30 May 2024
EMA/281845/2024
Committee for Medicinal Products for Human Use (CHMP)

Type II group of variations assessment report

Invented name: Remsima

International non-proprietary name: infliximab

Procedure No. EMEA/H/C/002576/II/0133/G

Note

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

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1. Background information on the procedure

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Celltrion Healthcare Hungary Kft. submitted to the European Medicines Agency on 30 June 2023 an application for a group of variations.

The following changes were proposed:

Variations requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, IIIA and IIIB
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Grouped application comprising three type II variations (C.I.4) as follows:
- Update of section 4.2, 4.8 and 5.1 of the SmPC in order to add 3-IV induction dosing regimen and dose escalation of subcutaneous maintenance dose from CT-P13 SC 120 mg Q2W to 240 mg Q2W for patients with loss of response and update efficacy and safety information based on Week 54 data from studies CT-P13 3.7 (ulcerative colitis) and CT-P13 3.8 (Crohn's disease), listed as a category 3 study in the RMP; Study CT-P13 3.7 is 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 and study CT-P13 3.8 is 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.
- Update of section 4.2 and 5.2 of the SmPC in order to add subcutaneous induction posology and pharmacokinetic information based on Population PK and PK-PD Modelling and Simulation.
- Update of section 4.2 of the SmPC in order to switch from high-dose IV maintenance (> 5 mg/kg) to subcutaneous maintenance dose of 120 mg Q2W based on data from REMSWITCH study (Effectiveness of Switching From Intravenous to Subcutaneous Infliximab in Patients With Inflammatory Bowel Diseases: the REMSWITCH Study).
The RMP version 16.1 has also been submitted. The Package Leaflet and Labelling are updated accordingly. In addition, the MAH took the opportunity to introduce minor updates to the PI.

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

After the first RSI the two latter variations were withdrawn. The first variation remained but the proposal for dose escalation in UC patients was withdrawn.

2. Overall conclusion and impact on the benefit/risk balance

Remsima (CT-P13, infliximab) was initially developed for intravenous (IV) infusion and was approved in the European Union (EU) in 2013 as a biosimilar product to Remicade for the treatment of rheumatoid arthritis (RA), adult Crohn's disease (CD), paediatric CD, ulcerative colitis (UC), paediatric UC, ankylosing spondylitis (AS), psoriatic arthritis (PsA) and psoriasis (Ps). The subcutaneous (SC) formulation of Remsima was later approved in the EU for the RA indication and adult CD, UC, AS, PsA and Ps indications. The originator Remicade is not available as an SC formulation. Therefore, Remsima SC is not bound by any originator's product information.

This grouped variation application initially concerned 3 Type II variations, as outlined in section 1. After the first assessment round several proposed amendments were withdrawn and only the following proposed updates of the SmPC for CD and UC indications remained:

1. Addition of a 3-IV induction dosing regimen (5 mg/kg at Weeks 0, 2 and 6) followed by SC maintenance treatment (120 mg Q2W) in addition to the approved 2-IV regimen (5 mg/kg at Weeks 0 and 2).
2. The possibility for dose adjustment from SC 120 mg (currently approved dose) to SC 240 mg for patients with loss of response in patients with CD.
3. Description of the two new phase 3 studies (in CD- and UC-patients)

Two new clinical studies (Studies CT-P13 3.7 and CT-P13 3.8 conducted in UC and CD patients, respectively) were introduced to the CT-P13 SC clinical development programme and results from these studies have been proposed to be included in the SmPC. Notably, in the current submission the overall B/R of induction/maintenance treatments was not questioned, as those have already been approved and included in the SmPC of IV and SC Remsima. It was evaluated if these new phase 3 studies provide statistically and clinically significant, robust and valuable information for the prescriber, enough to be placed into the SmPC 5.1 and to replace the earlier data from the previous smaller studies in CD and UC.

Proposed changes to the SmPC

Primary efficacy results in CD patients (Study CT-P13 3.8)

Out 396 CD patients who were enrolled and treated with CT-P13 5 mg/kg IV during induction, 343 patients were responders and were randomly assigned to study treatment and initiated the double-blind maintenance phase at Week 10 (231 and 112 patients in the CT-P13 SC 120 mg and Placebo SC groups, respectively).

The co-primary endpoints were clinical remission based on Crohn's Disease Activity Index (CDAI) at Week 54 and endoscopic response based on central Simplified Endoscopic Activity Score for Crohn's Disease (SES-CD) at Week 54. Patients who received an open-label dose escalation (to 240 mg) after W22 were automatically classified as non-responders although some of them did not lose response and some of the patients who lost response did not receive a dose escalation.

The proportion of patients who achieved clinical remission by CDAI at Week 54 was higher in the CT-P13 SC 120 mg group than Placebo SC group (144 [62.3%] and 36 [32.1%], respectively). The proportion of patients who achieved endoscopic response (defined as a 50% decrease in SES-CD score) at Week 54 was 118 [51.1%] and 20 [17.9%] in CT-P13 SC 120 mg and Placebo SC groups, respectively.

The intercurrent event of loss of response (LoR) was handled differently for different patients without any clear plan for the different handling in the protocol and this flaw in the study design could skew the results of the primary outcome. Moreover, some protocol violations occurred where patients received a dose escalation despite not meeting LoR criteria. However, the number of patients receiving dose escalation despite not meeting LoR criteria was small, the difference in the proportion of remitters is considered clinically meaningful and the magnitude of the difference sufficiently large to be relevant for the prescriber. Hence, inclusion of study Study CT-P13 3.8 results in SmPC 5.1 is considered acceptable even if there was some bias involved.

The open label extension phase of Study CT-P13 3.8 showed that the proportion of patients who achieved clinical remission was more or less maintained at Week 102 compared to Week 54. Of note, among patients originally randomised to placebo 27/112 (24%) were in clinical remission two years after a successful induction treatment with infliximab IV despite no active treatment after week 10.

Primary efficacy results UC patients (Study CT-P13 3.7)

Out of 548 UC patients who were enrolled and treated with CT-P13 5 mg/kg IV during induction, 438 patients were responders at week 10 and initiated the double-blind maintenance phase (294 and 144 patients in the CT-P13 SC 120 mg and Placebo SC groups, respectively). According to the presented results the proportion of patients who achieved a clinical remission by modified Mayo score at Week 54 was higher in the CT-P13 SC 120 mg treatment group (127 [43.2%]) than in the Placebo SC treatment group (30 [20.8%]). Of note, this outcome does not accurately reflect results for the prespecified primary endpoint.

However, in study 3.7, 81 [27.6%] and 70 [48.6%] UC patients in the CT-P13 SC and Placebo groups, respectively received an open-label dose adjustment to CT-P13 SC 240mg after week 22. The possibility to dose adjust is significantly intertwined in the primary endpoint as only patients who did not escalate the dose had a possibility to be responders at week 54. Moreover, the intercurrent event of loss of response was handled differently for different patients and this flaw in the study design could skew the results of the primary outcome. Some patients who lost response were dose adjusted and others were not, but these different pathways were neither randomised nor based on any predefined characteristics. Therefore, week 54 results cannot be presented in the SmPC without mentioning the possibility to dose adjust. However, describing the dose adjustment would be promoting an off-label posology, which is not acceptable.

Upon CHMP's repeated request for more detailed information, the MAH provided results which illustrated the consequence of inappropriate planning of the estimand, misalignment of dose escalation requirements and the schedule of assessments (SoA), and revealed poor adherence to the protocol:

One of the criteria for being a non-remitter/non-responder at W54 was based on having had dose-escalation. While it could have been acceptable to include "any LoR before W54" in the non-remitter/non-responder definition, the primary endpoint estimand was obviously inappropriate because the definition of LoR, prerequisites for dose escalation/no dose escalation and the SoA were not appropriately standardized in the protocol nor the conditions in the protocol consistently followed. According to the protocol definition, it was not possible to detect a LoR between W22 and 54 because no endoscopy was performed.

The intention of the study protocol was to reflect a treatment policy situation where a patient in case of loss of response could be taken off the treatment or continue in hope of better days to come. This approach led to a situation where some patients with LoR were immediately established as being treatment failures, while others, were considered non-responders only if they remained non-responders also at week 54. The criteria for continuing on randomised treatment despite LoR were never defined in the protocol. Moreover, in a real-world setting, an evaluation whether to continue treatment despite LoR would normally not last for several months. This issue, however, does not have a major impact on the interpretation of the W54 results as the number of patients continuing despite LoR is small.

However, some patients were switched to active treatment/dose escalated though not meeting the LoR criteria, i.e., "put on rescue therapy". In study 3.7 such physician decisions were abundant (35% of all dose escalations) and done off protocol, without prespecified criteria or any post hoc explanation. Therefore, the outcome does not reflect the prespecified primary endpoint, as the protocol defined all dose escalations to be consequences of LoR.

The reason for the high number of this type of protocol violations may be related to the definition of LoR. In the protocol, the LoR criteria were based on modified Mayo score (including the endoscopic subscore): *"an increase in modified Mayo score of ⩾2 points and ⩾30% from the Week 10 modified Mayo score with actual value of ⩾5 points, and endoscopic subscore of ⩾2 points."* However, the modified Mayo score was only recorded at weeks 10, 22 and 54. Hence, according to protocol it was not even possible to detect a

LoR between W22 and 54. Therefore, if not done on W22, the decisions to escalate the dose were probably

based on partial Mayo score (excluding the endoscopic subscore), which was recorded at every visit. The problem is that a patient who meets the hitherto undefined criteria for LoR by partial Mayo, would not necessarily be a non-responder according to the modified Mayo, which defines the primary endpoint. This issue could have been reflected in the SoA for example by ad hoc endoscopy if clinically indicated, but no such effort was done.

Ultimately, a total of 35% (50/144) of patients who received a dose adjustment did not meet LoR criteria and 10% of all patients in the SC 120mg group and 15% of the placebo group were classified as non-remitter/non-responder only due to dose escalation, not due to per protocol LoR. Hence, classifying patients with dose escalation as non-responders as if they were all patients who lost response after W22 is simply not reflecting reality nor the intended primary objective of the study as per protocol.

The definition of non-remitter/non-responder is equally relevant for the interpretation of the primary outcome as the definition of a "responder". Out of all non-responders at W54, only 5.5% were classified as non-responders based on clinical criteria, with no difference between treatment groups, while the rest of the non-responders were due to intercurrent events, mainly dose adjustment, which did not equal LoR.

To conclude, the off-label dose escalation after W22 meaningfully affects the interpretation of the results at W54 and the true impact of Remsima SC maintenance regimen cannot be estimated based on the results of this study. 35% of the dose escalations were not according to protocol, which introduces a major bias and puts the whole planning and conduct of the study into question. Therefore, the W54 results from study 3.7 are invalid for inclusion in the SPC.

While there is no doubt that Remsima SC is in fact more effective than placebo in the treatment of UC, the numerical magnitude of the treatment effect cannot be accurately estimated. The UC indication is already granted for both induction and maintenance therapy and it is not put into question, but no new useful information for the prescriber has been presented with this application.

New proposed 3-IV induction regimen

The new induction regimen proposed for Remsima SC in UC, CD and fistulising CD was used in studies 3.7 and 3.8 and it is identical to the induction regimens currently approved with IV Remsima for all above indications. Due to a shorter interval between the last IV dose and the first SC dose than previously approved, the new induction regimen will lead to somewhat higher exposure (AUC but not C_{max}) during weeks 10-14. Based on the previously established positive benefit-risk balance for very similar dosing regimens with Remsima SC, introduction of the 3-IV induction dosing regimen is acceptable (5 mg/kg at Weeks 0, 2 and 6) followed by SC maintenance treatment (120 mg Q2W from week 10).

Proposed dose escalation

Studies 3.7 and 3.8 were provided in support of a dose escalation from SC 120 mg to 240 mg for patients with loss of response. However, the study designs were not adequate to answer the question whether dose escalation is more effective (and sufficiently safe) compared to continuing treatment with SC 120 mg.

As there was no randomised treatment arm where patients with a loss of response continued on the previously assigned SC 120mg treatment, it is difficult to know how the disease would have progressed without the dose escalation. As UC and CD are fluctuating refractory diseases with sometimes long symptom free periods, some patients could have achieved remission again by week 54 after loss of response, even without dose escalation. Furthermore, as dose escalation was not mandatory for all patients who fulfilled the loss of response criteria, there is a potential for selection bias.

After the first RSI, the MAH withdrew this proposal for dose escalation for patients with UC. Therefore, the discussion below pertains only to study 3.8.

Efficacy of a dose increase in CD patients

A total of 41 patients in the CT-P13 SC 120 mg group and 48 patients in the placebo group experienced LoR prior to Week 54. Among these patients, 34/41 (82.9%) in CT-P13 SC 120 mg group and 41/48 (85.4%) in placebo group received adjusted dose while 7 patients in each group remained on the initially assigned treatment. A few patients received adjusted dose despite not being eligible for the dose adjustment, 5/182 (2.7%) in CT-P13 SC 120 mg group and 4/57 (7.0%) in placebo group. This protocol violation seems to be driven by the clinicians' desire to improve the treatment for poor responders but exposes poor adherence to GCP. However, the frequency of these protocol violations is small enough not to pursue the issue further.

Among the 34 patients with dose adjustment in the CT-P13 SC 120 mg group 17 (50%) patients achieved clinical remission by CDAI and 7 (20.6%) patients achieved endoscopic response at Week 54. On the other hand, in the 7 patients who experienced a LoR but did not receive a dose adjustment but continued on the initial CT-P13 SC 120 mg, regain of clinical remission occurred in 1/7 (14.3%) and endoscopic response re-emerged in 3 (42.9%) patients. Regain of CDAI response occurred in 21/34 (61.8%) patients with a dose escalation while patients who lost response but remained on active treatment had a renewed CDAI response in 2 (28.6%) cases. Spontaneous regain of CDAI response and CDAI remission was also seen in patients who remained on placebo (3 and 1 patients, respectively).

Although the numbers are small, and the subgroups are not comparable due to a lack of randomisation, it can be concluded that spontaneous regain of response is not negligible but regain of response according to CDAI is more common and the improvement in absolute CDAI score is more pronounced in patients with a dose adjustment than in those who remained on initial treatment despite a LoR. Some patients did not respond at all to the dose adjustment and some lost response again after a brief improvement but overall, a majority of patients in the active treatment arm who received an escalated dose had a positive outcome 16 weeks after dose adjustment.

A clear difference between patients who experienced LoR and those who did not is seen in terms of serum drug concentration before LoR. This finding supports the theory of loss of response being associated with suboptimal drug concentrations. As also mean anti-drug antibody (ADA) titres were substantially higher among patients who lost response compared to those who did not, it is reasonable to assume a causal relationship between loss of response, high ADA titres and decreased drug concentrations.

It has not been clarified how drug concentrations developed among those with a dose increase and for how long patients with high ADA titres at dose adjustment could maintain a potential benefit from a higher dose. However, as these are not issues which could affect the wording in SPC, they will not be pursued further. Due to the high ADA titres the mean drug concentrations are not expected to be twice as high as normal after a dose increase among patients who lost response. In study 3.8 satisfactory response rates were maintained for at least 16 weeks after dose adjustment.

The benefit of a dose escalation from infliximab 120mg SC Q2W to infliximab 240mg SC Q2W in case of a loss of response has been sufficiently demonstrated in CD patients.

Safety of a dose increase in CD patients.

The submitted safety results on subgroups administered the 120 mg and 240 mg dose show no dose-dependently increased risk for infection, serious adverse reactions, or systemic and localised injection reaction rates. The MAH had originally not described in detail the populations for the comparison between placebo and CT-P13 SC and between the 120 mg and 240 mg doses and how exposure time for each dose was accounted for in the analyses. Upon request, the MAH provided comparative safety analyses performed for the events that occurred on or after the first administration of each treatment of CT-P13 SC 120 mg or

240 mg for pooled data from all studies with either or both of these doses for all approved indications. Furthermore, analyses on events occurring prior to dose adjustment (CT-P13 SC 120 mg) vs. after dose adjustment (240 mg SC) and within the CT-P13 SC group and treatment-emergent adverse events (TEAEs) occurring prior to dose adjustment (placebo) vs after dose adjustment (from placebo to CT-P13 SC 240 mg) within the placebo group were submitted 1) for pooled population of all studies allowing dose escalation (Studies CT-P13 3.7, CT-P13 3.8 and CT-P13 1.6 Part 2) and 2) separately for study CT-P13 3.8 in Crohn's disease (but not for study CT-P13 3.7, since dose escalation is no more applied for ulcerative colitis). The data were calculated per 100 patient years and showed that the safety profile of higher dose of CT-P13 SC 240 mg is comparable to the approved dose of CT-P13 SC 120 mg (see section 13.2 of this AR). In study CT-P13 3.8, the mean and median duration for patients who received CT-P13 SC 240 mg were 58.9 weeks and 68.1 weeks, respectively, and 73 patients received CT-P13 SC 240 mg as maintenance treatment for at least 44 weeks. Hence, the long-term safety profile of CT-P13 SC 240 mg in subjects with CD is deemed to have been sufficiently demonstrated.

Conclusion

The CHMP concluded that the benefit-risk balance of Remsima remains positive.

New information was added to the SmPC, section 4.2, regarding the induction regimen in the treatment of CD and UC. The possibility for a dose adjustment to Remsima SC 240 mg has been added for CD patients with loss of response. Sections 5.1 and 4.8 of the SmPC were updated with the description of a new phase 3 study in CD-patients.

3. Recommendations

This application originally concerned the following changes:

Variations requested		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, IIIA and IIIB
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, IIIA and IIIB
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, IIIA and IIIB

Grouped application comprising three type II variations (C.I.4) as follows:
- Update of section 4.2, 4.8 and 5.1 of the SmPC in order to add 3-IV induction dosing regimen and dose escalation of subcutaneous maintenance dose from CT-P13 SC 120 mg Q2W to 240 mg Q2W for patients with loss of response and update efficacy and safety information based on Week 54 data from studies CT-P13 3.7 (ulcerative colitis) and CT-P13 3.8 (Crohn's disease), listed as a category 3 study in the RMP; Study CT-P13 3.7 is 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 and study CT-P13 3.8 is 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.
- Update of section 4.2 and 5.2 of the SmPC in order to add subcutaneous induction posology and pharmacokinetic information based on Population PK and PK-PD Modelling and Simulation.
- Update of section 4.2 of the SmPC in order to switch from high-dose IV maintenance (> 5 mg/kg) to subcutaneous maintenance dose of 120 mg Q2W based on data from REMSWITCH study (Effectiveness of Switching From Intravenous to Subcutaneous Infliximab in Patients With Inflammatory Bowel Diseases: the REMSWITCH Study).
The RMP version 16.1 has also been submitted. The Package Leaflet and Labelling are updated accordingly. In addition, the MAH took the opportunity to introduce minor updates to the PI.

- *Following the assessment of the submitted data and the consequent proposals for PI update, the following changes in the variation group were found not to be acceptable and were consequently withdrawn:*

- Update of section 4.2 and 5.1 of the SmPC in order to add dose escalation of subcutaneous maintenance dose from CT-P13 SC 120 mg Q2W to 240 mg Q2W for patients with loss of response and update efficacy and safety information based on Week 54 data from study CT-P13 3.7. Study CT-P13 3.7 is 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.

- *In addition, the following proposed changes were withdrawn:*

- Update of section 4.2 and 5.2 of the SmPC in order to add subcutaneous induction posology and pharmacokinetic information based on Population PK and PK-PD Modelling and Simulation.

- Update of section 4.2 of the SmPC in order to switch from high-dose IV maintenance (> 5 mg/kg) to subcutaneous maintenance dose of 120 mg Q2W based on data from REMSWITCH study (Effectiveness of Switching From Intravenous to Subcutaneous Infliximab in Patients With Inflammatory Bowel Diseases: the REMSWITCH Study).

- *The following changes are recommended for approval:*

- Addition of a 3-IV induction dosing regimen (5 mg/kg at Weeks 0, 2 and 6) followed by SC maintenance treatment (120 mg Q2W) in CD and UC patients;
- The possibility for dose adjustment from CT-P13 SC 120 mg to 240 mg for CD patients with loss of response;
- SmPC updates in sections 4.2, 4.8 and 5.1 regarding all of the above, including description of the phase 3 study 3.8 in CD patients.

This application concerns the following agreed changes:

Variation agreed		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, IIIA and IIIB

Update of section 4.2, 4.8 and 5.1 of the SmPC in order to add 3-IV induction dosing regimen based on Week 54 data from studies CT-P13 3.7 (ulcerative colitis) and CT-P13 3.8 (Crohn's disease), listed as a category 3 study in the RMP.

Study CT-P13 3.7 is 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 and study CT-P13 3.8 is 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.

The RMP version 16.2 was agreed. The Package Leaflet and Labelling are updated accordingly. In addition, the MAH took the opportunity to introduce minor updates to the PI.

Amendments to the marketing authorisation

In view of the data submitted with the group of variations, amendments to Annexes I, IIIA and IIIB and to the Risk Management Plan are recommended.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion Remsima-H-C-2576-II-0133.

For more information, please refer to the Summary of Product Characteristics.

Annex: Assessment comments on the type II variation

5. Introduction

Remsima (CT-P13, infliximab) was initially developed for intravenous (IV) infusion (hereafter referred to as CT-P13 IV) and was approved in the European Union (EU) in September 2013 as a biosimilar product to EU-approved Remicade for the treatment of rheumatoid arthritis (RA), adult Crohn's disease (CD), paediatric CD, ulcerative colitis (UC), paediatric UC, ankylosing spondylitis (AS), psoriatic arthritis (PsA) and psoriasis (Ps). The subcutaneous (SC) formulation of Remsima (hereafter referred to as CT-P13 SC) was also approved in the EU for the RA indication (EMEA/H/C/002576/X/0062) on 22 November 2019, and adult CD, UC, AS, PsA and Ps indications (EMEA/H/C/002576/II/0082) on 27 July 2020. Additionally, SC induction posology for RA indication (EMEA/H/C/002576/II/0095) was also approved on 30 April 2021.

According to the currently approved Summary of product characteristics (SmPC) for Remsima SC formulation (CT-P13 SC), two IV infusions of infliximab 5 mg/kg should be given 2 weeks apart prior to the initiation of maintenance therapy with Remsima SC for IBD indications. The first treatment with Remsima SC should be initiated as maintenance therapy 4 weeks after the second intravenous administration.

In this grouped Type II variation application, the Marketing Authorisation Holder (MAH) initially proposed several updates of the SmPC for CD and UC indications:

1. Addition of a 3-IV induction dosing regimen (5 mg/kg at Weeks 0, 2 and 6) followed by SC maintenance treatment (120 mg Q2W);
2. The possibility for dose adjustment from CT-P13 SC 120 mg to 240 mg for patients with loss of response;
3. Addition of a subcutaneous induction dosing regimen (240 mg at Week 0 followed by 120 mg at Weeks 1, 2, 3 and 4) followed by SC maintenance treatment (120 mg Q2W);
4. The possibility to switch from high-dose (> 5 mg/kg) IV maintenance to subcutaneous maintenance treatment
5. Major SmPC-updates on all of the above, including description of the two new phase 3 studies (CD and UC) in sections 5.1 and 4.8.

According to the MAH, introduction of a 3-IV induction option would allow greater treatment options for patients and healthcare professionals but the benefits of this option were not further discussed.

The possibility of a dose increase after loss of response would give another chance to show clinical response.

The benefits of subcutaneous induction without the need for IV loading is justified by improved subject convenience, reduced pharmacy preparation times and optimisation of medical resources.

Two clinical studies (Studies CT-P13 3.7 and CT-P13 3.8 conducted in UC and CD patients, respectively) are newly introduced to the CT-P13 SC clinical development programme and are used to support the changes. However, the proposed SC induction dosing regimen for CD and UC indications is only supported by population pharmacokinetic (PK) Modelling and Simulation analyses. Detailed information about the two clinical studies is summarized below in Table 2.

The switch from high-dose IV maintenance to subcutaneous maintenance treatment is supported by an observational study (REMSWITCH study in CD and UC patients), described in a peer reviewed journal, but with no CSR.

The proposed posology changes and supporting evidence are summarised in Table 1.

In addition to the tabulated changes, a new time point for decision making regarding maintenance treatment has been introduced for Crohn's disease. No justification was provided for this change.

There has been no scientific advice held regarding the changes proposed in this submission.

After the first RSI, the Applicant withdrew several parts of the grouped variation application. Discussion on the initially proposed changes is kept here for transparency.

In this assessment report, the product is referred to as CT-P13 SC or Remsima SC.

Table 2. Proposed Posology Changes and Supporting Evidences Included in This Submission

#	Proposed Change	Indications	Proposed Update to SmPC		Supporting Evidence	Related Sections
			Before Update	After Update		
1	3-IV induction dosing regimen	CD, UC	Treatment with Remsima administered subcutaneously should be initiated as maintenance therapy 4 weeks after the last administration of two intravenous infusions of infliximab 5 mg/kg given 2 weeks apart. The recommended dose for Remsima subcutaneous formulation is 120 mg once every 2 weeks. If a patient does not respond after 2 doses of intravenous infusions, no additional treatment with infliximab should be given. Available data do not support further infliximab treatment, in patients not responding within 6 weeks of the initial infusion.	Treatment with Remsima subcutaneous formulation should be initiated with loading doses of infliximab which may be intravenous or subcutaneous. When subcutaneous loading is used, Remsima 240 mg (double injection of Remsima 120 mg) should be given as a subcutaneous injection followed by additional subcutaneous injections of Remsima 120 mg at 1, 2, 3 and 4 weeks after the first injection, then every 2 weeks thereafter. If intravenous loading doses of infliximab are given to initiate treatment, 2 intravenous infusions of infliximab 5 mg/kg should be given at 2 weeks apart, and an additional intravenous infusion of infliximab 5 mg/kg may be given 4 weeks after the second infusion. The first treatment with Remsima administered subcutaneously should be initiated as maintenance therapy 4 weeks after the last administration of intravenous infusions. The recommended maintenance dose for Remsima subcutaneous formulation is 120 mg once every 2 weeks. Limited data in patients who initially responded to induction regimen with infliximab but who lost response indicate	PK, efficacy, safety and immunogenicity results from Studies CT-P13 3.7 (UC) and CT-P13 3.8 (CD)	2.7.2.2.1 2.7.3.2 2.7.4.2
2	Dose adjustment for patients with loss of response (LoR)	CD, UC			PK, efficacy, safety and immunogenicity results from Studies CT-P13 3.7 (UC) and CT-P13 3.8 (CD)	2.7.2.2.1 2.7.3.2 2.7.4.2
3	SC induction posology	CD, UC			Population PK and PK-PD Modelling and Simulation	2.7.2.3.3
				that some patients may regain response with dose escalation (see section 5.1). Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit after dose adjustment.		

