 (73.7%)		Study CT-P13 3.5. Part 2

Abbreviations: ISR: injection site reactions, ARR: Administration related reactions (including infusion-related reactions, acute and delayed hypersensitivity reactions). LS: least squares, SE: standard error, ADA: anti-drug antibodies. EOS: end of study, 8 weeks after last drug administration.
Note: ADA results are updated with the results obtained with the new New ADA ECL ACE Method.
* Infections, localised ISR and ARR results are data from the maintenance phase.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Although the SC infliximab is not fulfilling any unmet medical need, as such, 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 burden for hospitals and inconvenience to patients 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 usually affects the quality of life of patients. The fixed dose approach is simple and practical and may reduce 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 doses, which is especially important for patients with poor venous access. The shorter administration time is also a benefit for patients. In general, the efficacy of infliximab IV is well established. The efficacy of Remsima SC 120 mg has been compared to earlier approved Remsima IV and shown to be non-inferior to Remsima IV 3mg/kg in RA patients.

The provided data, including PK, PK-modelling and clinical efficacy and safety data, in IBD patients, supports non-inferiority of Remsima SC 120mg to Remsima IV 5 mg/kg also in CD and UC patients.

In general, the safety profile of infliximab IV is well established. However, after SC administration, especially the long-term, safety data is not extensive and safety data beyond the week 54 is missing. To date, a total of 751 subjects have received at least one dose of CT-P13 SC and of them 249 have been treated for up to a year. Based on the currently available safety database, the safety profile for Remsima SC and IV were in general comparable and only a few rare cases of SAEs were reported and ARR were rare. There were no unexpected unfavourable effects, and importantly immunogenicity was also comparable between the products. Furthermore, no deaths were reported in this study.

The single new TEAE, compared to IV Remsima, in study CT-P13 1.6 part 2, after SC dosing was local injections site reactions, which are common for SC dosing in general and also seen for Remsima SC in RA-indication. In all, the localised ISRs in the SC arm were all mild or moderate in severity and all manageable. Furthermore, this is not an unexpected event and implications for the B/R balance of this known risk, given the change in treatment setting (self-administration at home), have to be considered. However, a comparison of the incidence of patients with localised ISR has previously been conducted by the MAH (on data from study CT-P13 3.5 and from literature), to other licensed SC **TNFα-inhibitors.** It showed that the incidences of local injection site reactions were comparable to other licensed **TNFα-inhibitors,** which are used in the home-administration setting.

In spite of the apparent similarity and consistency of the Remsima SC safety findings compared to Remsima IV safety data and Remsima SC data in RA-indication, some uncertainties of the SC safety data remain, mainly related to up to tenfold higher C_{trough} levels with the SC 120mg posology compared to patients in AS, PsA and Ps-patients, in addition to long-term placebo-controlled maintenance studies in CD and UC-patients. This programme is considered adequate by CHMP.

Extrapolation of efficacy and safety to other indications

The indications sought, but not studied are Ankylosing Spondylitis (AS), Psoriatic Arthritis (PsA) and Psoriasis (Ps). Patients in these populations are generally younger, with less comorbidities and less concomitant medications than RA patients (the main source of efficacy and safety data for Remsima SC), in particular, the difference in use of IV and the impact of this in long-term use. From the safety point of view, the accrued Remsima SC safety data are considered supportive of the currently proposed extrapolation, from the source populations (RA and IBD) to the indications not studied (AS,

Ps and PsA), provided that, in light of the still existing uncertainties, an adequate and sufficiently robust post authorisation plan, also addressing the remaining SC safety concerns, will be set in place.

The MAH has proposed to further evaluate the safety of Remsima SC, in addition to patients with RA, also in patients with Ankylosing Spondylitis, Psoriatic Arthritis and Psoriasis. The planned post-authorisation safety study CT-P13 SC 4.9 is an observational, prospective cohort study, planned to include 576 patients (288 patients in each treatment group of Remsima IV and SC) who will be followed up for 24 months. In addition, two other placebo-controlled long-term maintenance studies, one in CD and one in UC patients have been planned. Overall, this post-approval PhV-programme seems robust enough, also from the safety point of view. .

The approved posology for Remsima IV in the indications As, PsA and Ps is the same as the posology for IBD, that is, 5mg/kg Q8W after loading. The proposed posology is 120 mg SC Q2W after loading, for all indications.