4	Switch from high-dose (> 5 mg/kg) IV maintenance to SC maintenance	CD	There is insufficient information regarding the switching of patients who received the intravenous infusions of infliximab higher than 3 mg/kg for rheumatoid arthritis or 5 mg/kg for Crohn's disease every 8 weeks to the subcutaneous formulation of Remsima.	There is insufficient information regarding the switching of patients who received the intravenous infusions of infliximab higher than 3 mg/kg for rheumatoid arthritis every 8 weeks to the subcutaneous formulation of Remsima.	PK, efficacy, safety and immunogenicity results from REMSWITCH study	2.7.2.3.5 2.7.3.4.4 2.7.4.6.3

Table 3. Overview of Clinical Development Program of CT-P13 SC

Protocol No.	Population	Design	Objective(s)	Study Treatment	Status
CT-P13 3.7	UC Enrolled: 548 Randomized (W10): 438 CT-P13 SC: 294 Placebo SC: 144	Randomized, placebo-controlled, double-blind, multicentre, parallel-group Phase 3 study to evaluate the efficacy, PK, PD and safety of CT-P13 SC as maintenance therapy in patients with moderately to severely active UC	**Primary Objective:** • To demonstrate superiority of CT-P13 SC over Placebo SC based on clinical remission at Week 54 **Secondary Objective:** • To evaluate additional efficacy, PK, PD and overall safety including immunogenicity	**<Induction phase> - Week 0 to 10** Three doses of CT-P13 IV 5 mg/kg at Weeks 0, 2 and 6 for all patients **<Maintenance phase> - Week 10 to 54** Arm 1: CT-P13 SC 120 mg via PFS at Week 10 and then every 2 weeks up to Week 54 Arm 2: Placebo SC (matching volume to CT- P13 SC 120 mg) via PFS at Week 10 and then every 2 weeks up to Week 54 **<Extension phase> - Week 56 to 102** CT-P13 SC 120 mg via PFS at Week 56 and then every 2 weeks up to Week 102	Ongoing
CT-P13 3.8	CD Enrolled: 396 Randomized (W10): 343 CT-P13 SC: 231 Placebo SC: 112	Randomized, placebo-controlled, double-blind, multicentre, parallel-group, Phase 3 study to evaluate the efficacy, PK, PD, usability and safety of CT-P13 SC as maintenance therapy in patients with moderately to severely active CD	**Primary Objective:** • To demonstrate superiority of CT-P13 SC over Placebo SC based on clinical remission and endoscopic response at Week 54 **Secondary Objective:** • To evaluate additional efficacy, PK, PD, usability and overall safety including immunogenicity	**<Induction phase> - Week 0 to 10** Three doses of CT-P13 IV (5 mg/kg) at Weeks 0, 2 and 6 for all patients **<Maintenance phase> - Week 10 to 54** • Arm 1: CT-P13 SC 120 mg via PFS at Week 10 and then every 2 weeks up to Week 54 • Arm 2: Placebo SC (matching volume to CT-P13 SC 120 mg) via PFS at Week 10 and then every 2 weeks up to Week 54 **<Extension phase> - Week 56 to 102** CT-P13 SC 120 mg via PFS or AI at Week 56 and then every 2 weeks up to Week 102	Ongoing

Abbreviations: AI, Auto-injector; CD, Crohn's disease; IBD, Inflammatory bowel disease; IV, Intravenous; PD, Pharmacodynamics; PFS, Pre-filled syringe; PK, Pharmacokinetics; SC, Subcutaneous; UC, Ulcerative colitis

6. Clinical Pharmacology aspects

6.1. Methods – analysis of data submitted

6.1.1. Bioanalytical methods

Bioanalytical methods applied in CT-P13 clinical program included the assays for quantifying human plasma concentration of CT-P13 and detecting anti-drug antibody (ADA) and neutralising antibody (NAb) after IV (Study CT-P13 3.7) and SC (Study CT-P13 3.8) injections. The fecal calprotectin (FC) and C-reactive protein (CRP) were also monitored as pharmacodynamic (PD) parameters in Studies CT-P13 3.7 and CT-P13 3.8. Table 3 provides an overview of the bioanalytical methods used in the clinical program for pharmacokinetics and immunogenicity testing. The reports in blue font are included in this Type II/133/G variation and are further discussed and assessed in this current AR whereas the reports in black font have been assessed and discussed in the context of previous regulatory submissions for this finished drug product.

Table 4. Overview of bioanalytical methods used in CT-P13 clinical studies.

Category	Method Platform	Validation Report+	Relevant Sequence
PK	MSD ECL	RBPQ7 (Original) RBPQ8 (Addendum 3) RBPQ8 (Addendum 5) RBPQ8 (Addendum 7) RBPQ14 (Addendum 6)	• Section 2.7.1 of SN0133 • Section 2.7.1 of SN0171 • Section 1.2.1
ADA	MSD ECL ACE	RLBH6 (Original) RLBH6 (Amendment 1) RLBH8 (Addendum 1) RLBH10 (Addendum 2)	• Section 2.7.2.4 of SN0171 • Section 1.2.2.1
NAb	New MSD ECL ACE	RMLA10 (Original)	• Section 1.2.2.2

+Reports in black font were submitted before in either SN0133 or SN171. Reports in blue font are newly included in this Type II variation.
Abbreviations: ACE, Affinity Capture Elution; ADA, Anti-drug antibody; ECL, Electrochemiluminescence; MSD, Meso Scale Discovery; NAb, Neutralising antibody; PK, Pharmacokinetics; SC, Subcutaneous

Detection of ADA in human serum by ECL-MSD based method

At the early phase of sample analysis for Study CT-P13 3.8, the ADA-assay showed poor performance with high run failure rate in reagent qualification runs. Positive controls failed to meet pre-defined acceptance criteria and negative controls showed large variance in response between wells. The root cause was identified in a thorough investigation as the quality of Pierce™ Streptavidin coated high capacity (SA) plates. Pierce™ SA plate was then replaced with SA plate manufactured by Roche, and additional method validation was performed by PPD Laboratory to confirm assay performance after the change of SA plate. The detailed validation report (RLBH10, Addendum 2) was provided in the submission and the summary of the validation results is presented in the Table 4.

Table 5. Validation summary of ADA detection assay (partial validation after change of SA plate)

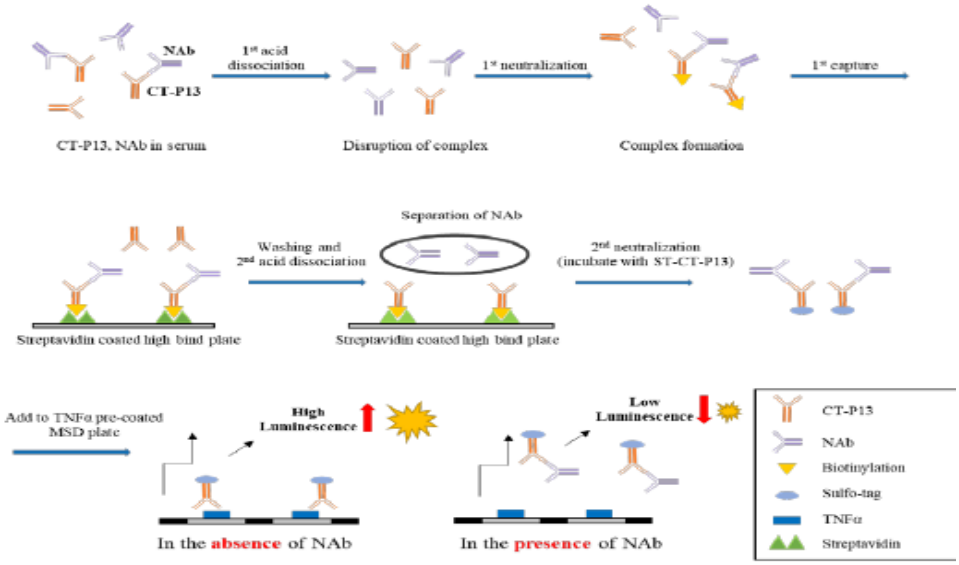
Aspect	Performance Parameters			
Project Code	RLBH10			
PC Characteristics	HCA233 (Human monoclonal anti-infliximab antibody in human serum)			
PC Concentrations	2.80, 5.00, 10.0, 100, and 1000 ng/mL			
Screening Assay Cut Point (Mean Plate NC x CPV)	CPV = 1.06 (Normal human serum)			
Specificity/Confirmatory Assay Cut Point	% Signal Inhibition = 22.2% (Normal human serum)			
Titre Assay Cut Point (Mean Plate NC x CPV)	CPV = 1.13 (Normal human serum)			
Sensitivity	Screening = 1.33 ng/mL, Confirmatory = 2.35 ng/mL for normal human serum			
LPC Determination	5.00 ng/mL The lower limits for run acceptance LPCs were determined to be 1.23 SNR for the screening assay and 30.7% for the confirmatory assay.			
Titre Precision	Acceptable with All the titres of 24 curves were within ± 1 dilution of the median titre (1:8 dilution).			
Intra-assay Statistics – RLU	**Level**	**Conc. (ng/mL)**	**Precision (%CV)**	
			Screening	**Confirmatory %Inhibitory**
	NC	N/A	1.23%	38.9%*
	LPC	2.80	1.30%	7.55%
	MPC	100	6.54%	0.651%
	HPC	1,000	4.52%	0.0578%
	* Since all replicate results for the inhibited NC confirmed negative, the assay performed as expected and intra-assay precision for the NC %inhibition was considered acceptable.			
Inter-assay Statistics – RLU or SNR	**Level**	**Conc. (ng/mL)**	**Precision (%CV)**	
			Screening	**Confirmatory %Inhibitory**
	NC	N/A	10.1% (RLU)	70.8%**
	LPC	2.80	6.23% (SNR)	18.3%
	LPC	5.00	6.92% (SNR)	11.6%
	MPC	100	17.2% (SNR)	1.60%
	HPC	1,000	15.9% (SNR)	0.171%
	** Since the replicate results for the inhibited NCs consistently confirmed negative and the mean % inhibition for the NC was 9.9% (below the CCP of 22.2%), the assay performed as expected and inter-assay precision for the NC %inhibition was considered acceptable.			
Drug Tolerance	≥25.0 ng/mL antibody detected in the presence of 120 µg/mL CT-P13 SC and CT-P13 IV			
Prozone or Hook Effect	A hook effect was observed at ADA concentrations above 6,250 ng/mL due to decreases in the RLUs relative to increasing ADA concentrations. However, ADA concentrations up to 25,000 ng/mL screened potential positive and confirmed positive.			

Source: RLBH10
Abbreviations: ACE, Affinity capture elution; ADA, Anti-drug antibody; Conc., Concentration; CCP, Confirmatory cut point; CPV, Cut point value; %CV, Percent coefficient of variation; ECL, Electrochemiluminescence; HPC, High positive control; IV, Intravenous; LPC, Low positive control; MPC, Medium positive control; MSD, Meso Scale Discovery; NC, Negative control; PC, Positive control; RLU, Relative light unit; SC, Subcutaneous; SNR, Signal to noise ratio

Detection of NAb in human serum by MSD ECL assay

Prior to Studies CT-P13 3.7 and CT-P13 3.8, the MSD ECL ACE based immunoassay containing acid sample treatment was tested in qualification runs to assure the appropriate assay performance. The results showed large well-to-well variance in negative and positive control responses, thus failing to meet the pre-defined acceptance criteria. Therefore, the new MSD ECL ACE method was developed and validated by PPD Laboratory. The new method utilises TNFα and Sulfo-tag CT-P13 as second capture and detection reagents on MSD plate respectively, whereas in old method the corresponding reagents are biotinylated CT-P13 and Sulfo-tag TNFα (Figure 1). A full validation report of new NAb-assay was provided in the submission and the results are summarized in Table 5.

Figure 1. Schematic diagram of the new MSD ECL ACE method for NAb detection in serum



Abbreviations: ACE, Affinity capture elution; ECL, Electrochemiluminescence; MSD, Meso Scale Discovery; NAb, neutralising antibody; ST, Sulfo-tag; TNFα, Tumor Necrosis Factor α

Table 6. Summary of the validation of the novel NAb detection method in healthy human serum.

Species/Matrix	Human Serum		
Analysis Method	new MSD ECL ACE		
Screening Assay Cut point	CPV for Healthy = 0.889 SNR CPV for UC = 0.861 SNR CPV for CD = 0.884 SNR		
Titration Assay Cut point	CPV for Healthy = 0.850 SNR CPV for UC = 0.823 SNR CPV for CD = 0.849 SNR		
MRD	1:10.7		
Sensitivity	58.7 ng/mL		
PC Characteristics	Human monoclonal anti-infliximab antibody HCA 213, purchased from BioRad		
PC Concentrations	119, 687 and 1,000 ng/mL		
Control Intra-assay Statistics - SNR	**Level**	**Conc. (µg/mL)**	**Precision (%CV)**
	NC	N/A	4.01
	LPC	119	6.17
	MPC	687	6.58
	HPC	1000	9.28
Control Inter-assay Statistics - RLU	**Level**	**Conc. (µg/mL)**	**Precision (%CV)**
	NC	N/A	12.9
	LPC	119	12.8
	MPC	687	12.1
	HPC	1000	14.2
Titre Precision	Acceptable with • All the titres of 24 curves were within ± 1 dilution of the median titre (1:8 dilution)		
Matrix Interference; Healthy	Acceptable with • 10/10 units meeting the acceptance criteria when analysed unfortified serums • 10/10 units meeting the acceptance criteria when fortified at the LPC level • 10/10 units meeting the acceptance criteria when fortified at the HPC level		
Matrix Interference; UC	Acceptable with • 10/10 units meeting the acceptance criteria when analysed unfortified serums • 10/10 units meeting the acceptance criteria when fortified at the LPC level • 10/10 units meeting the acceptance criteria when fortified at the HPC level		
Matrix Interference; CD	Acceptable with • 10/10 units meeting the acceptance criteria when analysed unfortified serums • 10/10 units meeting the acceptance criteria when fortified at the LPC level • 10/10 units meeting the acceptance criteria when fortified at the HPC level		
Drug Tolerance	• 500 and 1000 ng/mL antibody detected in the presence of up to 40 µg/mL drug • 119 ng/mL antibody detected in the presence of up to 30 µg/mL drug		
Hemolysis & Lipemia	• No apparent effect from hemolysis on the detection of anti-CT-P13 neutralising antibodies • No apparent effect from lipemia on the detection of anti-CT-P13 neutralising antibodies		
Target interference	No target interference was observed up to 2000 pg/mL of TNFα		
Prozone (Hook) Effect	No apparent prozone effect observed at concentrations up to 25,000 ng/mL		
Thawed Matrix Stability (Hours)	28 hours at room temperature		
Freeze/Thaw Stability (Cycles)	Six cycles thawed at room temperature		

Source: RMLA10

Abbreviations: ACE, Affinity capture elution; CD, Crohn's disease; CPV, Cut point value; %CV, Percent coefficient of variation; ECL, Electrochemiluminescence; HPC, High positive control; LPC, Low positive control; MPC, Medium positive control; MRD, Minimum required dilution; MSD, Meso Scale Discovery; NAb, Neutralising antibody; NC, Negative control; PC, Positive control; RLU, Relative light unit; TNFα, Tumor necrosis factor alpha; SNR, Signal-to-noise ratio; UC, Ulcerative colitis

CHMP comments (bioanalytical methods)

The Type II/133/G variation contains two clinical studies CT-P13 3.7 (with ulcerative colitis patients) and 3.8 (with Crohn's disease patients). The bioanalysis of clinical study samples included quantification of CT-P13 plasma concentration and PD markers as well as ADA and NAb detection in plasma. The plasma concentration and PD marker quantification methods are the same as used in earlier development and have been assessed and discussed within the context of previous regulatory submission. Therefore, these methods are left out of this assessment.

However, ADA and NAb detection methods both of which are MSD ECL based immunocapture assays showed at the early phase of sample analysis/reagent testing high run failure rate mainly due to large variation in controls, thus not meeting the pre-defined acceptance criteria. Therefore, both methods were modified and either partially or fully validated. In general, the validation of these modified methods has been done in accordance with the relevant EMA guideline and are shortly discussed below.

Determination of ADA in human serum

MAH informs that according to extensive investigation the Pierce™ streptavidin coated high capacity (SA) plates were the reason for poor performance of ADA method. Therefore, Pierce™ SA plates were changed to corresponding SA plates provided by Roche. Partial validation (RLBH10, Addendum 2) with new plates was performed. This is considered acceptable since otherwise, the method was not changed.

The partial validation with new SA plates provided by Roche was performed only in healthy human serum. Since the clinical studies are performed with ulcerative colitis and Crohn's disease patients, the MAH is requested to evaluate matrix interference of corresponding disease serum unless otherwise justified. The screening, confirmatory and tier cut points were determined in acceptable manner being relatively close to cut points in old method with Pierce™ SA plates. The intra- and inter-assay precision for screening and confirmation and titer precision met the acceptance criteria. Only the confirmatory precision of negative controls did not meet the acceptance criteria. However, this is considered acceptable since all replicate results for the inhibited negative controls were confirmed negative. The method with Roche SA plates was slightly less sensitive than the method with Pierce™ SA plates: screening sensitivity 1.33 ng/mL vs. 0.54 ng/mL and confirmatory sensitivity 2.35 ng/mL vs. 1.61 ng/mL. Also, drug tolerance of the method with Roche plates was slightly weaker: 25 ng/mL vs. 6.25 ng/mL of ADA in the presence of 120 µg/mL of CT-P13. However, the difference in sensitivity and drug tolerance is not considerable since the ADA concentrations in the clinical samples are high. The stability was assessed for 6 freeze/thaw cycles and storage at room temperature for 28 hours.

NAb detection in human serum

The Applicant modified NAb detection method (see principle of the method in Figure 6.1.1.1) by changing second capture and detection reagents as follows: TNFα and Sulfo-tag CT-P13 for new method and biotinylated CT-P13 and Sulfo-tag TNFα for old method. The new method was fully validated by PPD Laboratory in healthy and diseased (ulcerative colitis and Crohn's disease) serum, see validation report RMLA10. The screening and titration cut points and sensitivity were evaluated both in healthy and disease serum in acceptable manner. No hook effect nor target/matrix (=hemolysis, lipidemia and healthy/diseased serum) interference was observed. The drug tolerance of NAb-method was 119 ng/mL of NAbs detected in the presence of 40 µg/mL CT-P13. Overall, the method validation followed the current guidance and was considered acceptable.

The bioanalytical reports of clinical samples

The quantification of CT-P13 plasma concentration was reliable within the given accuracy and precision ranges and the performance of calibration curves was acceptable. The reasons for repeat analysis were presented and the required criteria for incurred method analysis was met. However, it should be noted that ISR analysis of clinical samples is still on-going. At this stage, the Applicant had re-assayed 9.87% of the samples and informs that approximately 10% of the clinical samples will be reflected in the final report. The MAH is requested to provide full ISR data once available.

Detection of ADA and NAb in clinical samples was reliable and the negative and positive controls met the acceptance criteria.

Updated comments (RSI AR)

The Applicant has performed matrix interference studies with the serum of ulcerative colitis and Crohn's disease patients. No interference was observed. Issue is considered resolved.

The full ISR data has been provided and is considered acceptable.

6.1.2. Population PK modelling

The objectives of population PK and PK-PD modelling and simulation (M&S) analyses were to update the previously developed population PK model of CT-P13, PK-PD model of CDAI scores, and PK-PD model of partial Mayo scores via inclusion of newly available PK and clinical efficacy data and to perform PK and PK-PD simulations in support of CT-P13 SC induction posology in patients with CD and UC.

CHMP comments

The variation of Remsima (aka CT-P13) SC induction posology in patients with CD and UC is supported only by population PK and PK-PD modelling and simulation analyses. There are no observed data with the proposed dosing regimen. The approved posology for Remsima SC in CD and UC is maintenance therapy (120 mg SC Q2W, starting at Week 6) after initial therapy with infliximab IV (5 mg/kg, infused at Week 0 and Week 2).

Considering the scope of the variation and the proposed and approved dosing regimens, the most critical M&S results are related to PK over the first 6 weeks of therapy.

N.B. The MAH's justifications for dose recommendation for SC induction regimen in treatment of moderately to severely active Crohn's disease, fistulising active Crohn's disease, and moderately to severely active ulcerative colitis, which are presented in Section 3.3 of Module 2.7.2, are based only on population PK modelling and simulations. PK-PD modelling and simulations were also conducted by the MAH; the pharmacometrics assessor's conclusion is that the PK-PD models are not appropriate to support the SC induction posology.

Updated comments (RSI AR)

The Applicant initially applied for SC induction dosing regimen in treatment of CD and UC, which was based only on population PK(/PD) modelling and simulations. The initial documentation and assessment (CHMP comments) are presented below.

The Applicant withdrew this part of the grouped variation application after the first RSI and corresponding changes are no longer proposed to the PI. Consequently, the related questions are no longer relevant.

A summary of the 12 clinical studies included in the population PK analysis is presented in Table 6. Eight studies (1.4, 1.1, 3.1, 3.4, 1.5, 3.5, 1.6, and 1.9) were included in a prior population PK model, which was assessed in variation II/95.

Table 7. Summary of studies included in the population PK analysis.

Study	Study Design	Pop	Doses	PK Sampling Time Points
IV formulation only				
CT-P13 1.4*	Randomized, double-blind, 3- arm, parallel-group, single-dose, PK, safety and immunogenicity	HV	Test: 5 mg/kg CT-P13 IV Reference: A) 5 mg/kg Remicade (EU) IV B) 5 mg/kg Remicade (US) IV	Pre-dose, EOI, 1 hour after EOI and then at 6, 12, 24, 48 and 72 h after SOI and on Day 8, 15, 29, 43 and 57 (after SOI).

Study	Study Design	Pop	Doses	PK Sampling Time Points
CT-P13 1.1*	Randomized, double-blind, multicenter, multiple-dose, 2-arm, parallel-group, efficacy, PK and safety	AS	Test: 5 mg/kg CT-P13 IV at Weeks 0, 2, 6, then every 8 weeks to Week 54 Reference: 5 mg/kg Remicade (EU) IV at Weeks 0, 2, 6, then every 8 weeks to Week 54	On dosing days samples were collected pre-dose, 15 minutes and 1h after EOI. Between dose 5 and 6 samples were also collected at 3, 8, 24, 192, 360, 696 and 1032 h after SOI.
CT-P13 3.1*	Randomized, double-blind, multicenter, multiple-dose, 2-arm, parallel-group, efficacy, PK, PD and safety	RA	Test: 3 mg/kg CT-P13 IV at Weeks 0, 2, 6, then every 8 weeks up to Week 54 (+MTX 12.5 to 25 mg/week) Reference: 3 mg/kg Remicade (EU) IV at Weeks 0, 2, 6, then every 8 weeks up to Week 54 (+MTX 12.5 to 25 mg/week)	On dosing days samples were collected pre-dose, 15 minutes and 1h after EOI.
CT-P13 3.4*	Randomized, double-blind, multicenter, 4-arm, parallel- group study comparing efficacy, safety, PK and immunogenicity	CD	1: CT-P13→ CT-P13 at Week 30 2: CT-P13→ Remicade at Week 30 3: Remicade→ Remicade at Week 30 4: Remicade → CT-P13 at Week 30 CT-P13 and Remicade dose: 5 mg/kg IV at Weeks 0, 2, 6 then every 8 weeks up to Week 54	On dosing days samples were collected pre-dose and within 15 minutes after EOI up to dose 5. At Week 22 (dose 5), samples were collected only pre-dose.
SC formulation				
CT-P13 1.5*	Open-label, dose escalating, single-dose, safety, and PK	HV	Test: 120, 180 or 240 mg CT-P13 SC Reference: 3 or 5 mg/kg CT-P13 IV	SC formulation: Pre-dose, 2, 3, 6, 12, 24, 48, 72 h and 7, 14, 28, 42, 56 and 84 days post-injection. IV formulation: Pre-dose, EOI, 3, 6, 12, 24, 48, 72 h and 7, 14, 28, 42, 56 and 84 days after SOI.
CT-P13 3.5	**Part 1:** Open-label, randomized, multicenter, 4-arm, parallel- group, PK, efficacy and safety	RA	Test: Initial 3 mg/kg CT-P13 IV at Weeks 0, 2 then 90, 120 or 180 mg CT-P13 SC at Week 6 and every other week up to Week 54 (+MTX 12.5 to 25 mg/week) Reference: 3 mg/kg CT-P13 IV at Weeks 0, 2, 6, then every 8 weeks up to Week 54 (+MTX 12.5 to 25 mg/week)	Cohort 1 (IV): On dosing days samples were collected pre-dose on all dosing days. At Week 22 samples were collected pre- dose, EOI, 3, 8, 24, 48, 96, 168 h and 14, 28 and 42 days after SOI. Cohorts 2-4 (SC): On dosing days samples were collected pre-dose at Weeks 0, 2, 6, 14, 22, 30, 38, 46 and 54. At Week 22, 24, 26 and 28 samples were collected alternatively for group A and B at 24, 48, 96, 168, 216 and 264 h or at 168 h post injection, and 14 days after Week 28 injection.
	Part 2: Double-blind, randomized, multicenter, parallel-group, PK, efficacy, PD and safety	RA	Test: Initial 3 mg/kg CT-P13 IV at Weeks 0, 2 then 120 mg CT-P13 SC at Week 6 and every other Week up to Week 54 (+MTX 12.5 to 25 mg/week) Reference: 3 mg/kg CT-P13 IV at Weeks 0, 2, 6, then every 8 weeks and switched to CT-P13 SC 120 mg at Week 30. Further doses with CT-P13 SC were given up to Week 54 (+MTX 12.5 to 25 mg/week)	On dosing days samples were collected pre-dose; Group A-D: at Week 22 samples were collected pre-dose, EOA and 1 after EOA for all groups and at 8, 24, 48, 96 h and 7, 9, 14 (pre-dose at Week 24), and 42 (pre-dose at Week 28) days after SOI, and pre-dose at Week 26 and 30. Samples were also obtained pre-dose at Weeks 38, 46 and 54.
CT-P13 1.6	**Part 1:** Open-label, randomized, multicenter, 4-arm, parallel- group, PK,	CD	Test: Initial 5 mg/kg CT-P13 IV at weeks 0, 2 then 120, 180 or 240 mg CT-P13 SC at Week 6 and every other Week up to Week 54	Cohort 1 (IV): On dosing days samples were collected pre-dose on all dosing days. At Week 22 samples were also collected EOI, 3, 8, 24, 48, 96, 168 h and 14, 28, 42

Study	Study Design	Pop	Doses	PK Sampling Time Points
	efficacy and safety		Reference: 5 mg/kg CT-P13 IV at Weeks 0, 2, 6, then every 8 weeks up to Week 54	days after SOI. Cohorts 2-4 (SC): On dosing days samples were collected pre-dose at Weeks 0, 2, 6, 8, 10, 14, 22, 30, 38, 46 and 54. At Week 22, 24, 26 and 28 samples were also collected alternatively for group A and B at 24, 48, 96, 168, 216 and 264 h or at 168 h post injection and 14 days after Week 28 injection.
	Part 2: Open-label, randomized, multicenter, parallel-group, PK, efficacy and safety	CD, UC	Test: Initial 5 mg/kg CT-P13 IV at Weeks 0, 2 then 120 mg (< 80 kg) or 240 mg (≥ 80 kg) CT-P13 SC at Week 6 and every other Week up to Week 54 Reference: 5 mg/kg CT-P13 IV at Weeks 0, 2, 6, then every 8 weeks up to Week 54	Arm 1 (IV): On dosing days samples were collected pre-dose on all dosing days. At Week 22 samples were collected pre-dose, EOI, 1, 8, 24, 48, 168 h and 14, 28, 42 days after SOI. Arm 2 (SC): On dosing days samples were collected pre-dose at Weeks 0, 2, 6, 14, 22, 30, 38, 46 and 54. At Week 22 samples were collected pre-dose in all groups. Samples were collected pre-dose, 24, 48, 72, 96, 120, 144, 168, 216, and 264 h at Week 22, 24, 26 and 28 in Group A, B, C and D, respectively. Samples were also obtained pre-dose at Weeks 38, 46 and 54.
CT-P13 1.9*	Open-label, randomized, 2-arm, parallel-group, single-dose, PK and safety	HV	Test: 120 mg CT-P13 SC via auto-injector Reference: 120 mg CT-P13 SC via pre- filled syringe	Pre-dose, 2, 6, 24, 48, 72, 96, 108, 120, 132, 144, 156, 168, 192, 216, 240, 288, 336, 672, 1008, 1344 and 2016 (Day 84) after the SOI.
CT-P13 3.7 (up to week 54)	Randomized, placebo controlled, double blind, 2-arm parallel group, PK, efficacy and safety.	UC	Test: CT-P13 5 mg/kg IV at Weeks 0, 2 and 6, then CT-P13 120 mg SC every other week from Week 10, up to Week 102. CT-P13 240mg SC every other week from Week 22, if loss of response. Reference: CT-P13 5 mg/kg IV at Weeks 0, 2 and 6, then placebo SC every other week from Week 10, up to Week 54. CT-P13 240mg SC every other week from Week 22, if loss of response.	Pre-dose at Weeks 0, 2, 6, 10, 14, 22 and within 15 minutes after EOI of Week 6. In addition, samples were collected any time between 48 hours and 72 hours after study drug administration of Week 22, any time between 120 hours and 168 hours after study drug administration of Week 22, and pre-dose of Week 24. Additional PK sample at time of dose adjustment
CT-P13 3.8 (up to week 54)	Randomized, placebo controlled, double blind, 2-arm parallel group, PK, efficacy and safety.	CD	Test: CT-P13 5 mg/kg IV at Weeks 0, 2 and 6, then CT-P13 120 mg SC every other week from Week 10, up to Week 102. CT-P13 240mg SC every other week from Week 22, if loss of response. Reference: CT-P13 5 mg/kg IV at Weeks 0, 2 and 6, then placebo SC every other week from Week 10, up to Week 54. CT-P13 240mg SC every other week from Week 22, if loss of response.	Pre-dose at Weeks 0, 2, 6, 10, 14, 22 and within 15 minutes after EOI of Week 6. In addition, samples were collected any time between 48 hours and 72 hours after study drug administration of Week 22, any time between 120 hours and 168 hours after study drug administration of Week 22, and pre-dose of Week 24. Additional PK sample at time of dose adjustment.
CT-P13 1.10	Open-label, randomized, 2-arm, parallel-group, single-dose, PK and safety	HV	CT-P13 120 mg SC or CT-P13 240 mg SC	Pre-dose, 2, 6, 24,48, 72, 96, 108, 120, 132, 144, 156, 168, 192, 216, 240, 288, 336, 672, 1008, 1344 and 2016 h after the SOI.
CT-P13 1.11	Open-label, randomized, 2-arm,	HV	Test: CT-P13 SC 120 mg via auto-injector	Pre-dose, 2, 6, 24,48, 72, 96, 108, 120, 132, 144, 156, 168, 192, 216, 240, 288, 336, 672,

Study	Study Design	Pop	Doses	PK Sampling Time Points
	parallel-group, single-dose, PK and safety		Reference: CT-P13 SC 120 mg via pre-filled syringe	1008, 1344 and 2016 h after the SOI.

* Immunogenicity data from studies 1.1, 1.4, 1.5, 1.9, 3.1, and 3.4 not used in current population PK analyses due to changes in bioanalytical assays
AS=ankylosing spondylitis; **CD**=Crohn's disease; **EOA**=end of administration; **EOI**=end of infusion; **HV**=healthy volunteers; **IV**=intravenous, **MTX**=methotrexate; **RA**=rheumatoid arthritis; **SC**=subcutaneous; **SOI**=start of infusion; **UC**=ulcerative colitis.

The data from studies CT-P13 3.7 and CT-P13 3.8 (up to 31st May 2022) were initially provided for modelling in a blinded form and the treatment of each subject was tentatively identified from the observed concentration versus time data. The blinded data were used to develop the current PK model. Subsequently, complete unblinded data (including treatment assignment) of patients who had completed week 54 were provided; these data superseded the prior blinded data. The developed PK model was re-run with the updated unblinded dataset.

PK Model development: A total of 52113 PK measurements obtained from 3114 subjects were available to educate development of the population PK model. As in prior population PK analyses, a total of 170 measurements from 12 subjects were excluded from the analysis as they were recruited into a fraudulent site (7 subjects from Study CT-P13 1.1) or due to scientific misconduct of the site (5 subjects from Study CT-P13 3.5), leaving 51943 measurements available. A summary of those measurements that were further excluded from the model development process is presented in Table 7. Overall, 43148 PK measurements from 2998 subjects were included in the population PK model development.

Table 8. Summary of Records Excluded from PK Model Development.

Description	Number of Observation Records	Number of Remaining Observation Records
Total Number of Available Observations in the Dataset		**51943**
Observation records from non-evaluable subjects [(a)]	43	51900
Observation records with missing concentration value	82	51818
Observation records missing an associated dosing record	4	51814
Pre-first dose samples	3069	48745
Outlier [(b)]	1	48744
Observation records below the limit of quantification	5023	43721
|CWRES| > 6 [(c)]	191	43530
Observation records from subjects with treatment unassigned (CT-P13 3.7 | CT-P13 3.8) [(d)]	382	43148
Total Number of Available Observations Employed for Model Development		**43148**

[(a)] The subject had no quantifiable post-dose concentrations or treatment information was missing.
[(b)] An incongruous data point in the concentration-time profile (Study CT-P13 1.4).
[(c)] Maximum number of exclusions at any point during model development. CWRES outliers were all reincluded in Run5056 (sensitivity analysis).
[(d)] Treatment could not be assigned according to the established criteria.

CHMP comments

According to Section 5.1.1.1 of the population PK/PD report, PK measurements from 3114 subjects were available for PK model development and after exclusions PK measurements from 2998 subjects were included in the population PK model development. According to Table 13 and Table 14 of the report (Summary of continuous and categorical covariates, respectively), 3017 subjects were included in the

population PK model development. Please clarify the discrepancy. In addition, please provide summaries of continuous and categorical covariates for the final unblinded dataset.

Updated comments (RSI AR)

The Applicant withdrew this part of the grouped variation application after the first RSI and corresponding changes are no longer proposed to the PI. The question above is no longer relevant.

PK Model update: A total of 53744 unblinded PK measurements obtained from 3253 subjects were available to educate update of the population PK model. As previously, a total of 170 measurements obtained from 12 subjects were excluded from the analysis as they were recruited into a fraudulent site (7 subjects from Study CT-P13 1.1) or due to scientific misconduct of the site (5 subjects from Study CT-P13 3.5), leaving 53574 measurements available. A summary of those measurements that were further excluded from the model update is presented in Table 8. Overall, 44779 PK measurements from 3198 subjects were included in the updated population PK analysis.

Table 9. Summary of Records Excluded from PK Model Update.

Description	Number of Observation Records	Number of Remaining Observation Records
Total Number of Available Observations in the Dataset		**53574**
Observation records from non-evaluable subjects [(a)]	72	53502
Observation records with missing concentration value	82	53420
Observation records missing an associated dosing record	4	53416
Pre-first dose samples	3179	50237
Outlier [(b)]	1	50236
Observation records below the limit of quantification	5259	44977
|CWRES| > 6 [(c)]	198	44779
Total Number of Available Observations Employed for Model Development		**44779**

[(a)] The subject had no quantifiable post-dose concentrations or treatment information was missing.
[(b)] An incongruous data point in the concentration-time profile (Study CT-P13 1.4).
[(c)] Maximum number of exclusions at any point during model development. CWRES outliers were all reincluded in Run5100 (sensitivity analysis).

NONMEM® version 7.4.3 was used for population PK and PK-PD modelling. Xpose, PsN and R were used for model diagnostics, graphical analysis, facilitation of NONMEM tasks, simulations, and statistical summaries. The FOCE-I method was initially used during PK model development. However, the estimation algorithm repeatedly failed to minimize successfully. Subsequently, a stochastic approximation expectation-maximization (SAEM) estimation algorithm to obtain all parameter estimates, followed sequentially by an Importance Sampling to obtain Objective Function and standard errors, was employed for all the population PK analyses.

6.1.3. Population PK-PD modelling

The Applicant had previously developed population PK-PD models to describe the effect of CT-P13 on the reduction of CDAI scores (patients with Crohn's disease) and partial Mayo scores (patients with ulcerative colitis). As with population PK analyses, data from studies CT-P13 3.7 and CT-P13 3.8 (up to 31st May 2022) were initially provided for modelling in a blinded form and the treatment of each subject was tentatively identified. The blinded data were used to develop the current PK-PD models. Subsequently, complete unblinded data (including treatment assignment) of patients who had completed week 54 in studies CT-

P13 3.7 and CT-P13 3.8 were provided; these data superseded the prior blinded data. The developed PK-PD models were re-run with the updated unblinded dataset. The first-order conditional estimation method with interaction (FOCE-I) in NONMEM was used for PK-PD analyses.

PK-PD model for CDAI score (Crohn's disease)

Model development: CDAI scores and PK data were available from studies CT-P13 3.4, CT-P13 1.6 Part 1 and Part 2, and CT-P13 3.8 (see Table 6.1.2.1). A total of 4737 quantifiable CDAI scores from 656 subjects were initially available. Subsequently, 62 observations were excluded from the analysis for study CT-P13 3.8 visits after nominal week 54. In addition, 57 CDAI scores obtained after Week 30 from Study CT-P13 1.6 Part 2 Arm 1, in which subjects switched from IV dosing to SC maintenance dosing at Week 30, were excluded. Then, 29 negative observations were noted. The anticipated lower bound of potential CDAI scores was 0. These anomalous observations were excluded. In addition, 266 CDAI scores were excluded from subjects whose treatment could not be identified because the data from study CT-P13 3.8 were blinded. Following these exclusions, 4323 remaining CDAI scores from 624 subjects were employed during model development: 641 scores from 97 subjects from Study CT-P13 1.6, 1064 scores from 220 subjects from Study CT-P13 3.4 and 2618 scores from 307 subjects Study CT-P13 3.8.

Model update: A total of 5287 quantifiable CDAI scores from 708 subjects were available for model update. Of these CDAI scores, 71 observations were for study 3.8 visits after nominal week 54 and they were excluded. In addition, 57 CDAI scores, obtained after Week 30 from Study CT-P13 1.6 Part 2 Arm 1, were excluded. Then, 28 negative observations were noted and excluded. Following these exclusions, 5131 remaining CDAI scores from 708 subjects were employed during the model update: 641 scores from 97 subjects from Study CT-P13 1.6, 1064 scores from 220 subjects from Study CT-P13 3.4 and 3426 scores from 391 subjects Study CT-P13 3.8.

PK-PD model for partial Mayo score (ulcerative colitis)

Model development: Partial Mayo score and PK data were available from studies CT-P13 1.6 Part 2 and CT-P13 3.7 (see Table 6.1.2.1). A total of 4476 quantifiable partial Mayo scores from 544 subjects were initially available. Of these, 1 partial Mayo score was excluded because the stop time of the IV was missing. Then, 107 partial Mayo scores were excluded from subjects whose treatment could not be identified because the data from study CT-P13 3.7 were blinded. Subsequently, 103 observations were excluded from the analysis for study 3.7 visits after nominal week 54. In addition, 104 partial Mayo scores, obtained after Week 30 from Study CT-P13 1.6 Part 2 Arm 1, in which subjects switched from IV dosing to SC maintenance dosing at Week 30, were excluded. Finally, 112 partial Mayo scores were excluded from subjects without PK information, resulting in 4049 partial Mayo scores from 516 subjects remaining for model development: 563 scores from 78 subjects from Study CT-P13 1.6 Part 2 and 3486 scores from 438 subjects from Study CT-P13 3.7.

Model update: A total of 5235 quantifiable partial Mayo scores from 616 subjects were available for model update. Of these, 1 partial Mayo score was excluded because the stop time of the IV was missing. Subsequently, 102 observations were excluded from the analysis for study 3.7 visits after nominal week 54. In addition, 104 partial Mayo scores, obtained after Week 30 from Study CT-P13 1.6 Part 2 Arm 1 were excluded, resulting in 5028 partial Mayo scores from 616 subjects remaining for inclusion in the model update: 563 scores from 78 subjects from Study CT-P13 1.6 and 4465 scores from 538 subjects from Study CT-P13 3.7.

6.2. Results

6.2.1. Observed pharmacokinetics

Summary statistics for observed infliximab C_{trough} and C_{max} in studies CT-P13 3.7 and CT-P13 3.8 are presented in Tables 6.2.1.1 and 6.2.1.2, respectively.

Table 10. Descriptive Statistics of Serum PK Parameters in Study CT-P13 3.7.

Parameter Visit Statistics		CT-P13 SC 120 mg N=286	Placebo N=140
C_{trough} (µg/mL)			
Week 0 (Pre-dose at Week 2)	n	286	139
	Mean ± SD	23.93 ± 11.35	23.80 ± 8.24
	CV%	47.4	34.6
	Median (Min, Max)	23.95 (0.10, 132.00)	23.40 (3.85, 57.20)
Week 2 (Pre-dose at Week 6)	n	284	140
	Mean ± SD	13.87 ± 7.69	14.79 ± 12.75
	CV%	55.4	86.2
	Median (Min, Max)	14.00 (0.10, 54.40)	14.05 (0.10, 115.00)
Week 6 (Pre-dose at Week 10)	n	282	139
	Mean ± SD	13.17 ± 6.72	12.88 ± 7.34
	CV%	51.0	57.0
	Median (Min, Max)	13.30 (0.10, 36.00)	13.00 (0.10, 43.20)
Week 12 (Pre-Dose at Week 14)	n	280	138
	Mean ± SD	15.43 ± 7.16	3.15 ± 2.60
	CV%	46.4	82.5
	Median (Min, Max)	15.55 (0.10, 36.10)	2.59 (0.10, 12.90)
Week 20 (Pre-Dose at Week 22)	n	267	135
	Mean ± SD	14.64 ± 7.83	0.21 ± 0.27
	CV%	53.4	130.4
	Median (Min, Max)	14.60 (0.10, 42.20)	0.10 (0.10, 2.06)
Week 28 (Pre-Dose at Week 30)	n	197	76
	Mean ± SD	16.25 ± 9.24	0.32 ± 1.77
	CV%	56.8	546.8
	Median (Min, Max)	16.10 (0.10, 45.10)	0.10 (0.10, 15.50)
Week 36 (Pre-Dose at Week 38)	n	186	66
	Mean ± SD	15.13 ± 9.07	0.12 ± 0.13
	CV%	59.9	108.2
	Median (Min, Max)	14.50 (0.10, 52.80)	0.10 (0.10, 1.11)
Week 44 (Pre-Dose at Week 46)	n	181	59
	Mean ± SD	15.34 ± 9.12	0.27 ± 1.00
	CV%	59.4	369.8
	Median (Min, Max)	14.80 (0.10, 52.20)	0.10 (0.10, 7.26)
Week 52 (Pre-Dose at Week 54)	n	181	58
	Mean ± SD	15.13 ± 9.33	0.39 ± 2.14
	CV%	61.7	546.8
	Median (Min, Max)	14.20 (0.10, 52.80)	0.10 (0.10, 16.40)
C_{max} (µg/mL)			
Week 6	n	281	138
	Mean ± SD	116.80 ± 44.78	117.96 ± 45.93
	CV%	38.3	38.9
	Median (Min, Max)	122.00 (0.10, 286.00)	120.00 (1.59, 233.00)

Note: Patients in "Placebo" group were administered CT-P13 5 mg/kg IV at Weeks 0, 2, and 6. All below the LLoQs after the first administration were set to LLoQ. For patients with dose adjustment, data collected before initiation of dose adjustment for both treatment groups were included in this summary.

C_{max}, Maximum serum concentration; **C_{trough}**, Trough serum concentration; **CV%**, Percent coefficient of variation; **LLoQ**, Lower limit of quantification; **Max**, Maximum; **Min**, Minimum; **PK**, Pharmacokinetics; **SC**, Subcutaneous; **SD**, Standard deviation

Table 11. Descriptive Statistics of Serum PK Parameters in Study CT-P13 3.8.

Parameter Visit Statistics		CT-P13 SC 120 mg (N=226)	Placebo (N=108)
C_{trough} (µg/mL)			
Week 0 (Pre-dose at Week 2)	n	225	107
	Mean ± SD	22.26 ± 8.56	21.04 ± 8.60
	CV%	38.4	40.9
	Median (Min, Max)	22.40 (0.10, 49.40)	21.10 (0.10, 39.40)
Week 2 (Pre-dose at Week 6)	n	225	105
	Mean ± SD	13.22 ± 7.88	13.52 ± 7.47
	CV%	59.6	55.2
	Median (Min, Max)	12.70 (0.10, 47.80)	13.80 (0.10, 27.90)
Week 6 (Pre-dose at Week 10)	n	222	107
	Mean ± SD	12.53 ± 7.34	14.14 ± 8.08
	CV%	58.6	57.1
	Median (Min, Max)	12.50 (0.10, 41.30)	14.30 (0.10, 46.40)
Week 12 (Pre-Dose at Week 14)	n	220	106
	Mean ± SD	14.65 ± 6.93	3.92 ± 3.35
	CV%	47.3	85.5
	Median (Min, Max)	14.05 (0.10, 35.20)	3.32 (0.10, 15.30)
Week 20 (Pre-Dose at Week 22)	n	215	104
	Mean ± SD	14.60 ± 8.90	0.49 ± 1.46
	CV%	60.9	295.0
	Median (Min, Max)	14.30 (0.10, 52.50)	0.10 (0.10, 11.00)
Week 28 (Pre-Dose at Week 30)	n	191	68
	Mean ± SD	14.80 ± 9.23	0.12 ± 0.09
	CV%	62.3	77.7
	Median (Min, Max)	14.80 (0.10, 55.80)	0.10 (0.10, 0.81)
Week 36 (Pre-Dose at Week 38)	n	177	58
	Mean ± SD	13.35 ± 8.41	0.10 ± 0.00
	CV%	63.0	5.0
	Median (Min, Max)	13.40 (0.10, 39.40)	0.10 (0.10, 0.14)
Week 44 (Pre-Dose at Week 46)	n	168	56
	Mean ± SD	13.62 ± 8.14	0.13 ± 0.20
	CV%	59.8	155.6
	Median (Min, Max)	14.40 (0.10, 29.10)	0.10 (0.10, 1.57)
Week 52 (Pre-Dose at Week 54)	n	161	50
	Mean ± SD	13.28 ± 8.83	0.29 ± 1.15
	CV%	66.5	404.3
	Median (Min, Max)	13.30 (0.10, 48.70)	0.10 (0.10, 8.22)
C_{max} (µg/mL)			
Week 6	n	220	101
	Mean ± SD	118.33 ± 51.87	110.31 ± 50.28
	CV%	43.8	45.6
	Median (Min, Max)	125.00 (0.10, 273.00)	121.00 (0.10, 187.00)

Note: Patients in "Placebo" group were administered CT-P13 5 mg/kg IV at Weeks 0, 2, and 6. All below the LLoQs after the first administration were set to LLoQ. For patients with dose adjustment, data collected before initiation of dose adjustment for both treatment groups were included in this summary.

C_{max}, Maximum serum concentration; **C_{trough}**, Trough serum concentration; **CV%**, Percent coefficient of variation; **LLoQ**, Lower limit of quantification; **Max**, Maximum; **Min**, Minimum; **PK**, Pharmacokinetics; **SC**, Subcutaneous; **SD**, Standard deviation

6.2.2. Population PK modelling and simulations

PK model development

As explained above, the population PK model was developed using partially blinded data. A previously developed population PK model developed following IV and SC administration to healthy volunteers and AS, CD, RA and UC patients was employed as the base PK model. It was a 2-compartment IV infusion model with linear first order elimination from the central compartment (V1), and an additional depot compartment with a first-order SC absorption rate constant term linked to the central compartment. Both types of clearance (CL and Q) and volume of distribution parameters (V1 and V3) were allometrically scaled as part of the structural model using estimated allometric exponents. In addition, covariate effects to describe the emergence of an immunogenic response [NAb status (yes/no) combined with ADA titre values, in a linear form), and its effect on CL, in a time-dependent manner, were included in the base structural model. Immunogenicity (ADA titre and NAb status) was set as "unknown" for patients in the older studies 1.1, 1.4, 1.5, 1.9, 3.1, and 3.4. The base model employed for subsequent covariate model development (Run5050) is summarized in Table 11.

Table 12. Parameter Estimates: Base model for model development (Run5050)

Parameter	Parameter Estimate		
	Typical Value	RSE (%) [b]	Shrinkage (%)
F	0.643	n/a	n/a
K_A (h^{-1})	0.00808	n/a	n/a
$CL_{imm\ unknown}$ (L/h)	0.0109	n/a	n/a
$CL_{imm\ known\ neg.}$ (L/h)	0.0134	n/a	n/a
CL_{NAb+} (proportional)	1.25	n/a	n/a
ADA_{slope} (linear)	0.00927	n/a	n/a
Q (L/h)	0.00188	n/a	n/a
V1 (L)	3.38	n/a	n/a
V3 (L)	0.712	n/a	n/a
Allometric exponent on CL | Q	0.727	n/a	n/a
Allometric exponent on V1 | V3	0.605	n/a	n/a
IIV CL [VAR (CV%)]	0.137 (38.4)	n/a	6.3
IIV V1 [VAR (CV%)]	0.145 (39.5)	n/a	14.4
Proportional residual error (SD) [a]	0.375	n/a	n/a

$CV\% = \sqrt{(\exp(\omega^2)-1)}*100$

[a] Additive residual error of the log transformed data. [b] RSE unavailable as covariance step was unsuccessful.

ADA_{slope}=slope of linear effect of positive ADA titre on CL; $CL_{imm\ unknown}$=typical value of clearance in all studies where immunogenicity data is unavailable; $CL_{imm\ known\ neg}$=typical value of clearance in all studies where immunogenicity data is available; CL_{NAb+}=proportional effect of positive NAb status on clearance; CV=coefficient of variation; ETA=individual random effects; F=bioavailability SC administration; IIV=inter-individual variability; K_A=absorption rate constant; n/a=not applicable; Q=intercompartmental CL; RSE=relative standard error; SD=standard deviation; V1=central volume of distribution: V3=peripheral volume of distribution; VAR=variance

The tested pre-specified covariates are summarized in Table 6.2.2.2. Insufficient data were available to explore the effects of pre-specified covariates fecal calprotectin, baseline CDAI or partial Mayo score, coadministration of azathioprine, 6-mercaptopurine or 'prior exposure to biologic therapy and/or JAK inhibitor' on the PK of CT-P13.

Table 13. . Tested covariates in population PK model

Covariate	
Age at screening (years)	CL, V1
Creatinine clearance (mL/min), according to the Cockroft-Gault formula	CL
Albumin at baseline (g/L)	CL, V1
CRP at baseline (nmol/L)	CL, V1
Gender	CL, V1
Race	CL, V1
Methotrexate coadministration (Binary variable if subject received the co-medication at any point during the study)	CL, V1
Disease duration (years)	CL, V1
Indication (disease state or healthy volunteer)	CL, V1
Immunogenic response (NAb status and ADA titer)	CL
CL=clearance; **V1**=central volume of distribution	

Covariates on CL and/or V1 were tested one at the time. A total of four covariates were associated with OFV decrease of more than 10.84 (corresponding to $p<0.001$; Chi-Square test, df=1) but were not considered by the MAH to have a meaningful impact on the parameter and, hence, were not added to the model (Table 13).

Table 14. Summary of statistically significant rejected covariate models.

Description	ΔOFV	MAH's comment
Including CRCL as a covariate of CL	-13.4	Approximately 5% change in CL at the 5th and 95th percentiles of the covariate. Small reduction in OFV. Negligible reduction in ETA variance. Overall, no justification for retention.
Including Gender as a covariate of CL	-31.1	Small (~9%) difference in CL across genders (well within 0.8-1.25 boundaries). Moderate reduction in OFV. Negligible reduction in ETA variance. No indication in exploratory plots that the covariate effect is required. Overall, no justification for retention.
Including Race (White vs Non-White) as a covariate of CL	-11.4	Small (~6%) change in CL between white and non-white. Small reduction in OFV. Negligible reduction in ETA variance. No indication in exploratory plots that the covariate effect is required. Overall, no justification for retention.
Including Indication as a covariate of V1	-148.3	Large reduction in OFV. Differences in V1 tend to zero; or are contained within 0.8-1.25 boundaries. Small reduction in ETA variance. No indication in exploratory plots that the covariate effect is required. Overall, no justification for retention.

Finally, inclusion of a partial OMEGA block (including covariance between the unexplained IIV of CL and V1) was explored (Run5055) and resulted in a statistically significant reduction in the OFV in comparison with Run5050 (ΔOFV -115.2). As such, Run5055 was declared the final model from the model development analysis with the partially blinded dataset. Parameter estimates and model diagram and equations are shown in Table 6.2.2.4 and Figure 6.2.2.1, respectively. Bootstrap analysis (1000 replicates) demonstrated close agreement with the parameter estimates from Run5055.