In CHMP Scientific Advice, the mechanism of action for infliximab was judged sufficiently similar within the IBD and AS-PsA-Ps-clusters, in spite of other possible modes of action (judged secondary). Therefore, the proposed clinical Remsima SC database was seen as sufficient to justify extrapolation for all indications currently approved for Remsima IV. It was noted that if the therapeutic equivalence 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, should be possible, given that SC dosing and regimen schedules for both the rheumatology and IBD indications are identified and the dosing in the AS-PsA-Ps-cluster is the same as in IBD. However, it was possibly not entirely clear at the time of the central CHMP scientific advice that approximately half of the studied IBD-population (in addition to all RA-patients) would be treated with concomitant immunosuppressants, as it was stated in the CHMP Advice dated September 2016 that *'the study is planned in IBD patients with minimal background immunomodulatory therapy'.*

With the current data, therapeutic equivalence has been demonstrated between Remsima SC 120 mg and Remsima IV 3 mg/kg in the RA setting. In addition, similar exposure and non-inferior C_{trough} levels were demonstrated with Remsima SC 120 mg compared to Remsima IV 5 mg /kg in an IBD population. With the proposed posology, the mean C_{trough} levels observed in both RA patients (study CT-P13 3.5 Part 2) and IBD patients (study CT-P13 1.6 Part 1 and Part 2) were well above the target levels in all weight bands.

Results from study CT-P13 1.1 performed by the MAH in AS patients and review of the published literature indicate that infliximab trough concentrations are associated with clinical response in AS, PsA and Ps. While it is difficult to estimate a specific target C_{trough}, an average C_{trough} of approximately 5 µg/mL in patients with AS, PsA and Ps seems likely to be associated with clinical efficacy. Of note, this threshold for efficacy is often in fact not met with the currently approved IV dosing and the proportion of patients who achieved the target C_{trough} 5 µg/mL was larger with SC 120 mg dosing than with IV 5mg/kg dosing in IBD patients. Since it is known that the IV dose is efficacious, it is expected that the proposed posology for the indications AS, PsA and Ps would result in a similar effect, if the same drug concentrations are achieved.

As stated above, patients with As, PsA and Ps generally use less CIM than RA patients, which could affect the formation of ADA, namely a lower immunosuppression could give rise to more ADA formation. This, in turn, could potentially increase clearance and decrease drug exposure in As, PsA and Ps patients. However, data from study CT-P13 1.6 in IBD patients showed that C_{trough} remained clearly higher with Remsima SC 120mg than with Remsima IV 5 mg/kg, even in patients without CIM and with positive NAb status. Hence, it is expected that the drug exposure in patients with AS, PsA and

Ps will be sufficient. It has even been postulated in the published literature that infliximab concentrations in AS and PsA patients could be somewhat higher than in RA patients.

The lesser use of concomitant immunosuppressive medication and following higher formation of ADA could also affect safety. Overall, based on the historical literature and immunogenicity data from CT-P13 IV/SC trials in RA and IBD patients, the results show that the concomitant use of immunosuppressant medication is correlated with a reduced ADA incidence rate. However, based on study CT-P13 1.6, the use of CIM did not shift the relative immunogenicity between formulations. Among patients who did not use CIM, 19/37 (51.4%) in the SC arm and 25/36 (69.4%) in the IV arm were ADA positive at week 30. These results supported the notion that the SC formulation is not more immunogenic in either users or non-users of CIM. The impact of immunosuppressant on the incidence of ARRs (including IRR, SIR and Delayed Hypersensitivity) and localised ISR was also comparable between the two formulations with no more incidences of localised ISR among non-users than users of CIM.

Overall safety was also comparable between SC and IV treatment arms in the IBD setting and incidence rates for infections, ARRs and other AEs were in line with previous findings in RA patients. Hence, while the present data on patients treated without CIM is limited, the available data do not raise concerns regarding immunogenicity and safety in patients without concomitant methotrexate or other immunosuppressive medication. This supports the validity of extrapolation of the data to the indications where use of CIM is less common than in RA. Moreover, further safety data in AS, PsA and Ps indications will be accrued in the post-approval pharmacovigilance programme.

Hence, considering the strength of the prior safety data, the overall quality of data, similarity and consistency of the Remsima SC safety findings, over indications and between the two formulations (excluding the elevated incidence of localised ISRs), the accrued Remsima SC safety data is considered by CHMP to support the currently proposed extrapolation also from the safety and efficacy point of view,.