Table 15. Parameter Estimates: Final PK Model from Model Development Analysis (Run5055)

Parameter	Parameter Estimate		
	Typical Value	RSE (%) [b]	Shrinkage (%)
F	0.644	1.8	n/a
K_A (h^{-1})	0.00823	2.2	n/a
$CL_{imm\ unknown}$ (L/h)	0.0113	1.2	n/a
$CL_{imm\ known\ neg.}$ (L/h)	0.0132	2.6	n/a
CL_{NAb+} (proportional)	1.24	3.0	n/a
ADA_{slope} (linear)	0.00872	35	n/a
Q (L/h)	0.00187	11	n/a
V1 (L)	3.36	1.2	n/a
V3 (L)	0.714	4.6	n/a
Allometric exponent on CL | Q	0.729	5.4	n/a
Allometric exponent on V1 | V3	0.628	6.9	n/a
IIV CL [VAR (CV%)]	0.149 (40.1)	5.0	6
CL~V1 [Covariance (Correlation)]	0.0603 (0.397)	12	n/a
IIV V1 [VAR (CV%)]	0.155 (40.9)	9.9	14.3
Proportional residual error (SD) [a]	0.374	1.4	n/a

$CV\% = \sqrt{(\exp(\omega^2)-1)*100}$

[a] Additive residual error of the log transformed data. [b] RSE of the IIV parameters relate to the untransformed parameter.

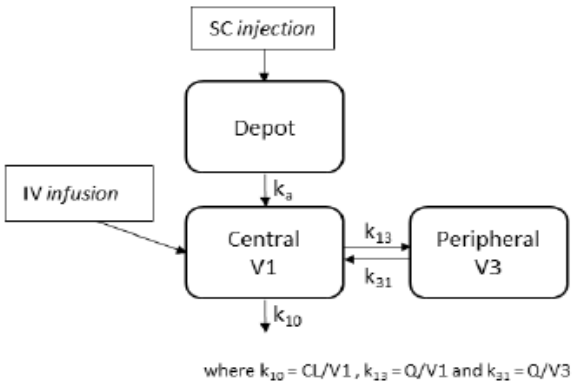
ADA_{slope}=slope of linear effect of positive ADA titre on CL; $CL_{imm\ unknown}$=typical value of clearance in all studies where immunogenicity data is unavailable; $CL_{imm\ known\ neg}$=typical value of clearance in all studies where immunogenicity data is available; CL_{NAb+}=proportional effect of positive NAb status on clearance; CV=coefficient of variation; ETA=individual random effects; F=bioavailability SC administration; IIV=inter-individual variability; K_A=absorption rate constant; n/a=not applicable; Q=intercompartmental CL; RSE=relative standard error; SD=standard deviation; V1=central volume of distribution: V3=peripheral volume of distribution; VAR=variance

Figure 2. . Final Population PK Model Obtained from Model Development (Run5055): Equations and Model Diagram

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

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

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



In studies CT-P13 1.6, CT-P13 1.10, CT-P13 1.11, CT-P13 3.5, CT-P13 3.7 & CT-P13 3.8,

$$CL = \theta_{CL,imm.known.neg} \cdot \left(\frac{WGTBL}{70}\right)^{\theta_{CL,exp}} \cdot \left(1 + \theta_{ADA.slope} \cdot ADA\_titre\right) \cdot (\theta_{CL.NAb+} \cdot NAb\_FLAG) \cdot e^{\eta CL}$$

In studies CT-P13 1.1, CT-P13 1.4, CT-P13 1.5, CT-P13 1.9, CT-P13 3.1 & CT-P13 3.4,

$$CL = \theta_{CL,imm.unknown} \cdot \left(\frac{WGTBL}{70}\right)^{\theta_{CL,exp}} \cdot e^{\eta CL}$$

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

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

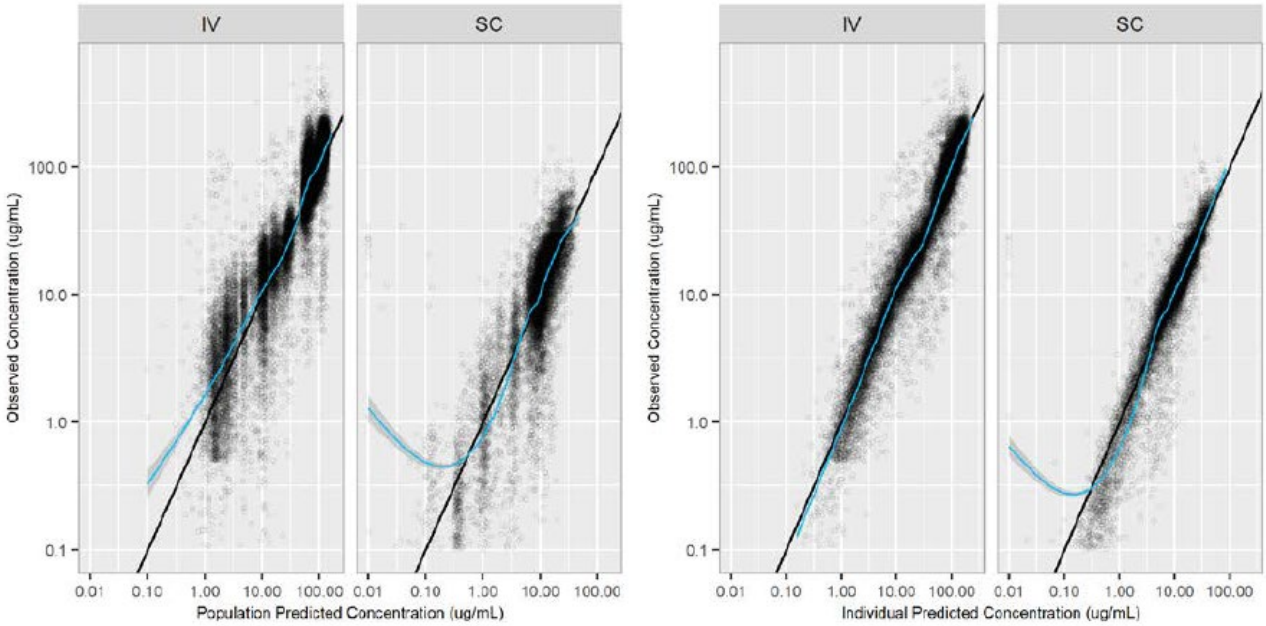
$$Q = \theta_{Q} \cdot \left(\frac{WGTBL}{70}\right)^{\theta_{CL,exp}}$$

Intravenous (**IV**) dose administration occurred directly into compartment 1. Subcutaneous (**SC**) dose administration occurred into depot compartment 0. Subcutaneous doses were subject to reduction commensurate with the absolute bioavailability of the SC dose (**F**).
A(0): Amount of drug in the SC depot compartment; **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; **CL**: clearance; **Q**: intercompartmental clearance; **WGTBL**: body weight at baseline; $\theta_{CL,exp}$: allometric scaling constant applied to clearance parameters; $\theta_{V,exp}$: allometric scaling constant applied to volume parameters; $\theta_{ADA.slope}$: slope of linear effect of positive ADA titre on CL; $(1+\theta_{ADA.slope} \cdot ADA\_titre)$ assumes a value of 1 when ADA_titre ≤ 0; $\theta_{CL,NAb+}$: proportional effect of positive NAb status on CL; NAb_FLAG: binary (1/0) variable which assumes the value of 1 only when NAb status is positive (once positive, always positive); $(\theta_{NAb+} \cdot NAb\_FLAG)$ assumes a value of 1 when NAb_FLAG = 0; **t**: time; η_x: Inter-individual random effects for the x^{th} parameter.

The sensitivity of the parameter estimates to the CWRES outliers was assessed via re-execution of the population PK model but with the re-inclusion of all CWRES outliers (Run5056. In general, all structural model parameters were subject to minimal change upon inclusion of the CWRES outliers (change in parameter values < 15 %), except for ADA_{slope} which was subject to a moderate change of approximately 29% (consistent with the moderate RSE of ADA_{slope} [~35%] in Run5055). As anticipated, the stochastic elements of the final model (IIV in V1 and the residual error component) also increased upon re-inclusion of the CWRES defined outliers. Overall, the model was not found to be sensitive to the re-inclusion of the CWRES outliers, giving confidence in the robustness of the parameter estimates obtained from the model.

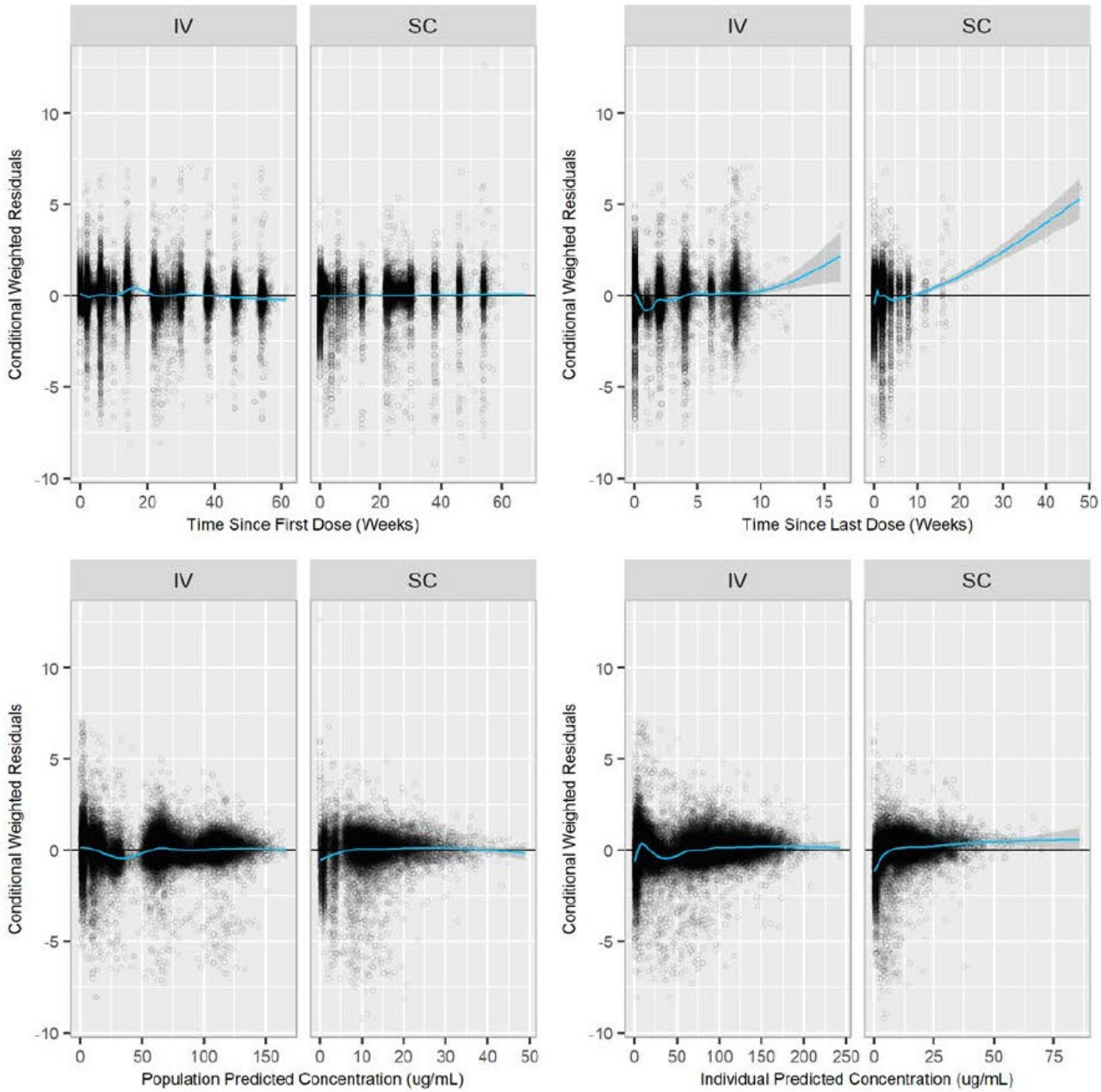
Goodness of fit (GOF) plots for Run5055, stratified by route of administration, are shown in Figures 3 and 4. The significant inflection in the CWRES versus Time Since Last Dose (Figure 4) was explained to be an artefact of very small number of datapoints. Specifically, a single iteration of |CWRES| > 6 exclusion was performed. Subsequently, following these exclusions, a very small number (~ 0.3 %) of additional datapoints were then associated with |CWRES| > 6, resulting in artefactual deviations in the CWRES plots. Selected prediction corrected VPC (pcVPC) plots are shown in Figure 5 and Figure 6. The MAH concluded that overall, the model description of the observed data was adequate.

Figure 3. Observed Versus Predicted Goodness of Fit Diagnostic Plots (Run5055)



Observed data are presented as black open symbols. The line of unity (the expectation) is shown in the solid black line. The blue line and associated grey area reflect a generalized additive smooth of the data, and associated 95% confidence interval.
SC=subcutaneous; IV=intravenous

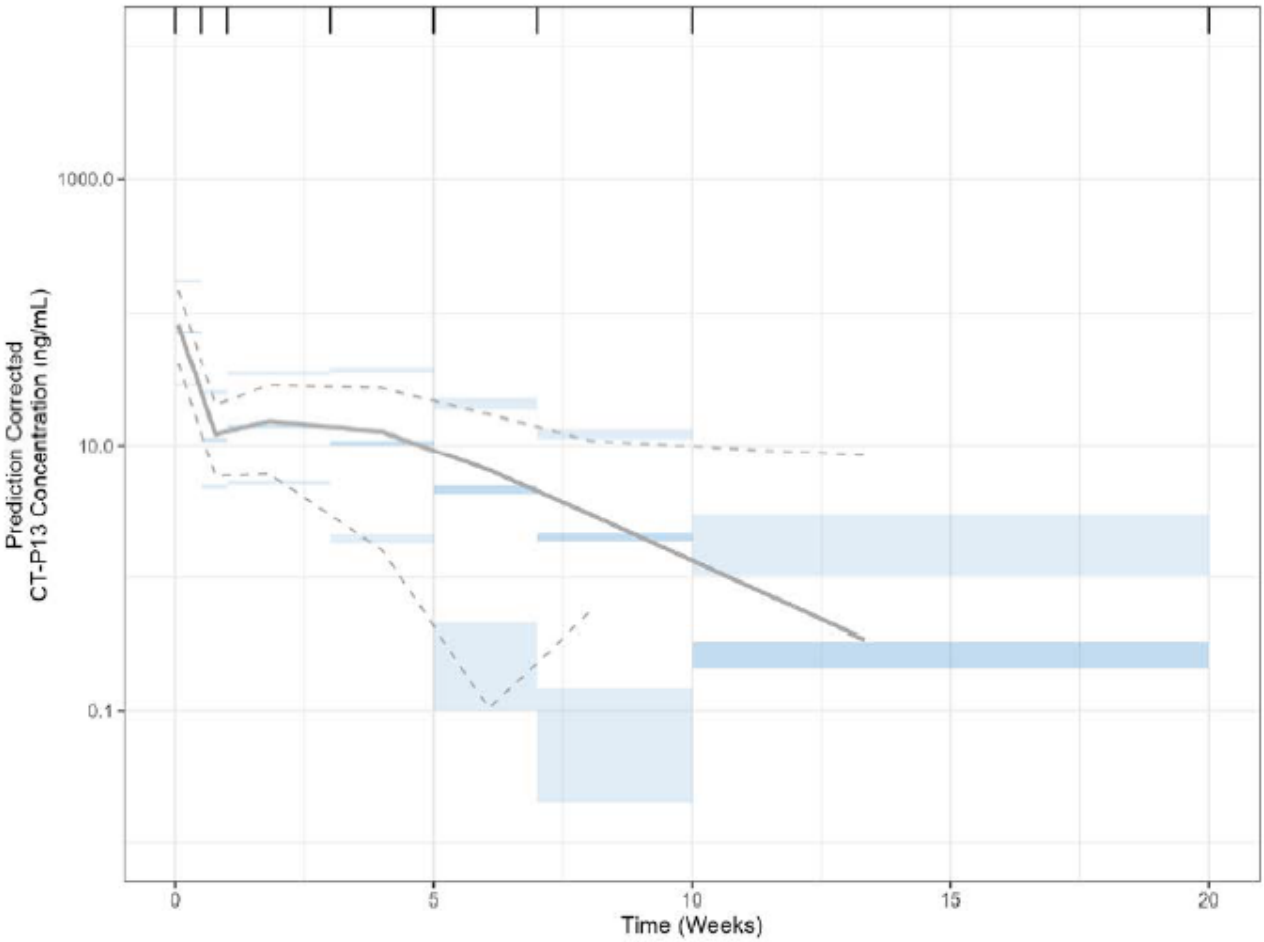
Figure 4. CWRES Goodness of Fit Diagnostic Plots (Run5055)



Observed data are presented as black open symbols. The horizontal line with y intercept = 0 (the expectation) is shown as a solid black line. The blue line and associated grey area reflect a generalized additive smooth of the data, and associated 95% confidence interval.

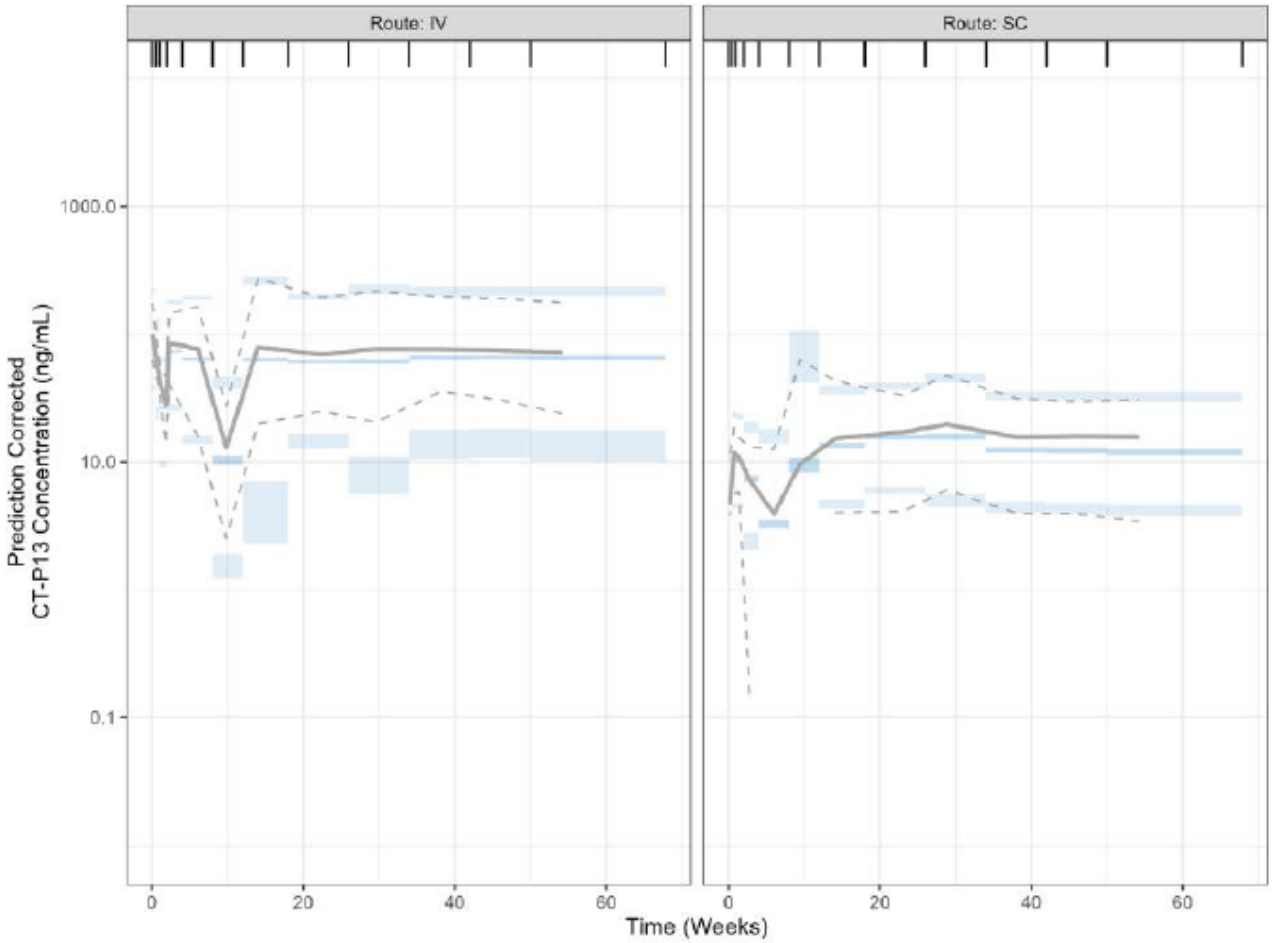
CWRES=conditional weighted residual; SC=subcutaneous; IV=intravenous

Figure 5. pcVPC Plot: Time after Last Dose (Run5055; Individual Observations Omitted for Clarity)



The median prediction corrected observed concentrations are represented by a grey solid line. The 5th and 95th percentiles of the prediction corrected observed concentrations are represented by dashed grey lines. The dark blue shaded area represents the 95% confidence intervals of the median of the prediction corrected model predicted data. The light blue shaded areas represents the 95% confidence intervals of the 5th and 95th percentiles of the prediction corrected model predicted data. The pcVPC was obtained from the model including the residual error term. Negative prediction corrected concentrations, associated with the 5th percentile of the last bin, were not able to be represented on this logarithmic presentation.

Figure 6. pcVPC Plot: Time after First Dose, Stratified by Route of Administration (Run5055; Individual Observations Omitted for Clarity)



The median prediction corrected observed concentrations are represented by a grey solid line. The 5th and 95th percentiles of the prediction corrected observed concentrations are represented by dashed grey lines. The dark blue shaded area represents the 95% confidence intervals of the median of the prediction corrected model predicted data. The light blue shaded areas represents the 95% confidence intervals of the 5th and 95th percentiles of the prediction corrected model predicted data. The pcVPC was obtained from the model including the residual error term.
IV=intravenous; SC=subcutaneous

PK model update

As explained above, the population PK model that was developed using partially blinded data was updated when unblinded data were available. The PK model described in Figure 6.2.2.1 was re-run with the updated unblinded dataset (Run5102). Parameter estimates obtained from Run5102 (Table 6.2.2.5) were estimated with moderate to high precision and were in close agreement with the parameter estimates from Run5055). Bootstrap analysis demonstrated close agreement with the parameter estimates from Run5102.

Table 16. Parameter Estimates: Updated Final Population PK Model (Run5102)

Parameter	Parameter Estimate		
	Typical Value	RSE (%) [b]	Shrinkage (%)
F	0.667	1.3	n/a
K_A (h^{-1})	0.00820	1.9	n/a
$CL_{imm\ unknown}$ (L/h)	0.0117	1.1	n/a
$CL_{imm\ known\ neg.}$ (L/h)	0.0134	0.98	n/a
CL_{NAb+} (proportional)	1.24	2.5	n/a
ADA_{slope} (linear)	0.00814	24	n/a
Q (L/h)	0.00212	9.7	n/a
V1 (L)	3.41	0.92	n/a
V3 (L)	0.737	4.4	n/a
Allometric exponent on CL | Q	0.730	5.2	n/a
Allometric exponent on V1 | V3	0.642	6.4	n/a
IIV CL [VAR (CV%)]	0.154 (40.8)	4.3	5.5
CL~V1 [Covariance (Correlation)]	0.0761 (0.494)	9.1	n/a
IIV V1 [VAR (CV%)]	0.154 (40.8)	7.4	14.7
Proportional residual error (SD) [a]	0.375	1.3	n/a

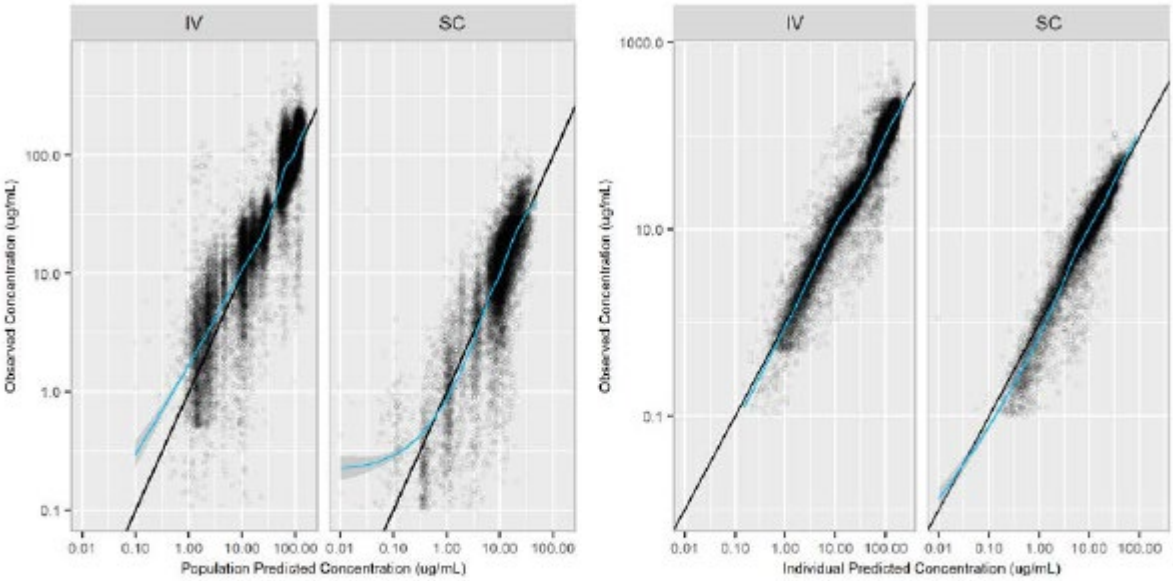
$CV\% = \sqrt{(\exp(\omega^2)-1)*100}$

[a] Additive residual error of the log transformed data. [b] RSE of the IIV parameters relate to the untransformed parameter.

ADA_{slope}=slope of linear effect of positive ADA titer on CL; $CL_{imm\ unknown}$=typical value of clearance in all studies where immunogenicity data is unavailable; $CL_{imm\ known\ neg}$=typical value of clearance in all studies where immunogenicity data is available; CL_{NAb+}=proportional effect of positive NAb status on clearance; CV=coefficient of variation; ETA=individual random effects; F=bioavailability SC administration; IIV=inter-individual variability; K_A=absorption rate constant; n/a=not applicable; Q=intercompartmental CL; RSE=relative standard error; SD=standard deviation; V1=central volume of distribution: V3=peripheral volume of distribution; VAR=variance

GOF plots and selected pcVPC plots for Run5102 are shown in Figure 7 to Figure 10. The MAH concluded that overall, the model description of the observed data was adequate.

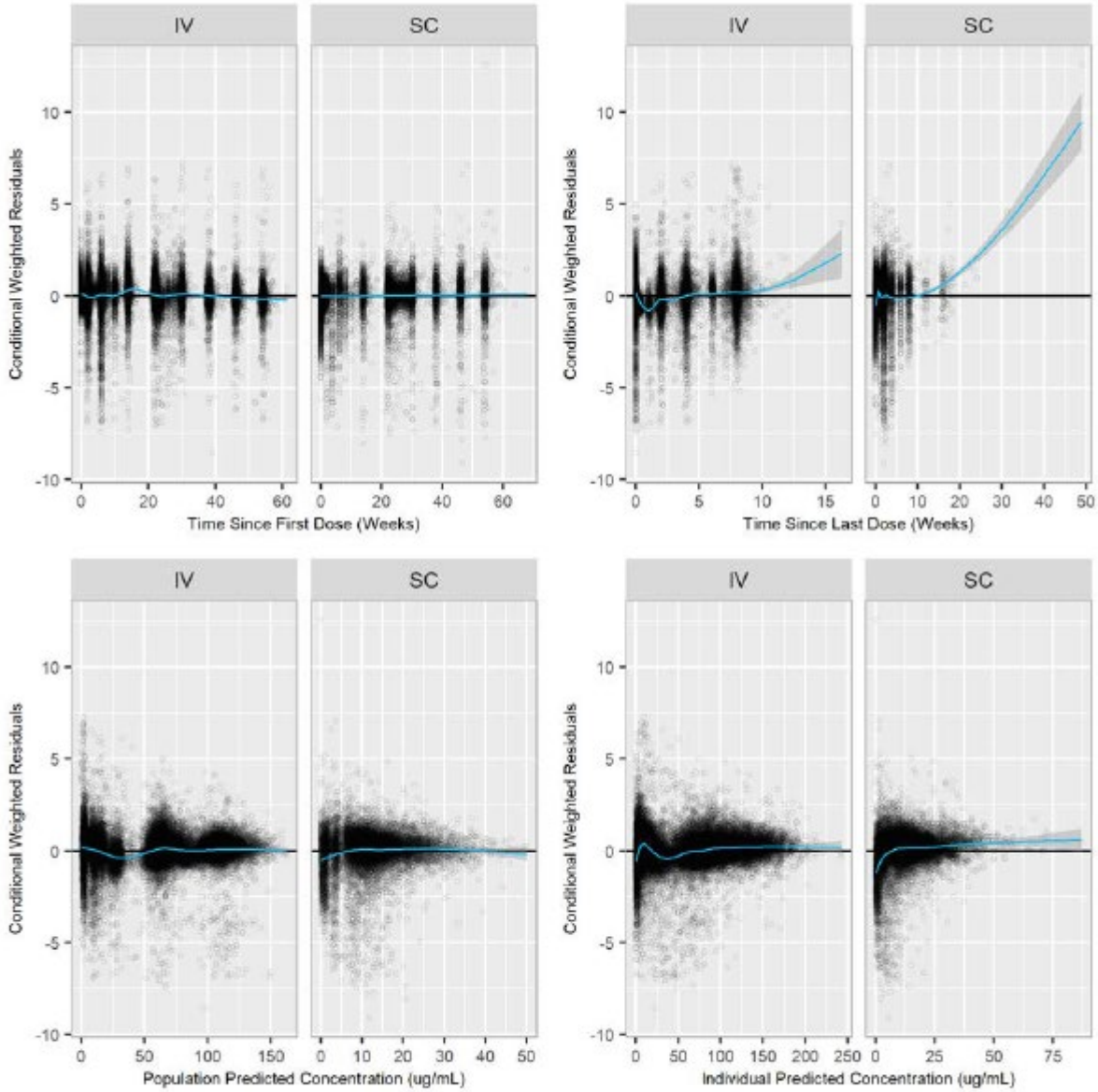
Figure 7. Observed Versus Predicted Goodness of Fit Plots (Run5102)



Observed data are presented as black open symbols. The line of unity (the expectation) is shown in the solid black line. The blue line and associated grey area reflect a generalized additive smooth of the data, and associated 95% confidence interval.

SC=subcutaneous; IV=intravenous

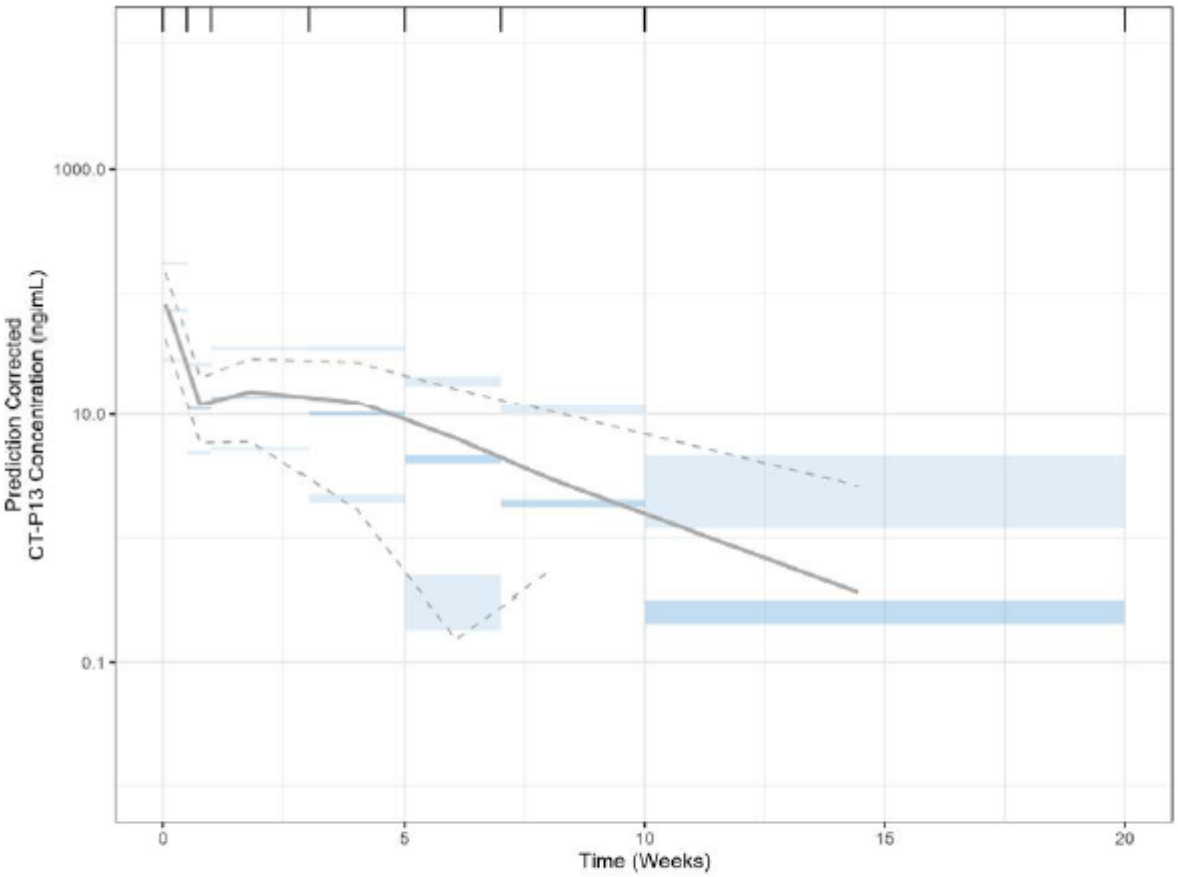
Figure 8. CWRES Goodness of Fit Diagnostic Plots (Run5102)



Observed data are presented as black open symbols. The horizontal line with y intercept = 0 (the expectation) is shown as a solid black line. The blue line and associated grey area reflect a generalized additive smooth of the data, and associated 95% confidence interval.

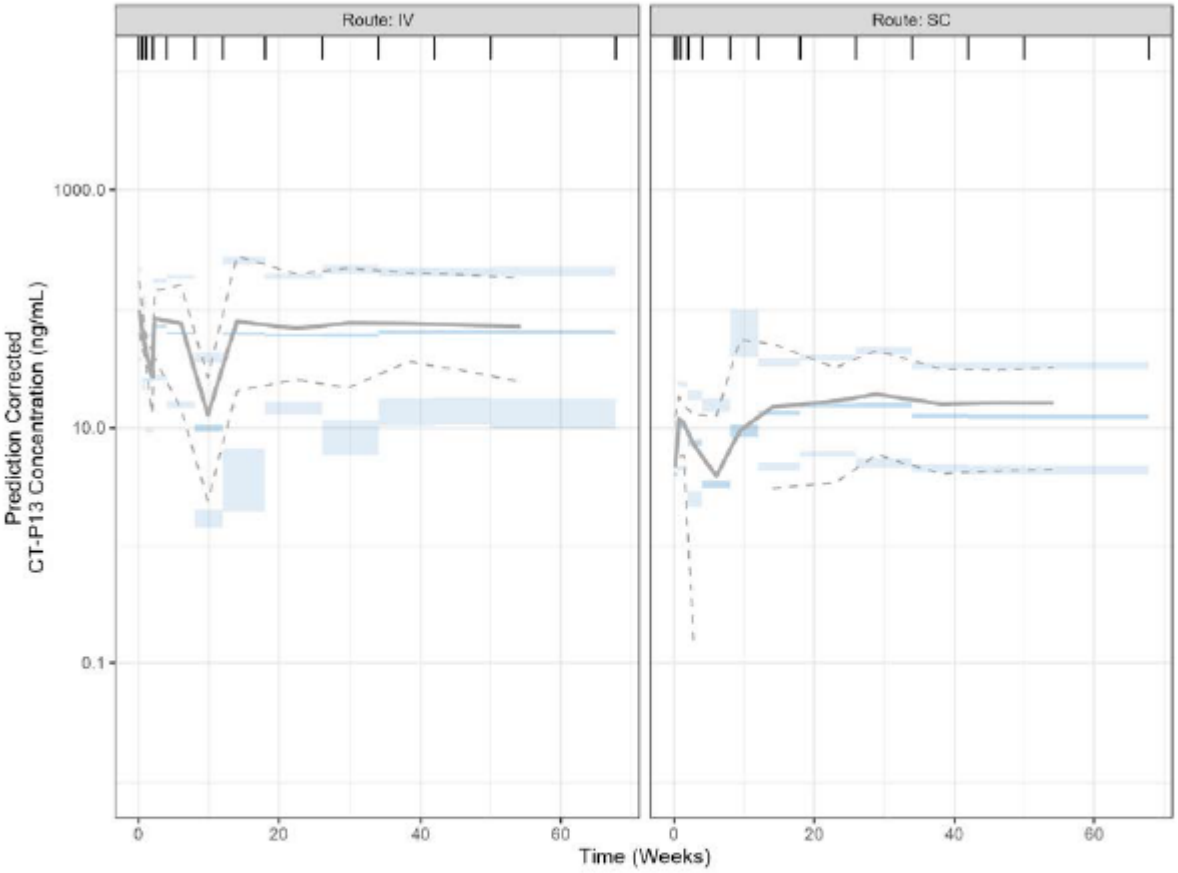
CWRES=conditional weighted residual; SC=subcutaneous; IV=intravenous

Figure 9. pcVPC Plot: Time after Last Dose (Run5102; Individual Observations Omitted for Clarity)



The median prediction corrected observed concentrations are represented by a grey solid line. The 5th and 95th percentiles of the prediction corrected observed concentrations are represented by dashed grey lines. The dark blue shaded area represents the 95% confidence intervals of the median of the prediction corrected model predicted data. The light blue shaded areas represents the 95% confidence intervals of the 5th and 95th percentiles of the prediction corrected model predicted data. The pcVPC was obtained from the updated model, including the residual error term. Negative prediction corrected concentrations, associated with the 5th percentile of the last bin, were not able to be represented on this logarithmic presentation.

Figure 10. pcVPC Plot: Time after First Dose, Stratified by Route of Administration (Run5102; Individual Observations Omitted for Clarity)



The median prediction corrected observed concentrations are represented by a grey solid line. The 5th and 95th percentiles of the prediction corrected observed concentrations are represented by dashed grey lines. The dark blue shaded area represents the 95% confidence intervals of the median of the prediction corrected model predicted data. The light blue shaded areas represents the 95% confidence intervals of the 5th and 95th percentiles of the prediction corrected model predicted data. The pcVPC was obtained from the updated model, including the residual error term.
IV=intravenous; SC=subcutaneous

CHMP comments

ADA and NAb were shown to have relevant impact on CL in prior population PK models for CT-P13 and this was confirmed in current analyses. MAH's bioanalytical methods for ADA and NAb have been amended over time and it is appropriate to set the ADA/NAb status for subjects in old studies as unknown. The MAH should confirm that immunogenicity samples (ADA and NAb) from studies CT-P13 1.6, 1.10, 1.11, 3.5, 3.7, and 3.8 were measured using the same methods, or if the methods were not the same that the results of the methods are comparable.

Pre-selected potential covariates were formally tested in univariate analyses during model development. Some of them were statistically significant (based on ΔOFV) but not included in the PK model. MAH's justifications for not including these covariates in the model are considered acceptable. The partial OMEGA block (CL – V1) was added to the model only after testing the covariates. Generally, it is preferable to (re)test covariates after the structural model is finalised. However, it is considered unlikely that this would affect the conclusions of covariate testing and the issue is not pursued.

As noted by the MAH, there is marked deviation in CWRES vs time since last dose plot driven by few data points after > 10 weeks since last dose. A proportional plus additive residual error model might describe the data better than the proportional model.

The current population PK model appears to have significant model misspecifications according to the pcVPCs stratified by route of administration (Figure 6.2.2.9) which should be addressed by the Applicant. The below issues are considered critical in case a modelling and simulation approach is utilized to support a dosing regimen that has not been tested in clinical studies.

a) The median profile for the observed data is not adequately described by the model predictions. Infliximab may have non-linear PK with respect to dose/concentration and/or time (i.e., target-mediated drug disposition) which is not accounted for. The Applicant should address this limitation by exploring model(s) for non-linear PK and update the final model as appropriate.

b) The variability (i.e., outer percentiles) is over-predicted for the IV route and under-predicted for the SC route, which is problematic considering that the Applicant propose to use the PK model to support a new SC induction regimen. Potential differences in variability between IV and SC is an important aspect for assessing the new SC induction regimen. The SC dosing may display higher variability than IV due to variability in rate and extent of absorption from the subcutaneous injection site. The Applicant should resolve the misspecification in variability, for example by exploring inter-individual variability in KA and/or F and update the SC induction regimen predictions.

The provided pcVPC plots are not sufficient. The scope of the current variation application is to add induction regimen for Remsima SC in treatment of CD and UC, i.e., the MAH proposes a new dosing regimen for the first 6 weeks of treatment. Additional pcVPC plots should be provided for the final PK model with x-axis showing 6 weeks after the first dose and 6 weeks after the last dose. Binning should be selected carefully to avoid artefacts in the plots. Plots should be stratified at least by route of administration, SC dose, immunogenic response (unknown/no/yes), and separate plots should be provided for patients with CD and UC (stratified by route of administration).

Updated comments (RSI AR)

The Applicant withdrew this part of the grouped variation application after the first RSI and corresponding changes are no longer proposed to the PI. The questions above are no longer relevant.

PK simulations

The aim of these simulations was to support the development of an SC induction posology in patients with UC and CD (i.e., SC dosing over the first 6 weeks of treatment).

Simulations were performed in virtual subjects of body weights 50 to 150 kg (in stratifications of 10 kg). A virtual population of 1000 patients was obtained from a uniform distribution in each of the ten 10 kg categories, ranging from 50 kg to 150 kg (total number of virtual patients = 10,000). Simulations were performed using the final population PK model assuming perfect adherence to the planned treatment regimen, for 14 weeks. All simulations included unexplained IIV but did not include parameter uncertainty or residual error.

Exposure to CT-P13 following administration of four Test SC induction regimens (Scenarios A – D; Table 6.2.2.6) was compared to that obtained following administration of the approved IV treatment regimen (Reference; Table 16). The analyses were stratified to explore the effect of body weight (in 10 kg strata) on exposure to CT-P13.

Table 17. Simulated Test and Reference Dose Regimen Scenarios

Scenario	Week						
	0	1	2	3	4	6	8 to 14
Scenario A	240 mg	-	240 mg	-	240 mg	120 mg	120 mg Q2W
Scenario B	240 mg	120 mg	120 mg	120 mg	120 mg	120 mg	120 mg Q2W
Scenario C	240 mg	240 mg	240 mg	120 mg	120 mg	120 mg	120 mg Q2W
Scenario D	240 mg	240 mg	240 mg	240 mg	120 mg	120 mg	120 mg Q2W
Reference	5 mg/kg IV	-	5 mg/kg IV	-	-	5 mg/kg IV	-

Simulated concentration-time curves of CT-P13 for Weeks 0-6 following administration of each of the Test Scenarios, superimposed on the Reference, are presented in Figure 6.2.2.10 (weight range 50 to 150 kg, N=10,000). Summary statistics for PK parameters AUC, C_{trough}, and C_{max} for the Test Scenarios and the Reference are presented in Tables 6.2.2.7 to 6.2.2.9.

During the induction phase (weeks 0-6 of treatment) the median total exposure, as evidenced by AUC_{W0-2} and AUC_{W0-6}, was significantly lower for each Test Scenario than for the IV Reference treatment (Table 17, Table 18). As shown in Figure 11, the median CT-P13 concentration for Scenario B was consistently lower compared with that of the Reference Regimen over the first four weeks of treatment, although the C_{trough} levels at Week 2 and 4 are rather close to concentrations of the Reference regimen.

Figure 11. Simulated Median (5th - 95th percentile) CT-P13 Concentration vs Time Profiles Following Administration of Test Scenario A, B, C, D and Reference Regimen for Weeks 0-6.

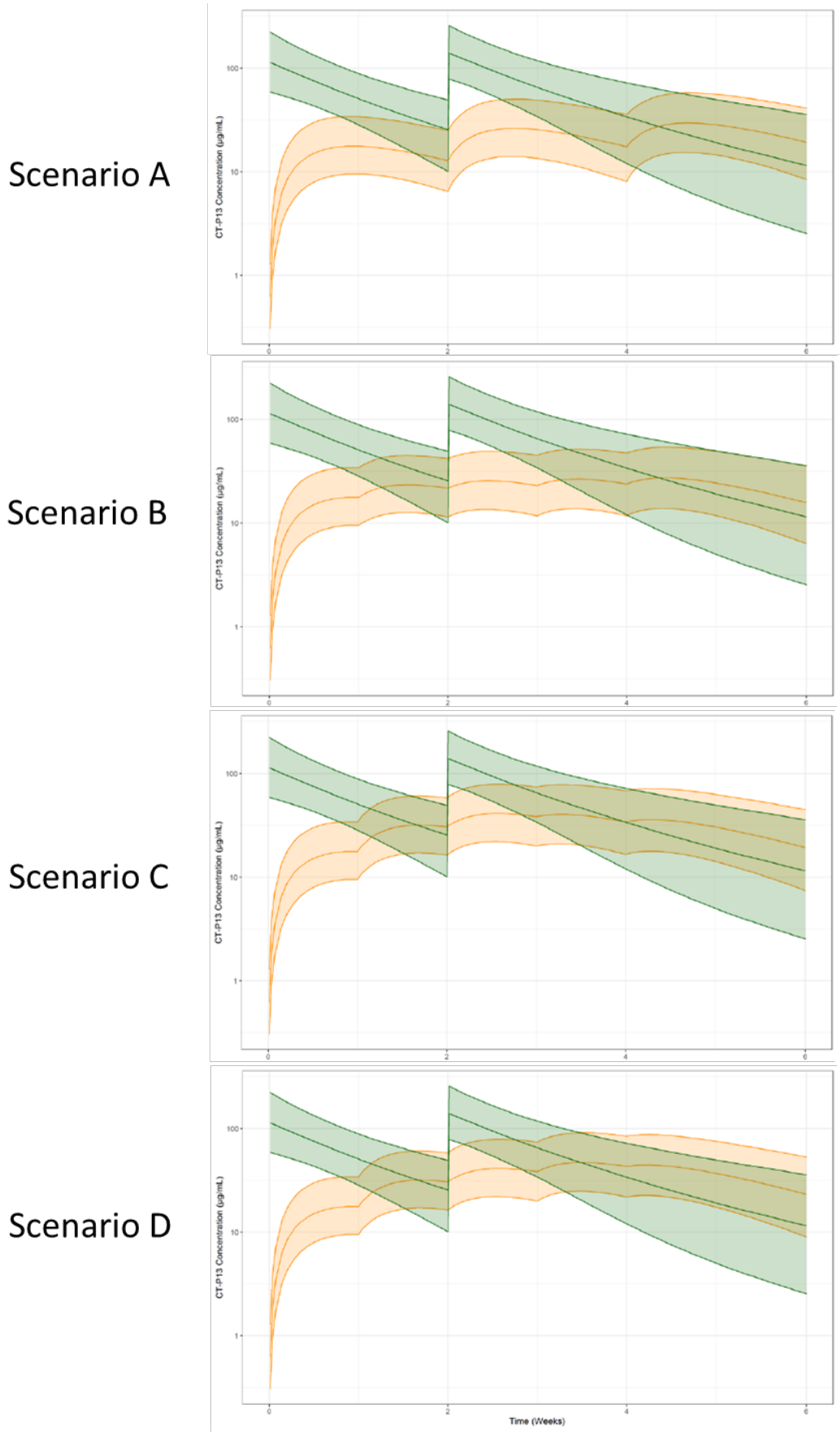


Table 18. . Summary Statistics [Median (5^{th} – 95^{th} Percentile)] of AUC Following Administration of Test Scenario and Reference Regimens.

Treatment Regimen	AUC (µg.h/mL)			
	AUC_{W0-2}	AUC_{W0-6}	AUC_{W0-14}	AUC_{W6-14}
Scenario A	4840 (2610 - 9280)	21000 (11000 - 40900)	42900 (21200 - 87200)	21800 (10100 - 47300)
Scenario B	5930 (3200 - 11400)	22200 (11500 - 43200)	43000 (21200 - 87400)	20700 (9600 - 44900)
Scenario C	7030 (3790 - 13600)	30000 (15600 - 58500)	52300 (25700 - 107000)	22000 (9930 - 49500)
Scenario D	7030 (3790 - 13600)	33300 (17300 - 64900)	56900 (28000 - 117000)	23300 (10400 - 53200)
Reference	19200 (11100 - 33600)	50700 (27700 - 91100)	83100 (43400 - 158000)	32200 (15700 - 68000)

Scenario A: CT-P13 240 mg SC at Weeks 0, 2, and 4, followed by CT-P13 120 mg SC Q2W from Week 6
Scenario B: CT-P13 240 mg SC at Week 0, followed by CT-P13 120 mg SC at Weeks 1, 2 and 3, followed by CT-P13 120 mg SC Q2W from Week 4
Scenario C: CT-P13 240 mg SC at Weeks 0, 1, and 2, followed by CT-P13 120 mg SC at Week 3, followed by CT-P13 120 mg SC Q2W from Week 4
Scenario D: CT-P13 240 mg SC at Weeks 0, 1, 2 and 3, followed by CT-P13 120 mg SC Q2W from Week 4
Reference: CT-P13 5 mg/kg IV at Weeks 0, 2 and 6.
AUC: area under the concentration versus time curve; **AUC_{W0-2}**: AUC between Weeks 0 and 2; **AUC_{W0-6}**: AUC between Weeks 0 and 6; **AUC_{W0-14}**: AUC between Weeks 0 and 14; **AUC_{W6-14}**: AUC between Weeks 6 and 14.
IV: intravenous; **SC**: subcutaneous; **Q2W**: dosing every two weeks

Table 19. Summary Statistics [Median (5^{th} – 95^{th} Percentile)] of C_{trough} Following Administration of Test Scenario and Reference Regimens.

Treatment Regimen	C_{trough} (µg/mL)					
	$C_{trough,W1}$	$C_{trough,W2}$	$C_{trough,W3}$	$C_{trough,W4}$	$C_{trough,W6}$	$C_{trough,W14}$
Scenario A	n/a	12.9 (6.45 - 25.1)	n/a	17.5 (8.01 - 35.9)	19.2 (8.42 - 41.0)	10.7 (4.38 - 25.4)
Scenario B	17.7 (9.51 - 34.0)	21.7 (11.5 - 41.7)	23.1 (11.7 - 45.2)	23.8 (11.8 - 47.4)	15.7 (6.35 - 35.4)	10.6 (4.36 - 25.1)
Scenario C	17.7 (9.51 - 34.0)	30.6 (16.4 - 58.4)	38.3 (20.0 - 74.2)	34.1 (16.6 - 68.1)	19.4 (7.41 - 45.0)	10.8 (4.38 - 26.0)
Scenario D	17.7 (9.51 - 34.0)	30.6 (16.4 - 58.4)	38.3 (20.0 - 74.2)	43.0 (21.9 - 84.4)	23.2 (8.97 - 53.2)	10.9 (4.40 - 26.6)
Reference	n/a	25.5 (10.1 - 49.5)	n/a	n/a	11.5 (2.54 - 35.8)	2.00 (0.303 - 11.2)

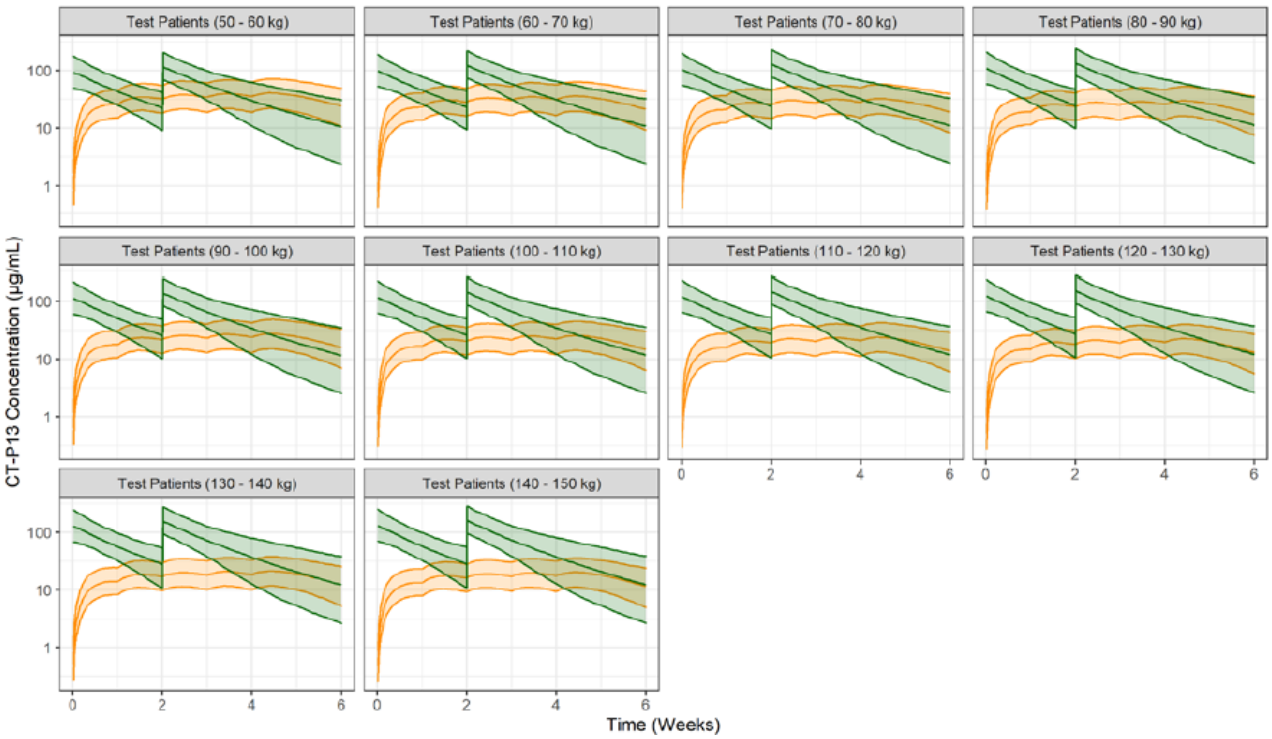
Scenario A: CT-P13 240 mg SC at Weeks 0, 2, and 4, followed by CT-P13 120 mg SC Q2W from Week 6
Scenario B: CT-P13 240 mg SC at Week 0, followed by CT-P13 120 mg SC at Weeks 1, 2 and 3, followed by CT-P13 120 mg SC Q2W from Week 4
Scenario C: CT-P13 240 mg SC at Weeks 0, 1, and 2, followed by CT-P13 120 mg SC at Week 3, followed by CT-P13 120 mg SC Q2W from Week 4
Scenario D: CT-P13 240 mg SC at Weeks 0, 1, 2 and 3, followed by CT-P13 120 mg SC Q2W from Week 4
Reference: CT-P13 5 mg/kg IV at Weeks 0, 2 and 6.
C_{trough}: trough concentration; **$C_{trough,W1}$**: C_{trough} at Week 1; **$C_{trough,W2}$**: C_{trough} at Week 2; **$C_{trough,W3}$**: C_{trough} at Week 3; **$C_{trough,W4}$**: C_{trough} at Week 4; **$C_{trough,W6}$**: C_{trough} at Week 6; **$C_{trough,W14}$**: C_{trough} at Week 14.
IV: intravenous; **SC**: subcutaneous; **Q2W**: dosing every two weeks; **n/a**: not applicable

Table 20. Summary Statistics [Median (5^{th} – 95^{th} Percentile)] of C_{max} Following Administration of Test Scenario and Reference Regimens.