Thus, the use of Remsima SC is considered acceptable to the CHMP, with the proposed posology in all the sought indications and also in the home-setting.

3.7.2. Balance of benefits and risks

In general, the efficacy and safety profile of infliximab IV is well established. The efficacy and safety of Remsima SC was demonstrated to be non-inferior to that of IV Remsima in RA patients with a 120mg Q2W dosing and line extension in this indication was approved in 2019. In RA patients, the exposure to infliximab was somewhat higher with Remsima SC 120mg Q2W than with Remsima IV Q8W 3mg/kg, but this high exposure did not translate into a higher risk for infections or other adverse events, excepting higher localised ISR. However, the number of patients (157) exposed to long term treatment with Remsima SC was limited and some uncertainty remained regarding the effect of higher C_{trough} levels of infliximab on the potential risk of some rare adverse events (for example, infections, malignancies and cardiac AEs). This was considered acceptable to the CHMP since the MAH committed to a post-approval PV programme (including a non-interventional study in patients with RA).

This indication extension variation focused on demonstrating comparable PK, efficacy and safety between Remsima SC and Remsima IV in CD and UC indications, resulting in the possibility to extrapolate efficacy and safety to the rest of the sought indications (AS, PsA, Ps). The main concerns in relation to the new proposed indications (CD, UC, AS, PsA and Ps) was the dosing and the possibility of higher immunogenicity due to a lower rate of MTX or other concomitant immunosuppressants in these populations. It was agreed through multiple central Scientific Advices (January 2016, September 2016, December 2017, April 2018) 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 should be possible given that SC dosing and regimen schedules for both the rheumatology and the IBD indications were identified.

The data presented within this application confirmed that C_{trough} will be several folds higher with the proposed 120mg posology of Remsima SC than with the approved Remsima IV posology across all weight bands, also in IBD patients. Thus, the main premise for ensuring non-inferior efficacy in all patients was fulfilled. The initial uncertainty pertaining to comparability of exposure in terms of AUC was clarified by the MAH. Although up to 48% lower AUC was predicted in some patients treated with Remsima SC 120 mg, subgroup analyses showed no indication of decreasing efficacy of Remsima SC in relation to lower AUC.

Also efficacy data support non-inferiority in both CD and UC patients, with clinically meaningful response rates in both treatment arms.

The clearly higher C_{trough} drug concentrations during SC administration did not seem to translate into a higher risk for infections or other adverse events, excepting higher localised ISR. The safety profiles for SC and IV were in general comparable. The only new unfavourable effect identified after SC dosing were localised injection site reactions (ISR), which were observed in 22.7% of patients in the SC arm and were all mild or moderate in severity and all manageable. In addition, immunogenicity was comparable between SC and IV formulations (if anything, immunogenicity was lower in SC group). Exploratory graphical PK/PD analyses for safety did not suggest strong associations between exposure and IRR and infections. The results should be interpreted cautiously due to limited number of events in patients treated with the SC formulation.

The overall safety profile of the IBD patients treated with Remsima 120mg Q2W SC was no worse compared to Remsima IV, even after switching, and comparable with the known safety profile of infliximab. Infliximab is known to be immunogenic, however, administration related reactions, including infusion-related reactions, systemic injection reactions and delayed hypersensitivity reactions were, overall, rare and the incidences similar between the two treatment arms and similar, or even lower, to those in the pivotal RA study. The single notable finding among otherwise comparable safety data between two treatment arms was the higher proportion of patients that reported localised ISR in the SC group. The rates were, however, comparable to rates for other licenced SC **TNFα-inhibitors,** which are also used in the home-administration setting. Apart from this, the safety profile of Remsima SC appears to be quite consistently similar to the previously described data, and thus provides grounds for extrapolation of safety.

The impact of concomitant immunosuppressive medication (CIM) on immunogenicity was comparable between treatment arms and the SC formulation was non-inferior to IV in both users and non-users of CIM in terms of both ADA formation, and safety (including hypersensitivity reactions). The formation of ADAs, also in relation to the number of adverse events was similar to that observed in previous trials with infliximab. The data did not sustain any previous concerns regarding the effect of MTX or other CIM on the safety of Remsima SC. However, the number of patients treated without CIM is still very limited and safety in this subpopulation needs to be followed-up in a post-approval PhV programme. Extrapolation of the results to indications not studied is considered approvable, as all other concerns in this AR are resolved.