Treatment Regimen	C_{max} (µg/mL)						
	$C_{max,W0}$	$C_{max,W1}$	$C_{max,W2}$	$C_{max,W3}$	$C_{max,W4}$	$C_{max,W6}$	$C_{max,W12}$
Scenario A	18.0 (9.70 - 34.5)	n/a	26.4 (14.2 - 50.7)	n/a	29.7 (15.5 - 58.0)	22.8 (11.1 - 46.9)	16.7 (8.19 - 35.0)
Scenario B	17.8 (9.62 - 34.4)	23.6 (12.8 - 45.2)	25.7 (13.6 - 49.5)	26.6 (13.8 - 52.0)	27.3 (13.9 - 54.0)	20.1 (9.62 - 42.0)	16.6 (8.15 - 34.6)
Scenario C	17.8 (9.62 - 34.4)	32.0 (17.3 - 61.4)	41.4 (22.3 - 79.3)	40.4 (21.0 - 78.4)	35.9 (17.8 - 71.5)	23.0 (10.5 - 49.7)	16.8 (8.21 - 35.8)
Scenario D	17.8 (9.62 - 34.4)	32.0 (17.3 - 61.4)	41.4 (22.3 - 79.3)	47.3 (24.9 - 91.6)	44.5 (22.7 - 87.5)	26.0 (11.7 - 56.9)	17.0 (8.25 - 36.7)
Reference	113 (58.8 - 223)	n/a	140 (78.6 - 258)	n/a	n/a	127 (71.0 - 241)	n/a

Scenario A: CT-P13 240 mg SC at Weeks 0, 2, and 4, followed by CT-P13 120 mg SC Q2W from Week 6
Scenario B: CT-P13 240 mg SC at Week 0, followed by CT-P13 120 mg SC at Weeks 1, 2 and 3, followed by CT-P13 120 mg SC Q2W from Week 4
Scenario C: CT-P13 240 mg SC at Weeks 0, 1, and 2, followed by CT-P13 120 mg SC at Week 3, followed by CT-P13 120 mg SC Q2W from Week 4
Scenario D: CT-P13 240 mg SC at Weeks 0, 1, 2 and 3, followed by CT-P13 120 mg SC Q2W from Week 4
Reference: CT-P13 5 mg/kg IV at Weeks 0, 2 and 6.
C_{max}: maximum concentration; **$C_{max,W0}$**: C_{max} after dosing at Week 0; **$C_{max,W1}$**: C_{max} after dosing at Week 1; **$C_{max,W2}$**: C_{max} after dosing at Week 2; **$C_{max,W3}$**: C_{max} after dosing at Week 3; **$C_{max,W4}$**: C_{max} after dosing at Week 4; **$C_{max,W6}$**: C_{max} after dosing at Week 6; **$C_{max,W12}$**: C_{max} after dosing at Week 12.
IV: intravenous; **SC**: subcutaneous; **Q2W**: dosing every two weeks; **n/a**: not applicable

Figure 12. Median (5^{th}-95^{th} Percentiles) Simulated CT-P13 Concentration vs Time Profiles Following Administration of Test Scenario B and Reference Regimens (Week 0-6), by 10 kg Weight Strata.



Test Scenario B (orange): CT-P13 240 mg SC at Week 0, followed by CT-P13 120 mg SC at Weeks 1, 2 and 3, followed by CT-P13 120 mg SC Q2W from Week 4.
Reference (green): CT-P13 5 mg/kg IV at Weeks 0, 2 and 6.
IV: intravenous; **SC**: subcutaneous; **Q2W**: dosing every two weeks.

Table 21. Geometric Mean Ratio and Associated 90% Confidence Intervals of AUC: Scenario B Versus Reference Regimen, by Body Weight.

Weight Strata	Geometric Mean Ratio and Associated 90% Confidence Interval			
	AUC_{W0-2}	AUC_{W0-6}	AUC_{W0-14}	AUC_{W6-14}
All Patients (50 - 150 kg)	0.311 (0.308 - 0.314)	0.439 (0.435 - 0.443)	0.518 (0.513 - 0.523)	0.641 (0.634 - 0.648)
Patients (50 - 60 kg)	0.538 (0.525 - 0.551)	0.761 (0.742 - 0.780)	0.898 (0.874 - 0.923)	1.11 (1.08 - 1.15)
Patients (60 - 70 kg)	0.456 (0.445 - 0.467)	0.645 (0.629 - 0.661)	0.761 (0.740 - 0.782)	0.940 (0.911 - 0.970)
Patients (70 - 80 kg)	0.395 (0.386 - 0.405)	0.559 (0.545 - 0.573)	0.659 (0.642 - 0.678)	0.816 (0.791 - 0.842)
Patients (80 - 90 kg)	0.349 (0.341 - 0.358)	0.494 (0.481 - 0.506)	0.582 (0.566 - 0.598)	0.720 (0.698 - 0.743)
Patients (90 - 100 kg)	0.313 (0.306 - 0.320)	0.442 (0.431 - 0.453)	0.521 (0.507 - 0.536)	0.645 (0.625 - 0.666)
Patients (100 - 110 kg)	0.283 (0.277 - 0.290)	0.400 (0.390 - 0.410)	0.472 (0.459 - 0.485)	0.584 (0.566 - 0.603)
Patients (110 - 120 kg)	0.259 (0.253 - 0.265)	0.366 (0.356 - 0.375)	0.431 (0.419 - 0.443)	0.534 (0.517 - 0.551)
Patients (120 - 130 kg)	0.239 (0.233 - 0.244)	0.336 (0.328 - 0.345)	0.396 (0.386 - 0.408)	0.491 (0.476 - 0.507)
Patients (130 - 140 kg)	0.221 (0.216 - 0.226)	0.312 (0.304 - 0.320)	0.367 (0.357 - 0.377)	0.455 (0.441 - 0.470)
Patients (140 - 150 kg)	0.206 (0.201 - 0.211)	0.290 (0.283 - 0.298)	0.342 (0.333 - 0.352)	0.424 (0.411 - 0.437)

Scenario B: CT-P13 240 mg SC at Week 0, followed by CT-P13 120 mg SC at Weeks 1, 2 and 3, followed by CT-P13 120 mg SC Q2W from Week 4. **Reference**: CT-P13 5 mg/kg IV at Weeks 0, 2 and 6.
AUC: area under the concentration versus time curve; **AUC_{W0-2}**: AUC between Weeks 0 and 2; **AUC_{W0-6}**: AUC between Weeks 0 and 6; **AUC_{W0-14}**: AUC between Weeks 0 and 14; **AUC_{W6-14}**: AUC between Weeks 6 and 14.
IV: intravenous; **SC**: subcutaneous; **Q2W**: dosing every two weeks

Table 22. Geometric Mean Ratio and Associated 90% Confidence Intervals of C_{trough}: Scenario B Versus Reference Regimen, by Body Weight.

Weight Strata	Geometric Mean Ratio and Associated 90% Confidence Interval		
	$C_{trough,W2}$	$C_{trough,W6}$	$C_{trough,W14}$
All Patients (50 - 150 kg)	0.898 (0.889 - 0.907)	1.43 (1.41 - 1.46)	5.41 (5.30 - 5.51)
Patients (50 - 60 kg)	1.51 (1.47 - 1.56)	2.40 (2.29 - 2.52)	8.52 (8.01 - 9.06)
Patients (60 - 70 kg)	1.29 (1.25 - 1.33)	2.05 (1.96 - 2.15)	7.42 (6.97 - 7.89)
Patients (70 - 80 kg)	1.13 (1.09 - 1.16)	1.80 (1.71 - 1.89)	6.59 (6.20 - 7.01)
Patients (80 - 90 kg)	1.00 (0.973 - 1.03)	1.60 (1.52 - 1.68)	5.95 (5.59 - 6.33)
Patients (90 - 100 kg)	0.903 (0.876 - 0.931)	1.44 (1.37 - 1.51)	5.43 (5.10 - 5.78)
Patients (100 - 110 kg)	0.822 (0.797 - 0.848)	1.31 (1.25 - 1.38)	5.00 (4.70 - 5.33)
Patients (110 - 120 kg)	0.755 (0.732 - 0.778)	1.21 (1.15 - 1.27)	4.65 (4.36 - 4.95)
Patients (120 - 130 kg)	0.698 (0.676 - 0.720)	1.12 (1.06 - 1.18)	4.34 (4.08 - 4.62)
Patients (130 - 140 kg)	0.649 (0.629 - 0.670)	1.04 (0.991 - 1.09)	4.08 (3.83 - 4.34)
Patients (140 - 150 kg)	0.607 (0.588 - 0.626)	0.975 (0.928 - 1.02)	3.85 (3.61 - 4.10)

Scenario B: CT-P13 240 mg SC at Week 0, followed by CT-P13 120 mg SC at Weeks 1, 2 and 3, followed by CT-P13 120 mg SC Q2W from Week 4. **Reference**: CT-P13 5 mg/kg IV at Weeks 0, 2 and 6.
C_{trough}: trough concentration; **$C_{trough,W2}$**: C_{trough} at Week 2; **$C_{trough,W6}$**: C_{trough} at Week 6; **$C_{trough,W14}$**: C_{trough} at Week 14. **IV**: intravenous; **SC**: subcutaneous; **Q2W**: dosing every two weeks

Table 23. Geometric Mean Ratio and Associated 90% Confidence Intervals of C_{max}: Scenario B Versus Reference Regimen, by Body Weight.

Weight Strata	Geometric Mean Ratio and Associated 90% Confidence Interval		
	$C_{max,W0}$	$C_{max,W2}$	$C_{max,W6/12}$
All Patients (50 - 150 kg)	0.158 (0.156 - 0.159)	0.183 (0.181 - 0.185)	0.130 (0.128 - 0.131)
Patients (50 - 60 kg)	0.279 (0.272 - 0.287)	0.325 (0.317 - 0.334)	0.233 (0.227 - 0.240)
Patients (60 - 70 kg)	0.235 (0.229 - 0.241)	0.273 (0.267 - 0.280)	0.195 (0.190 - 0.201)
Patients (70 - 80 kg)	0.202 (0.197 - 0.208)	0.236 (0.230 - 0.242)	0.168 (0.163 - 0.172)
Patients (80 - 90 kg)	0.178 (0.173 - 0.183)	0.207 (0.202 - 0.212)	0.147 (0.143 - 0.151)
Patients (90 - 100 kg)	0.159 (0.154 - 0.163)	0.184 (0.180 - 0.189)	0.131 (0.127 - 0.134)
Patients (100 - 110 kg)	0.143 (0.139 - 0.147)	0.166 (0.162 - 0.170)	0.117 (0.114 - 0.121)
Patients (110 - 120 kg)	0.130 (0.127 - 0.134)	0.151 (0.147 - 0.155)	0.107 (0.104 - 0.109)
Patients (120 - 130 kg)	0.119 (0.116 - 0.123)	0.139 (0.135 - 0.142)	0.0975 (0.0949 - 0.100)
Patients (130 - 140 kg)	0.110 (0.107 - 0.113)	0.128 (0.125 - 0.131)	0.0898 (0.0874 - 0.0923)
Patients (140 - 150 kg)	0.102 (0.0997 - 0.105)	0.119 (0.116 - 0.122)	0.0833 (0.0811 - 0.0856)

Scenario B: CT-P13 240 mg SC at Week 0, followed by CT-P13 120 mg SC at Weeks 1, 2 and 3, followed by CT-P13 120 mg SC Q2W from Week 4. **Reference**: CT-P13 5 mg/kg IV at Weeks 0, 2 and 6.
C_{max}: maximum concentration; **$C_{max,W0}$**: C_{max} after dosing at Week 0; **$C_{max,W2}$**: C_{max} after dosing at Week 2; **$C_{max,W6/12}$**: C_{max} after dosing at Week 6 (Reference regimen) in comparison with Week 12 (Test Regimen);
IV: intravenous; **SC**: subcutaneous; **Q2W**: dosing every two weeks

CHMP comments

SC maintenance dosing (120 mg Q2W) starting at Week 6 is already approved for Remsima in treatment of CD and UC. Therefore, the main issue for the current variation application is whether the MAH can exclude the possibility of worsening of efficacy and safety during the first 6 weeks of treatment with the proposed SC induction dosing regimen (Scenario B: 240 mg SC at Week 0, followed by 120 mg SC at Weeks 1, 2 and 3, followed by 120 mg SC Q2W from Week 4).

As shown in Figure 6.2.2.10 and Tables 6.2.2.7 to 6.2.2.9, the simulated concentration-time profiles and exposure parameters (C_{trough}, AUC, C_{max}) over the first 6 weeks are markedly different between the approved IV dosing regimen and the proposed SC dosing regimen (Scenario B: 240 mg SC at Week 0, followed by 120 mg SC at Weeks 1, 2 and 3, followed by 120 mg SC Q2W from Week 4).

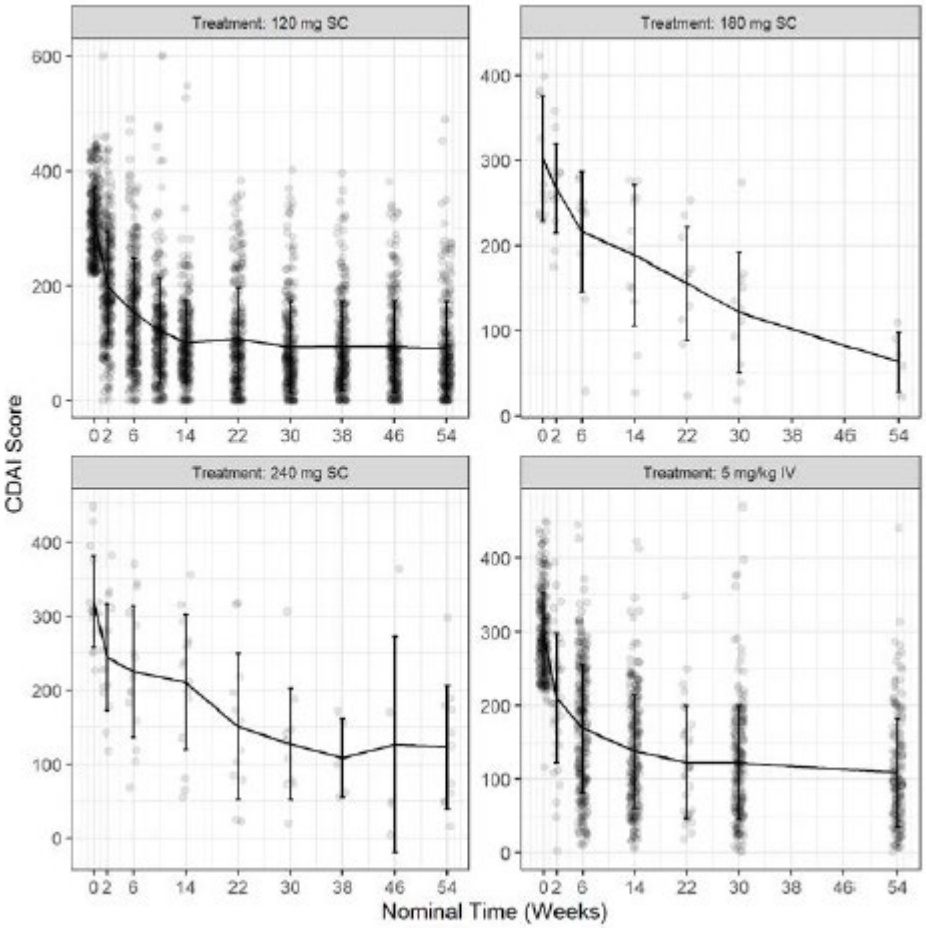
In addition, if there is a change from body weight based IV dose (5 mg/kg) to a flat SC dose (120 mg) patients with high body weight will have lower exposure than patients with low body weight (see Figure 6.2.2.11 and Tables 6.2.2.10 to 6.2.2.12).

6.2.3. Population PK-PD modelling and simulations

PK-PD model for CDAI score

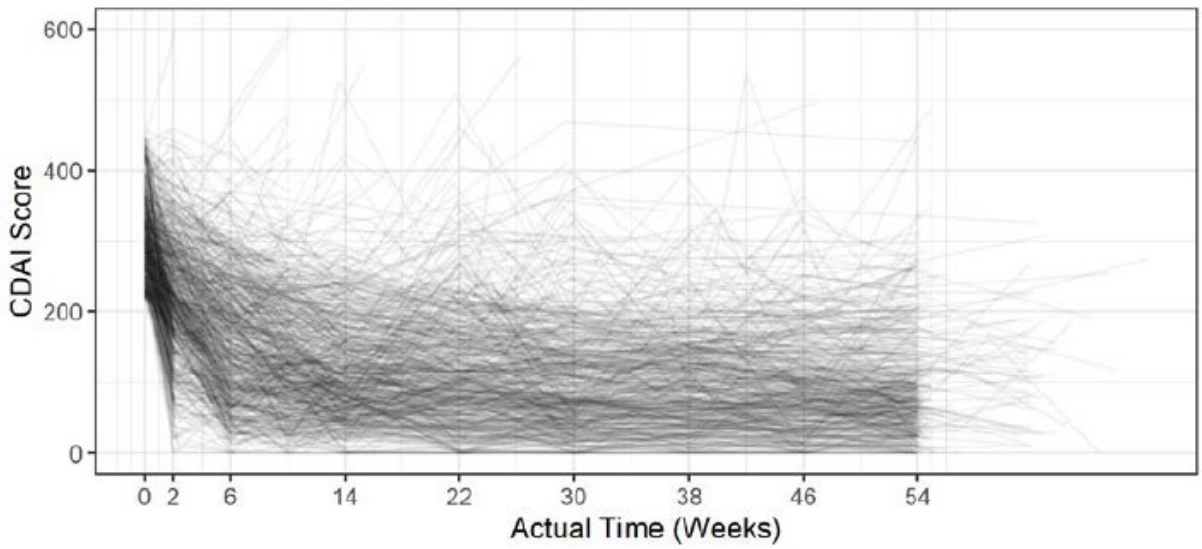
The observed CDAI scores, stratified by maintenance dosing regimen, are presented in Figure 14. The induction regimen (initial 2 or 3 doses) was administered intravenously in each study. The mean CDAI score decreased rapidly over the first 1 to 2 months (i.e., during the induction treatment with IV infliximab) and tended to plateau at approximately Week 14. However, individual CDAI scores fluctuated markedly over time (Figure 15).

Figure 13. . Observed Individual and Mean (± SD) CDAI Score Versus Nominal Time Since First Dose Profiles, Stratified by Maintenance Dosing Regimen.



"Treatment" indicates the maintenance dosing regimen administered after the IV induction phase. Observed data are presented as a jitter plot for ease of visualization.
CDAI=Crohn's disease activity index; **IV**=intravenous (Q8W maintenance regimen);
SC=subcutaneous (Q2W maintenance regimen).

Figure 14. Individual CDAI Scores Versus Actual Time Since First Dose Profiles (All Patients)

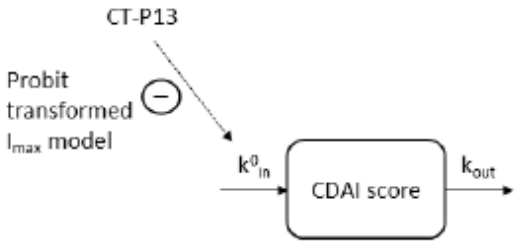


Model development: The CDAI score was characterized by an indirect response model wherein a probit transformed inhibitory I_{max} model was used to describe the suppressive effect of CT-P13 on the zero-order rate constant of CDAI score production (k_{in}) while the baseline CDAI score was defined as the ratio of k_{in} to the first order rate constant of the amelioration of CDAI score (k_{out}). Model structure is shown in Figure 15.

Figure 15. Equations and Model Diagram: Population PK-PD Model of CDAI Score.

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

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



where k^0_{in} = Baseline CDAI score (R0) * k_{out}

$$k_{out,i} = \theta_{kout}$$

$$Baseline\ CDAI\ score_i = \theta_{BASE} \cdot exp^{\eta BASE}$$

$$I_{max,i} = \Phi(\theta_{Imax} + \eta_{Imax})$$

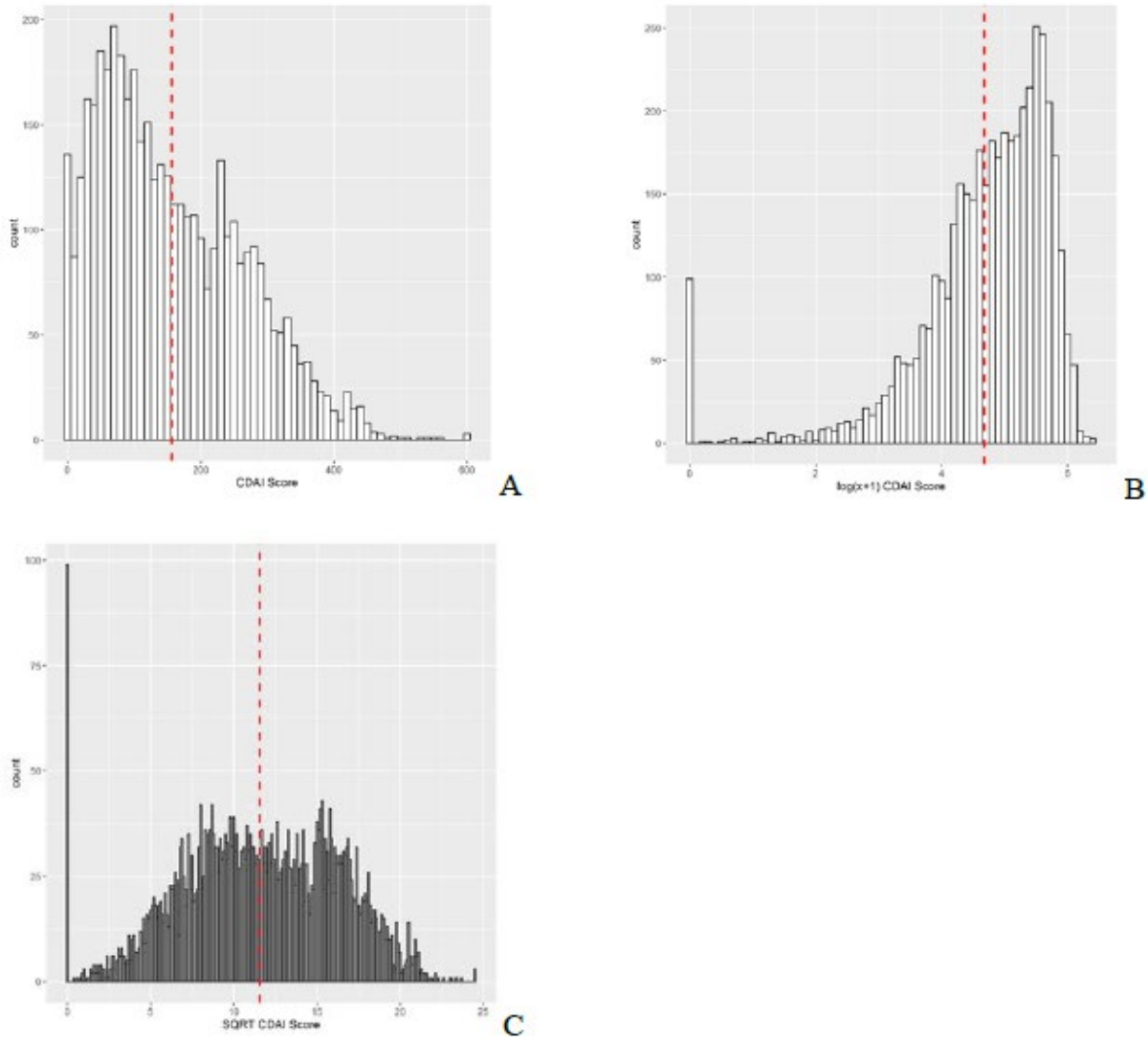
$$IC_{50,i} = \theta_{IC50}$$

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 i^{th} individual; Φ: cumulative distribution function of the normal distribution; θ_x typical value of the x^{th} parameter; η_x: Inter-individual random effects for the x^{th} parameter.

Initially, the model was applied to untransformed CDAI score data (Run6001). Data driven optimization of the random effects model was performed, resulting in model which included IIV for baseline CDAI score and in the probit transformed I_{max}, with correlation between the unexplained IIV in baseline CDAI score and I_{max} implemented via an off-diagonal element of the OMEGA block and an additive residual error (Run6011). However, VPCs indicated that the candidate model Run6011 was not acceptable (overprediction of the central tendency and underprediction at the 5^{th} percentile).

The untransformed CDAI score data had a positively skewed distribution (Figure 16 A). To improve the description of the CDAI score data, the data was transformed. Initially, a log(x+1) transformation was applied, but problems with skewness (Figure 16 B) and model performance were not solved. Subsequently, the square root transformation of the CDAI score was used, which pushed the data closer to a normal distribution (Figure 6.2.3.4, C), albeit with a zero value inflation. The model was applied to the square root transformed CDAI score data with exclusion of the zero values (2.3 % of the data) and the random effects structure was optimized, resulting in a model with IIV in baseline CDAI score and I_{max}, and an additive residual error on square root transformed data (Run6028). Finally, zero values were reincluded in the analysis (Run6044), without affecting the estimated parameter values. Run6044 was declared the final base model. Parameter estimates obtained from Run6044 are summarized in Table 23. Bootstrap estimates were in close agreement with the final model parameter estimates.

Figure 16. A Distribution of untransformed and transformed CDAI Scores.



A: untransformed data; **B:** log(x+1) transformed data; **C:** square root transformed data.

Table 24. Parameter Estimates: Population PK-PD model of CDAI Score (Run6044)

Parameter	Parameter Value	RSE [(c)] (%)	Shrinkage (%)	Parameter Value (Original Scale)
Baseline CDAI Score	5.69	0.175	n/a	296
k_{out} (/hr)	-6.30	1.50	n/a	0.00184
I_{max}	0.351	8.68	n/a	0.637
IC_{50} (µg/mL)	-50.5	12.2	n/a	1.17×10^{-22}
Additive Residual Error (SD)	-2.74	2.15	n/a	7.50
Unexplained IIV in Baseline CDAI Score [VAR (CV%)] [(a)]	0.0106 (10.3)	44.6	60.4	n/a
Unexplained IIV in I_{max} [VAR (CV%)] [(b)]	0.468 (68.4)	8.27	14	n/a

Parameter units are those associated with the original scale.
[(a)] CV% = $\sqrt{(\exp(\omega^2)-1)*100}$ [(b)] CV% = $\sqrt{\omega^2*100}$ [(c)] RSE of the IIV parameters relate to the untransformed parameter
CV=coefficient of variation; IIV=interindividual variability; IC_{50}=drug concentration that produces 50% of maximum inhibition; I_{max}=maximum fractional ability of the drug to affect baseline CDAI score; k_{out}=first-order rate constant for the amelioration of response; n/a=not applicable; RSE=relative standard error; SD=standard deviation; VAR=variance

Exploratory graphical analysis suggested no strong relationship between the potential covariates (baseline CDAI score, age, albumin, disease duration, gender, race, and concomitant treatment with 6-mercaptopurine, azathioprine, and methotrexate) and IIV in I_{max}. Subsequent model based assessment of selected covariate effects was conducted (Table 24); none of the covariates were considered clinically relevant by the MAH. Hence, Run6044 was retained as the final PK-PD model for CDAI score.

Table 25. . Summary of tested covariate models: PK-PD model for CDAI score.

Description	ΔOFV	MAH's comment
univariate analysis: Age on I_{max}	-13.609	Moderate impact at high values of AGE (not really observed in the exploratory plot); limited (2.33%) reduction in variance of ETA; moderate dOFV ~ -13.6; Percentage change in within bioequivalence boundaries. => rejected
univariate analysis: Baseline albumin on I_{max}	-12.751	Moderate impact at high values of baseline albumin (not really observed in the exploratory plot); limited (2.16%) reduction in variance of ETA; moderate dOFV ~ -12.8; Percentage change in within bioequivalence boundaries. => rejected
univariate analysis: Baseline CDAI on I_{max}	-41.106	Moderate impact at high values of baseline CDAI (not really observed in the exploratory plot); 4.46% reduction in variance of ETA; large dOFV ~ -41.1; Percentage change outside bioequivalence boundaries. Variability of BASE moved to covariate effect on Imax, using the baseline twice => rejected
univariate analysis: Race on I_{max}	-0.183	No statistically significant dOFV => rejected

Model update

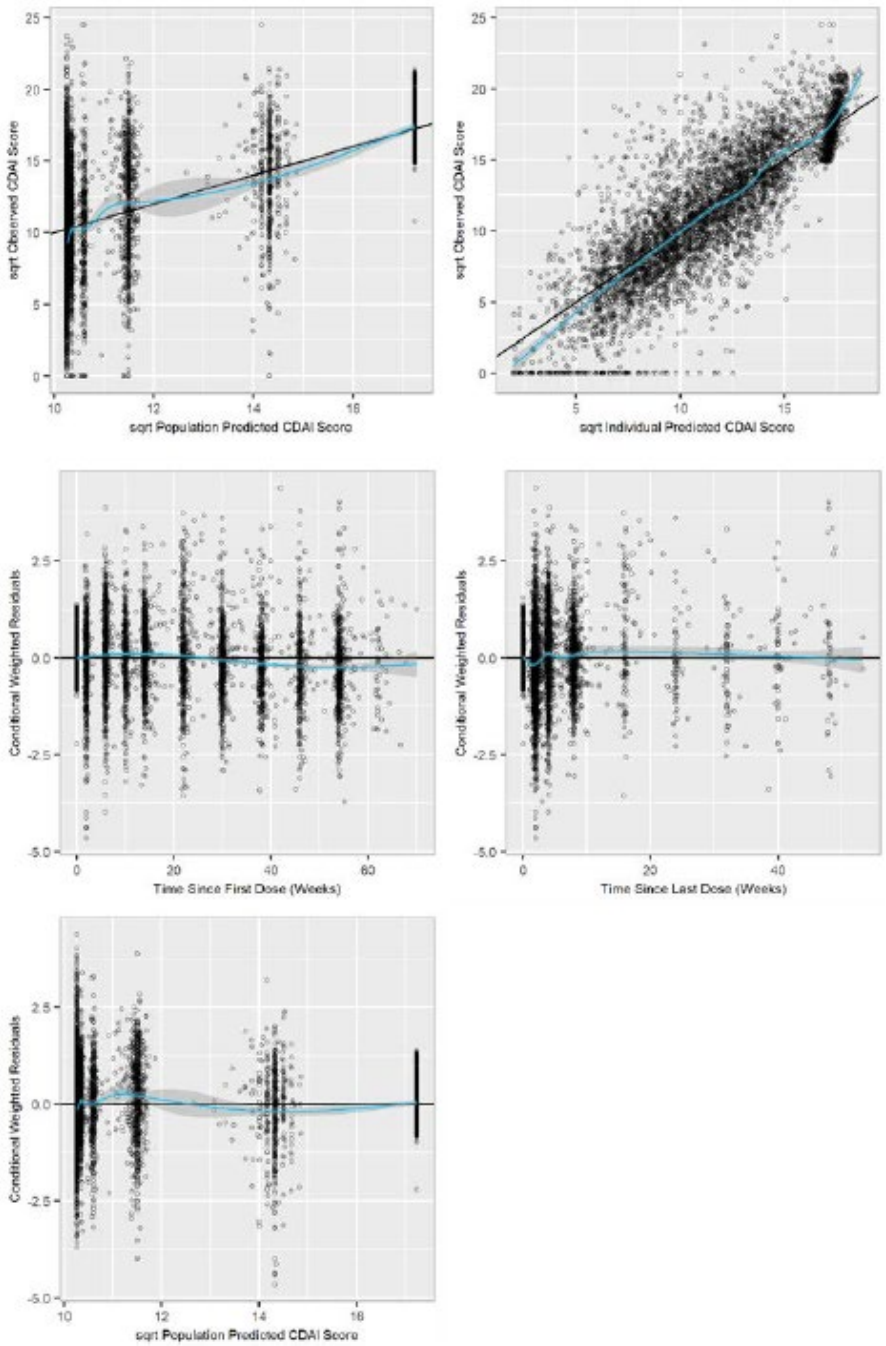
As explained above, the population PK-PD model for CDAI score that was developed using blinded data from study CT-P13 3.8 was updated when unblinded data were available (Run6145). Parameter estimates obtained from Run6145 are summarized in Table 25. GOF plots and pcVPC plots for Run6145 are shown in Figure 17 and Figure 18, respectively.

Table 26. Parameter Estimates: Final Updated PK-PD Model for CDAI Score (Run6145).

Parameter	Parameter Value	RSE [c] (%)	Shrinkage (%)	Parameter Value (Original Scale)
$\log_e$(Baseline CDAI Score)	5.70	0.164	n/a	297
$\log_e(k_{out})$ (/h)	-6.24	1.50	n/a	0.00195
I_{max} [c]	0.376	7.51	n/a	0.647
$\log_e(IC_{50})$ (µg/mL)	-49.2	9.16	n/a	4.29×10^{-22}
Additive Residual Error (SD)	-2.79	1.91	n/a	7.77
Unexplained IIV in Baseline CDAI Score [VAR (CV%)] [a]	0.0104 (10.2)	46.2	61.2	n/a
Unexplained IIV in I_{max} [VAR (CV%)] [b]	0.472 (68.7)	7.72	13.4	n/a

Parameter units are those associated with the original scale.
[a] CV% = $\sqrt{(\exp(\omega^2)-1)*100}$ [b] CV% = $\sqrt{\omega^2*100}$ [c] RSE of the IIV parameters relate to the untransformed parameter [c] probit transformed
CV=coefficient of variation; IIV=interindividual variability; IC_{50}=drug concentration that produces 50% of maximum inhibition; I_{max}=maximum fractional ability of the drug to affect baseline CDAI score; k_{out}=first-order rate constant for the amelioration of response; n/a=not applicable; RSE=relative standard error; SD=standard deviation; VAR=variance

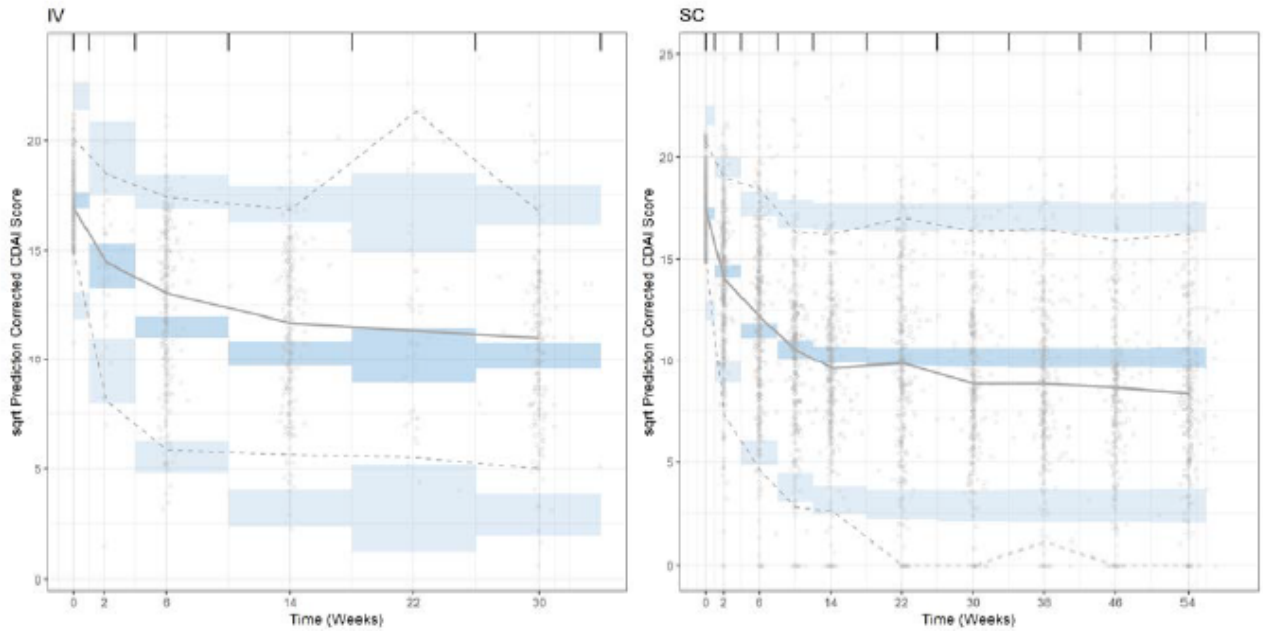
Figure 17. Goodness of Fit Diagnostic Plots: Final Updated PK-PD Model for CDAI Score (Run6145)



Observed data are presented as black open symbols. The line of unity (the expectation) is shown in the solid black line. The blue line and associated grey area reflect a generalized additive smooth of the data, and associated 95% confidence interval.

Note: Plots of CWRES are presented from run6146, which is equivalent to run6145 (see Table 70 for further details)

Figure 18. Prediction Corrected VPC, Stratified by Maintenance Dose Route of Administration (Square Root Transformed): Final Updated PK-PD Model for CDAI Score (Run6145).



Route reflects the maintenance dosing regimens, administered after the IV loading dose phase applicable in each study.

Prediction corrected square root observed CDAI scores are represented by open grey symbols. The median prediction corrected square root observed CDAI scores are represented by a grey solid line. The 5th and 95th percentiles of the prediction corrected square root observed CDAI scores are represented by dashed grey lines. The dark blue shaded area represents the 95% confidence intervals of the median of the prediction corrected model predicted data. The light blue shaded areas represent the 95% confidence intervals of the 5th and 95th percentiles of the prediction corrected model predicted data. The pcVPC was obtained from the updated model, including the additive residual error, resulting in the negative scores returned by the simulation.

IV=intravenous; SC=subcutaneous

CHMP comments

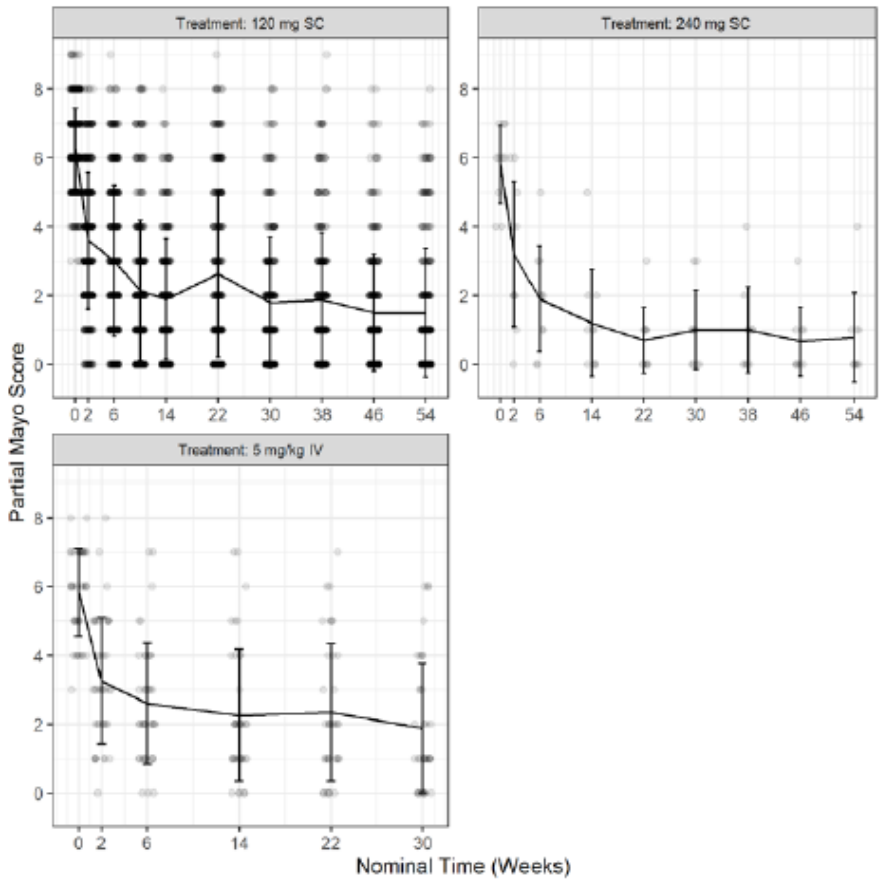
The estimate of IC_{50} of the final PK-PD model for CDAI score is extremely small (4.29×10^{-22} µg/mL; Run6145). For comparison, the lower limit of quantitation (LLOQ) is 1×10^{-1} µg/mL. It is not plausible that 50% of the drug effect is achieved with concentration markedly below the LLOQ. Therefore, the PK-PD model developed by the MAH is not considered adequate to predict the efficacy of an untested infliximab dose regimen in treatment of Crohn's disease. Other aspects of the PK-PD model have not been assessed in detail due to an unplausible crucial parameter estimate.

The Applicant conducted PK-PD simulations for dose regimen Scenarios A, B, C, D, and Reference (see Population PK modelling and simulations for description of the regimens) to support the SC induction posology in patients with Crohn's disease. In brief, the PK-PD model indicated that the clinical response is identical for each Test Scenario and the Reference regimen. This is not surprising because the PK-PD model predicts that maximal response will be achieved if CT-P13 concentration is ≥ LLOQ. Detailed results of the simulations are omitted because the PK-PD model is not considered adequate.

PK-PD model for partial Mayo score

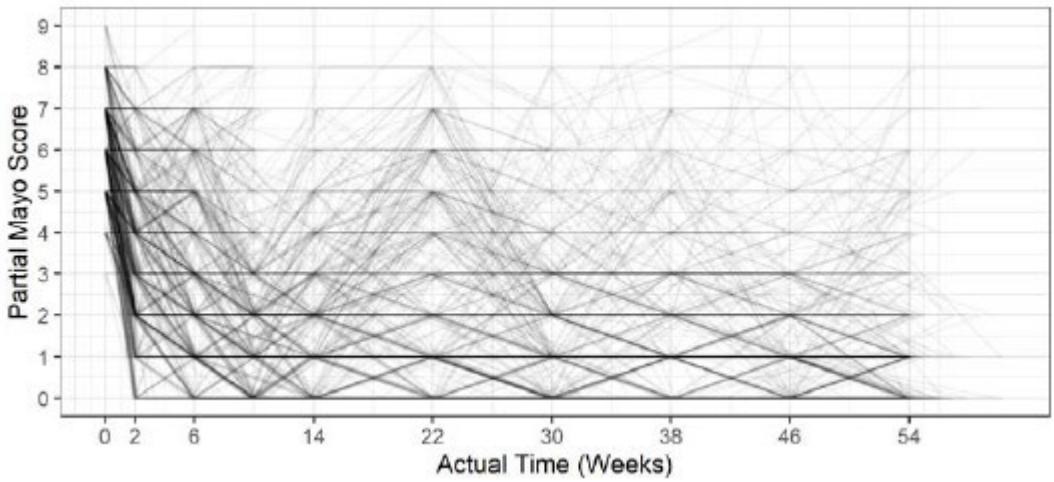
The observed partial Mayo scores, stratified by maintenance dosing regimen, are presented in Figure 19. The induction regimen (initial 2 or 3 doses) was administered intravenously in each study. The mean partial Mayo score decreased rapidly over the first 1 to 2 months (i.e., during the induction treatment with IV infliximab) and tended to plateau at approximately Week 14. However, individual partial Mayo scores fluctuated markedly over time (Figure 20).

Figure 19. Observed Individual and Mean (± SD) Partial Mayo Score Versus Nominal Time Since First Dose Profiles, Stratified by Maintenance Dosing Regimen.



End-of-Study visit data excluded from plot. Observed data (independent variable = planned time) are presented as a jitter plot for ease of visualization.
Treatment reflects the maintenance dosing regimens, administered after the IV loading dose phase applicable in each study.
IV=intravenous; SC=subcutaneous; Q2W=dosing every 2 weeks; Q8W=dosing every 8 weeks

Figure 20. Individual Partial Mayo Scores Versus Actual Time Since First Dose Profiles (All Patients)

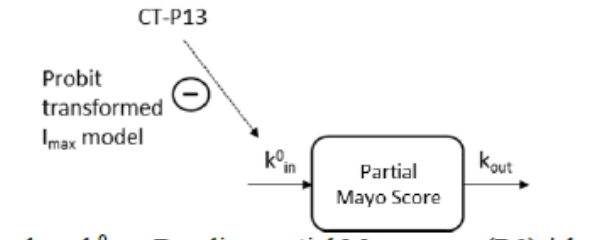


Model development: The partial Mayo score was characterized by an indirect response model wherein a probit transformed inhibitory I_{max} model was used to describe the suppressive effect of CT-P13 on the zero-order rate constant of partial Mayo score production (k_{in}) while the baseline partial Mayo score was defined as the ratio of k_{in} to the first order rate constant of the amelioration of partial Mayo score (k_{out}). Model structure is shown in Figure 21.

Figure 21. . Equations and Model Diagram: Population PK-PD Model of Partial Mayo Score.

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

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



where k^{0}_{in} = Baseline partial Mayo score (R0) * k_{out}

$$k_{out,i} = \theta_{kout} \cdot exp^{\eta kout}$$

$$k_{in,i}^{0} = logit(\theta_{Base}) * k_{out}$$

$$I_{max,i} = \Phi(\theta_{Imax} + \eta_{Imax})$$

$$IC_{50,i} = \theta_{IC50}$$

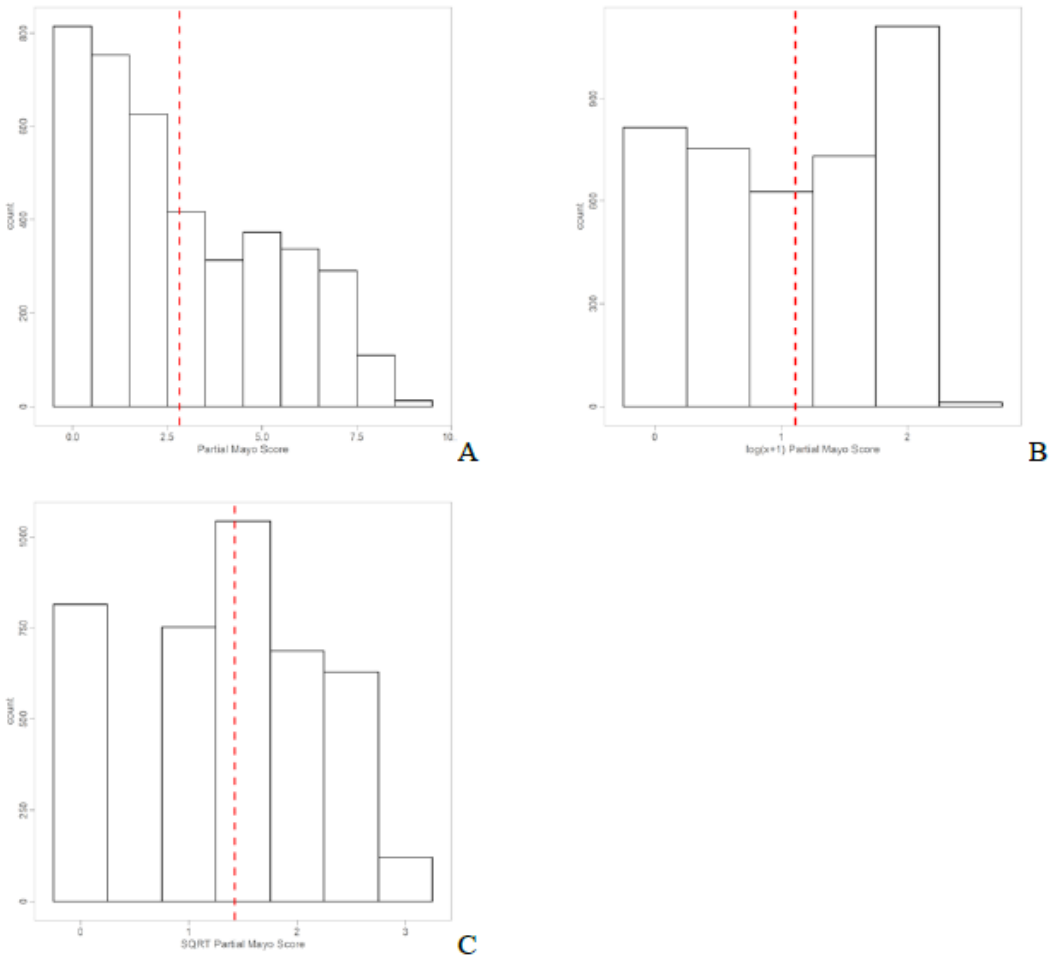
k_{in}: apparent zero-order rate constant for production of the response; k_{out}: first-order rate constant for the amelioration of response; I_{max}: maximum fractional ability of the drug to affect baseline partial Mayo score; IC_{50}: drug concentration that produces 50% of maximum inhibition; $I_{max,i}$: I_{max} value in the i^{th} individual; Φ: cumulative distribution function of the normal distribution; θ_x typical value of the x^{th} parameter; η_x: Inter-individual random effects for the x^{th} parameter; logit: logit transformation of the baseline partial Mayo score to restrict baseline partial Mayo score to be restrained between 0 and 9.

Initially, the model was applied to untransformed partial Mayo score data (Run7001). Data driven optimization of the random effects model was performed, resulting finally in a model with IIV for k_{out} and for the probit transformed I_{max} (Run7007). However, VPCs indicated that the candidate model Run7007 was not acceptable (underprediction of the central tendency of the CT-P13 effect and overprediction of the CT-P13 effect at the lower scores).

The untransformed partial Mayo data had a positively skewed distribution (Figure 6.2.3.10, A). To improve the description of the partial Mayo score data, the data was transformed. Initially, a log(x+1) transformation was applied, reducing the skewness of the distribution (Figure 6.2.3.10, B). The model was applied to the log(x+1) transformed data and the random effects model was reoptimized, resulting in a model with IIV for k_{out} and the probit transformed I_{max}, and an additive residual error on log(x+1) transformed data (Run7012).

An alternative transformation of the partial Mayo score data was also evaluated: the square root transformation, which pushed the data even closer to a normal distribution (Figure 22, C). The random effects structure was reevaluated with square root transformed data, and found again to be optimal with IIV in k_{out} and I_{max} (Run7024). VPC plots indicated that overall, the first 22 weeks of score data were better described by based on the log(x+1) transformation (Run7012) than based on the square root transformation (Run7024), and Run7012 was declared the final base model. Parameter estimates obtained from Run7012 are summarized in Table 26. Successful minimization was obtained in 83.3% of bootstrap analyses, demonstrating moderate robustness of the model. The median of the bootstrap estimates was in close agreement with the final parameter estimates from the final model obtained during the model development analyses (Run7012). The range in the confidence intervals for each parameter was broadly proportional to the RSE of the parameter obtained from the final model, except for the IC_{50} for which a wide range in CI was returned from the bootstrap analyses.