C_{trough} was reasoned to be the most important parameter in relation to efficacy. Maintaining a C_{trough} substantially higher than the concentration seen with approved posology of Remsima IV should be enough to ensure efficacy of Remsima SC 120 mg Q2W in all patients. Hence, the proposed posology of 120 mg regardless of body weight is considered acceptable for all patients in all indications as satisfactory responses to the RSI have been provided.

The MAH's initial proposal to recommend a dose escalation in case of loss of response, and thus allowing a dose of 240 mg Remsima SC to be administered to all patients, including those with a body weight <80 kg, is not supported by sufficient evidence. Additional efficacy and sufficient safety of 240mg SC, especially for patients weighing <80 kg, have not been confirmed. Of note, IV Remsima and IV Remicade do not have this dose increase possibility stated for UC in the SmPC. Therefore, it is not possible to include such an option for Remsima SC in this indication without robust clinical data. The proposal for dose escalation was withdrawn by the MAH.

Based on these considerations, the data provided, the benefit/risk balance is positive for the use of Remsima SC in adult patients with CD, UC, AS, PsA and Ps.

3.8. Conclusions

The overall B/R of Remsima SC is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication of the subcutaneous formulation of Remsima, to add treatment of adult patients with Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and psoriasis in line with the adult indications of the IV formulation; consequently, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC and relevant sections of the Package leaflet are updated. An updated RMP (version 12.2) has also been submitted.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, IIIB and to the Risk Management Plan are recommended.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion Remsima EMEA/H/C/002576/II/0082.

Reminders to the MAH

1. In accordance with Article 13(3) of Regulation (EC) No 726/2004 the Agency makes available a European Public Assessment Report (EPAR) on the medicinal product assessed by the Committee for Medicinal Products for Human Use. The EPAR is first published after the granting of the initial marketing authorisation (MA) and is continuously updated during the lifecycle of the medicinal product. In particular, following a major change to the MA, the Agency further publishes the assessment report of the CHMP and the reasons for its opinion in favour of granting the change to the authorisation, after deletion of any information of a commercially confidential nature.

    Should you consider that the CHMP assessment report contains commercially confidential information, please provide the EMA Procedure Assistant your proposal for deletion of commercially confidential information (CCI) in "track changes" and with detailed justification by 10 July 2020. The principles to be applied for the deletion of CCI are published on the EMA website at https://www.ema.europa.eu/en/documents/other/heads-medicines-agencies/european-medicines-agency-guidance-document-identification-commercially-confidential-information_en.pdf.

    In addition, should you consider that the CHMP assessment report contains personal data, please provide the EMA Procedure Assistant your proposal for deletion of these data in "track changes" and with detailed justification by 10 July 2020. We would like to remind you that, according to Article 4(1) of Regulation (EU) 2016/679 (General Data Protection Regulation, "GDPR") 'personal data' means any information, relating to an identified or identifiable natural person (the 'data subject'). An identifiable natural person is one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, an online identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that natural person.

    It is important to clarify that pseudonymised data are also considered personal data. According to Article 4(5) of GDPR pseudonymisation means that personal data is processed in a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information (e.g. key-coded data).

    Accordingly, the name and the patient identification number are two examples of personal data which may relate to an identified or identifiable natural person. The definitions also encompass for instance: office e-mail address or phone number of a company, data concerning health, e.g. information in medical records, clinical reports or case narratives which relates to an identifiable individual."

2. The MAH is reminded to submit an eCTD closing sequence with the final documents provided by Eudralink during the procedure (including final PI translations, if applicable) within 15 days after the Commission Decision, if there will be one within 2 months from adoption of the CHMP Opinion, or prior to the next regulatory activity, whichever is first. If the Commission Decision will be adopted within 12 months from CHMP Opinion, the closing sequence should be submitted within 30 days after the Opinion. For additional guidance see chapter 4.1 of the Harmonised Technical Guidance for eCTD Submissions in the EU.

3. The MAH is reminded that, at the same time as the submission on the eCTD closing sequence mentioned above, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

4. If the approved RMP is using Rev. 2 of the 'Guidance on the format of the RMP in the EU' and the RMP 'Part VI: Summary of the risk management plan' has been updated in the procedure, the

MAH is reminded to provide to the EMA Procedure Assistant by Eudralink a PDF version of the 'Part VI: Summary of the risk management plan' as a standalone document, within 14 calendar days of the receipt of the CHMP Opinion. The PDF should contain only text and tables and be free of metadata, headers and footers.