Figure 22. Distribution of Untransformed and Transformed Partial Mayo Score.



A: untransformed data; *B:* log(x+1) transformed data; *C:* square root transformed data

Table 27. Parameter Estimates: Population PK-PD model of Partial Mayo Score (Run7012)

Parameter	Parameter Value	RSE [c] (%)	Shrinkage (%)	Parameter Value (Original Scale)
Baseline partial Mayo Score	0.606	5.05	n/a	5.82
k_{out} (/h)	-6.04	1.46	n/a	0.00238
I_{max}	0.578	8.67	n/a	0.718
IC_{50} (µg/mL)	-41.9	0.655	n/a	6.17×10^{-19}
Additive Residual Error (SD)	0.392	2.43	n/a	0.48
Unexplained IIV in k_{out} [VAR (CV%)] [a]	0.961 (127)	12.2	35.8	n/a
Unexplained IIV in I_{max} [VAR (CV%)] [b]	0.954 (97.7)	10.0	17.3	n/a

Parameter units are those associated with the original scale.
[a] CV% = $\sqrt{(\exp(\omega^2)-1)*100}$ [b] CV% = $\sqrt{\omega^2*100}$ [c] RSE of the IIV parameters relate to the untransformed parameter.
CV=coefficient of variation; IIV=interindividual variability; IC_{50}=drug concentration that produces 50% of maximum inhibition; I_{max}=maximum fractional ability of the drug to affect baseline partial Mayo score; k_{out}=first-order rate constant for the amelioration of response; n/a=not applicable; RSE=relative standard error; SD=standard deviation; VAR=variance

Exploratory graphical analysis suggested no strong relationship between the potential covariates (baseline partial Mayo score, age, albumin, disease duration, gender, race, and concomitant treatment with 6-mercaptopurine, azathioprine, and methotrexate) and IIV in I_{max}. Subsequent model based assessment of selected covariate effects was conducted (Table 27); none of the covariates were considered clinically relevant by the MAH. Hence, Run7012 was retained as the final PK-PD model for partial Mayo score.

Table 28. Summary of tested covariate models: PK-PD model for Partial Mayo score.

Description	ΔOFV	MAH's comment
univariate analysis: Baseline albumin on I_{max}	-13.532	Minimization terminated, no covariance step; reduction in variance of ETA Imax 4.02%; Statistically significant dOFV ~ -13.5; impact at high and low values of BALB (13.9 and -11.67) within bioeq. bounds=> rejected
univariate analysis: Baseline albumin on I_{max}; changed initials	-13.518	Minimization terminated no covariance step; rounding issues could not be resolved
univariate analysis: Baseline partial Mayo Score on I_{max}	-21.159	reduction in variance of ETA Imax 4.87%; statistically significant dOFV ~ -21.2.; Impact at high and low values of BMAYO (18.1 and 9.6%) within bioeq. Bounds => rejected

Model update

As explained above, the population PK-PD model for partial Mayo score that was developed using blinded data from study CT-P13 3.7 was updated with unblinded data (Run7114). Parameter estimates obtained from Run7114 are summarized in Table 28. GOF plots and pcVPC plots for Run7114 are shown in Figure 23 and Figure 24, respectively.

Table 29. Parameter Estimates: Final Updated PK-PD Model for Partial Mayo Score (Run7114).

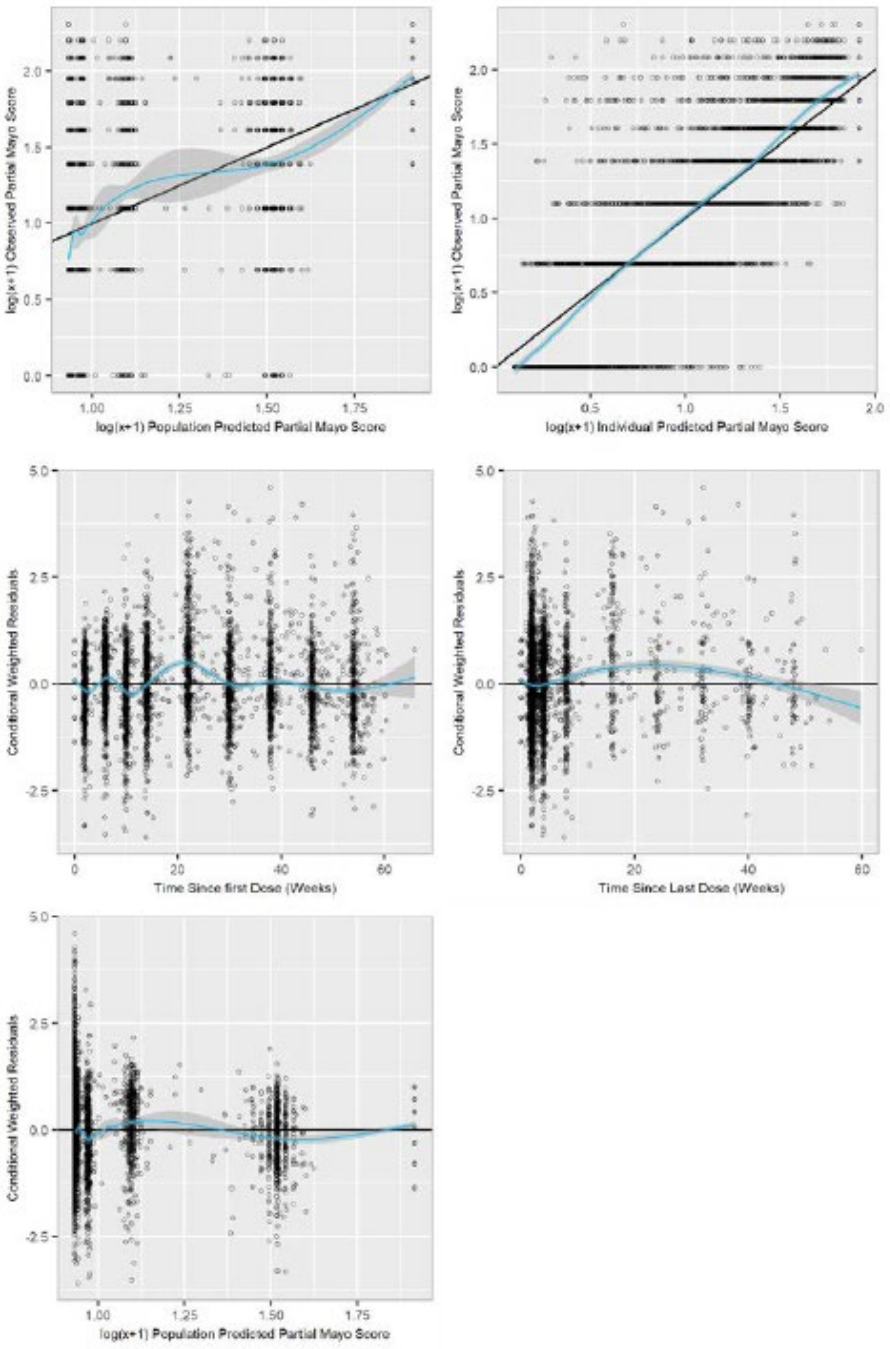
Parameter	Parameter Value	RSE [c] (%)	Shrinkage (%)	Parameter Value (Original Scale)
Baseline partial Mayo Score [d]	0.598	0.202	n/a	5.81
$\log_e(k_{out})$ (/h)	-6.11	0.204	n/a	0.00222
I_{max} [e]	0.628	0.200	n/a	0.735
$\log_e(IC_{50})$ (µg/mL)	-40.0	0.785	n/a	4.08×10^{-18}
Additive Residual Error (SD)	0.388	0.206	n/a	0.475
Unexplained IIV in k_{out} [VAR (CV%)] [a]	0.911 (122)	15.8	34	n/a
Unexplained IIV in I_{max} [VAR (CV%)] [b]	0.871 (93.3)	0.545	16.1	n/a

Parameter units are those associated with the original scale.

[a] $CV\% = \sqrt{(\exp(\omega^2)-1)}*100$ [b] $CV\% = \sqrt{\omega^2}*100$ [c] RSE of the IIV parameters relate to the untransformed parameter [d] transformed to limit to the plausible range of baseline values (as described in Section 3.3.4.1.4)
[e] probit transformed

CV=coefficient of variation; IIV=interindividual variability; IC_{50}=drug concentration that produces 50% of maximum inhibition; I_{max}=maximum fractional ability of the drug to affect baseline partial Mayo score; k_{out}=first-order rate constant for the amelioration of response; n/a=not applicable; RSE=relative standard error; SD=standard deviation; VAR=variance

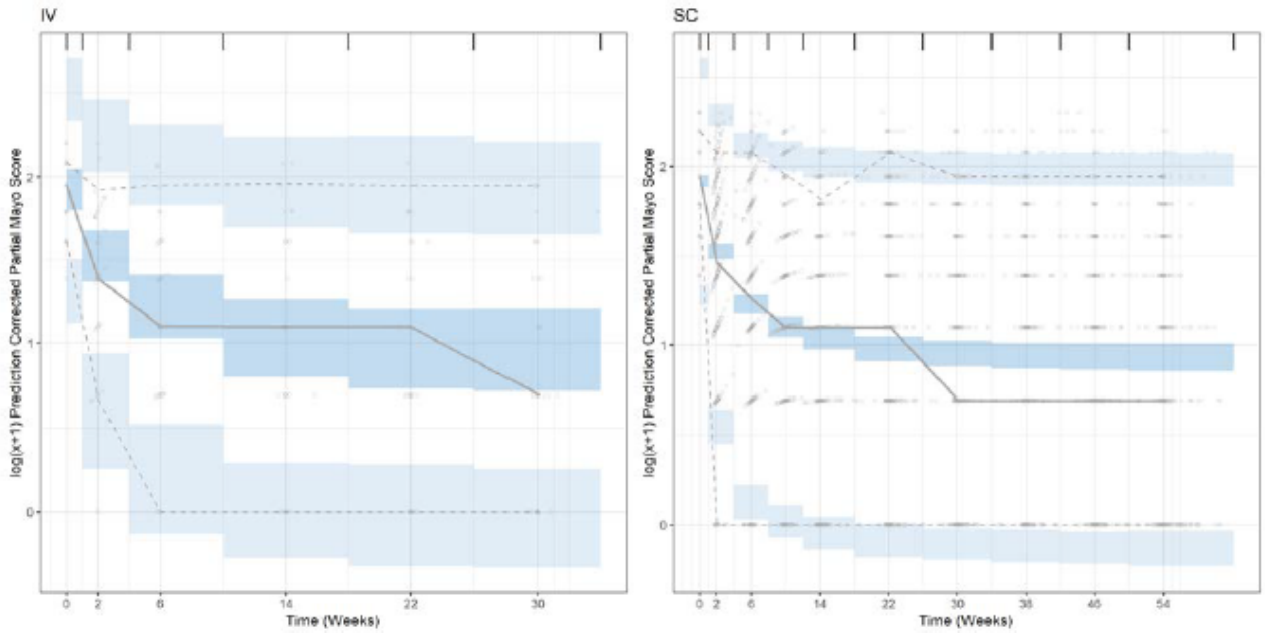
Figure 23. Goodness of Fit Diagnostic Plots: Final Updated PK-PD Model for Partial Mayo Score (Run7114)



Observed data are presented as black open symbols. The line of unity (the expectation) is shown in the solid black line. The blue line and associated grey area reflect a generalized additive smooth of the data, and associated 95% confidence interval.

Note: Plots of CWRES are presented from run7117, which is equivalent to run7114 (see Table 74 for further details)

Figure 24. Prediction Corrected VPC, Stratified by Maintenance Dose Route of Administration [log(x+1) transformed]: Final Updated PK-PD Model for Partial Mayo Score (Run7114).



Route reflects the maintenance dosing regimens, administered after the IV loading dose phase applicable in each study.

Prediction corrected log(x+1) observed partial Mayo scores are represented by open grey symbols. The median prediction corrected log(x+1) observed partial Mayo scores are represented by a grey solid line. The 5th and 95th percentiles of the prediction log(x+1) corrected partial Mayo scores are represented by dashed grey lines. The dark blue shaded area represents the 95% confidence intervals of the median of the prediction corrected model predicted data. The light blue shaded areas represent the 95% confidence intervals of the 5th and 95th percentiles of the prediction corrected model predicted data. The pcVPC was obtained from the updated model, including the additive residual error, resulting in the negative scores returned by the simulation. The baseline observations are overlapping, as there was no IIV included on baseline score the prediction correction for these points does not result in a scatter like seen for the other later points.

IV=intravenous; SC=subcutaneous

CHMP comments

The estimate of IC_{50} of the final PK-PD model for partial Mayo score is extremely small (4.08×10^{-18} µg/mL; Run7114). For comparison, the lower limit of quantitation (LLOQ) is 1×10^{-1} µg/mL. It is not plausible that 50% of the drug effect is achieved with concentration markedly below the LLOQ. Therefore, the PK-PD model developed by the MAH is not considered adequate to predict the efficacy of an untested infliximab dose regimen in treatment of ulcerative colitis. Other aspects of the PK-PD model have not been assessed in detail due to an unplausible crucial parameter estimate.

The MAH conducted PK-PD simulations for dose regimen Scenarios A, B, C, D, and Reference (see Population PK modelling and simulations above for description of the regimens) to support the SC induction posology in patients with ulcerative colitis. In brief, the PK-PD model indicated that the clinical response is identical for each Test Scenario and the Reference regimen. This is not surprising because the PK-PD model predicts that maximal response will be achieved if CT-P13 concentration is ≥ LLOQ. Detailed results of the simulations are omitted because the PK-PD model is not considered adequate.

6.3. Discussion

Bioanalytical methods

In general, the validation of modified ADA- and Nab-analytical methods was appropriate. Some concerns were raised concerning matrix interference (ADA-method), drug tolerance (NAb-method) and lacking bioanalytical data. The Applicant provided the requested data, and the questions were resolved.

Population PK modelling

The population PK model is based on a large number of observations following IV and SC administration, including dense PK sampling following single SC doses in healthy subjects. In the RSI, questions were raised on population PK model dataset, bioanalytical methods, and potential misspecifications. The population PK model was used to support the SC induction dosing regimen for CD and UC indications, which was withdrawn. Consequently, the related RSI questions are no longer relevant and the Applicant did not response to them.

Population PK-PD modelling

The MAH developed two PK-PD models: one for CDAI score and the other for partial Mayo score. The models had similar structure, CDAI (or partial Mayo) score was characterized by an indirect response model wherein a probit transformed inhibitory I_{max} model was used to describe the suppressive effect of CT-P13 on the zero-order rate constant of CDAI (or partial Mayo) score production. The models were only informed by studies which used IV induction regimen during the first 6 to 10 weeks. In both PK-PD models the estimate of IC_{50} was extremely small, several fold lower than the LLOQ of serum infliximab concentration. The IC_{50} estimates are not plausible. The consequence of extremely small IC_{50} estimates is that the PK-PD models will predict that any detectable concentration will be sufficient to elicit near-maximal response, and thus the models will predict no efficacy differences between SC and IV induction regimens. The submitted PK-PD models for CDAI score and partial Mayo score were not considered adequate to support the variation application to add SC induction posology in treatment of CD and UC.

Type II variation to add subcutaneous induction regimen in treatment of CD and UC

It needs to be mentioned that SC loading regimen for weeks 0 to 6 in treatment of RA was approved for Remsima based on modelling and simulation in procedure EMEA/H/C/002576/II/0095. The PK-PD model for DAS28 score supporting that application was not considered appropriate for simulations (refer to assessment reports of procedure II/0095). However, PK simulations indicated sufficient exposure with the SC loading regimen. An important basis for approval of procedure II/0095 was that in treatment of RA the most important time to assess the efficacy is relatively late, at 3 to 6 months of treatment (CPMP/EWP/556/95 Rev. 2, and differences in exposure during the first 6 weeks of treatment were not expected to have clinically relevant effect on efficacy at months 3 to 6. In contrast, the EMA Guideline on the development of new medicinal products for the treatment of Ulcerative Colitis (CHMP/EWP/18463/2006 Rev.1) and the EMA Guideline on the development of new medicinal products for the treatment of Crohn's Disease (CPMP/EWP/2284/99 Rev. 2) state that for the demonstration of short-term efficacy ("induction of remission"), significant effects would need to be demonstrated at early time point (usually 6-12 weeks).

SC maintenance regimen (120 mg Q2W starting at Week 6) in treatment of CD and UC in adult patients is already approved for Remsima. Therefore, the main issue for this variation application is whether the MAH can exclude the possibility of worsening of efficacy and safety during the first 6 weeks of treatment with the proposed SC induction regimen (Scenario B: 240 mg SC at Week 0, followed by 120 mg SC at Weeks 1, 2 and 3, followed by 120 mg SC Q2W from Week 4) compared with the approved IV induction regimen.

The MAH's justifications for adding SC induction regimen in treatment of CD and UC, presented in Module 2.7.2 of the dossier, are based entirely on PK simulations. There are no data from human clinical trial

studies for the proposed SC induction dosing regimen and the presented population PK-PD models are not considered adequate for predicting the efficacy of untested dose regimens.

As discussed in the Q&A document by EMA [Model-based approaches for approval of alternative dosing regimens and routes of administration of (anti PD-1 and PD-L1) monoclonal antibodies], model-based approaches may be acceptable as the main source of evidence to inform approval of alternative posology or route of administration for monoclonal antibodies, provided that the relevant PK metrics (such as C_{min}, AUC or C_{max}) will be similar to the exposure reached with the dosing regimen for which positive benefit/risk has been established. The relevance of the PK parameter/metric and the acceptance criteria for PK comparability for the efficacy and safety should be adequately justified based on established exposure-response relationship. It is the uncertainty of the exposure-response relationship that is a crucial weakness in the justifications by the MAH. In their population PK-PD models for CDAI score and partial Mayo score the estimated IC_{50} (i.e., infliximab concentration associated with 50% of maximal response) was 4.29 x 10^{-22} and 6.17 x 10^{-19} µg/mL, respectively, which are not plausible values.

In terms of PK, the MAH seeks to justify the efficacy of the proposed SC induction regimen by stating that the predicted median C_{trough} at Week 2 was slightly lower and at Week 6 slightly higher than the corresponding C_{trough} values of the IV induction regimen (see Table 6.2.2.8) and, overall, higher than a therapeutic threshold of 5 µg/mL which was based on studies by Morita et al. 2016 and Bortlik et al. 2013. However, in these studies only one PK sample, C_{trough} drawn during maintenance therapy phase, was evaluated. Therefore, the data are insufficient to unequivocally demonstrate that the pivotal PK exposure parameter for efficacy is C_{trough} and not, e.g., AUC. In addition, exposure-response relationship for the maintenance therapy phase may not be directly applicable to the induction therapy phase because during the first weeks of treatment the levels of the target (i.e., soluble and membrane-bound TNF-α) may be significantly higher compared with the maintenance phase when the disease activity is attenuated. Hence, it cannot be assumed without justifications that the target concentration should be the same during induction and maintenance therapy.

The MAH stated that they do not foresee safety risk with the proposed SC induction regimen because the predicted C_{max} and AUC are much lower than those of the approved IV induction regimen. It is acknowledged that the predicted C_{max} and AUC values over the first 6 weeks of treatment are much lower for the SC induction regimen compared with the approved IV induction regimen even in patients with the lowest body weight (50-60 kg) and safety risks related to increased exposure during that time are not expected.

The MAH's justifications for the proposed SC induction regimen in treatment of CD and UC were not sufficient and an MO was raised. The Applicant withdrew this part of the grouped variation application after the first RSI and corresponding changes are no longer proposed to the PI.

7. Clinical Efficacy aspects

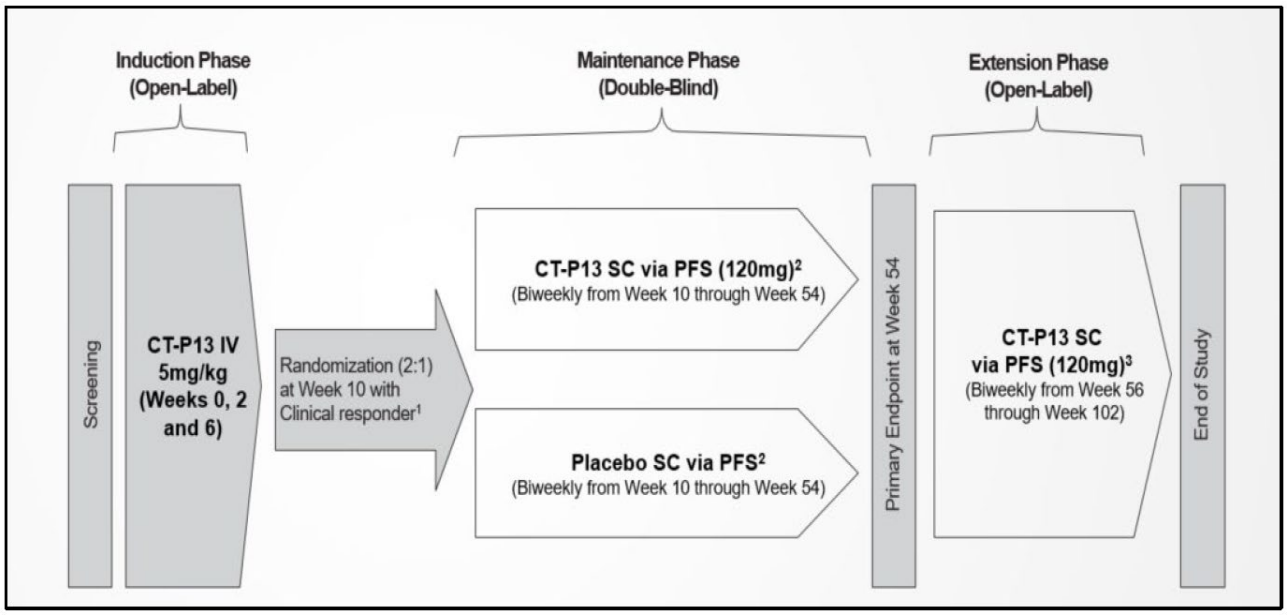
The first proposed variation is as follows:

- Update of section 4.2, 4.8 and 5.1 of the SmPC in order to add 3-IV induction dosing regimen and dose escalation of subcutaneous maintenance dose from CT-P13 SC 120 mg Q2W to 240 mg Q2W for patients with loss of response and update efficacy and safety information based on Week 54 data from studies CT-P13 3.7 (ulcerative colitis) and CT-P13 3.8 (crohn's disease), listed as a category 3 study in the RMP; Study CT-P13 3.7 is 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 and study CT-P13 3.8 is 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.

In EMA: deletion not agreed. This is part of assessment.

Study CT-P13 3.7 was a randomised, placebo-controlled, double-blind, multicentre, parallel-group Phase 3 study to evaluate the efficacy, PK, PD and safety of CT P13 SC as maintenance therapy in patients with moderately to severely active UC. The duration of the study will be up to 112 weeks, which includes screening (up to 6 weeks) and treatment period (up to the last dosing visit of study drug at Week 102) followed by EOS visit (after 4 weeks off dose period). With this variation application, data up to week 54 was submitted. The Week 54 visit date of the last patient was 07 July 2022 and after further data cleaning, the database was locked for this analysis on 15 September 2022.

Figure 25. Overview of study design



Abbreviations: IV, intravenous; PFS, pre-filled syringe; SC, subcutaneous.

1. Clinical response by modified Mayo score: a decrease in modified Mayo score from baseline of at least 2 points and at least 30%, with an accompanying decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1 point.
2. From Week 22 through Week 54, dose adjustment was allowed. The patients who received CT-P13 SC 120 mg could increase the dose to CT-P13 SC 240 mg every 2 weeks, and the patients who received Placebo SC could receive CT-P13 SC 240 mg every 2 weeks, if they initially responded but then lost response according to the loss of response criteria.

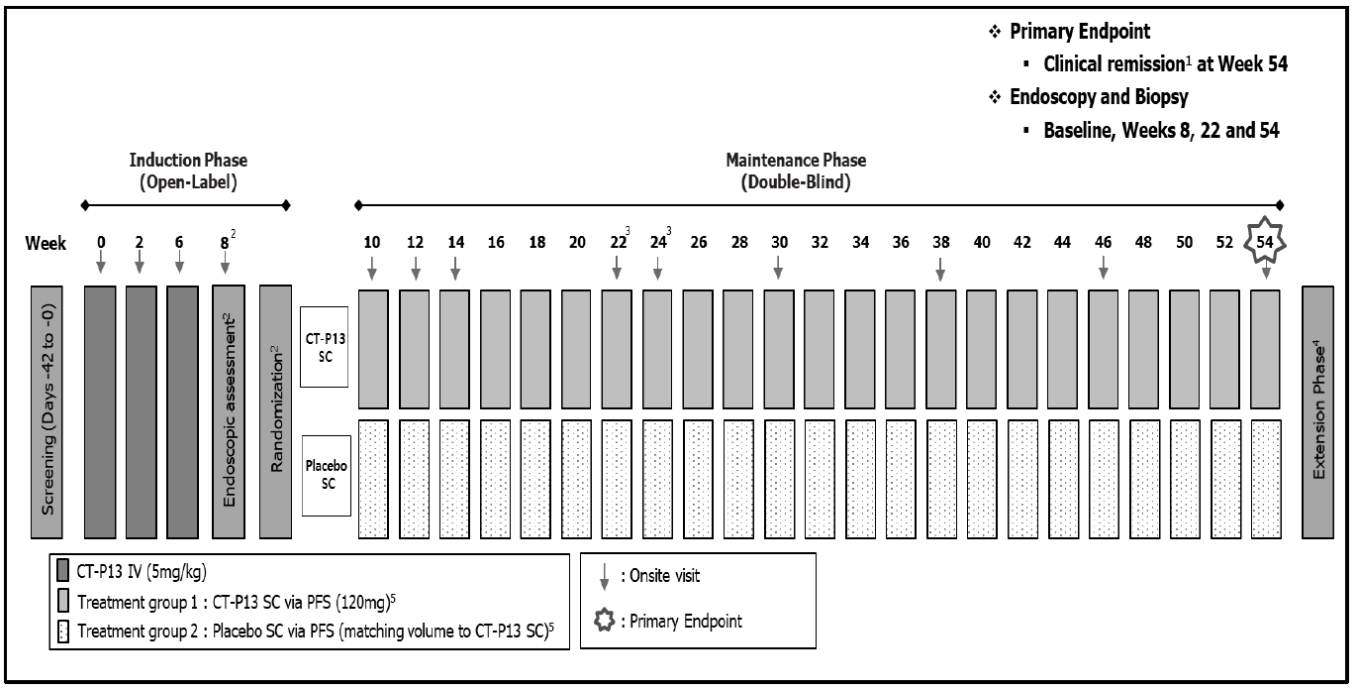
3. In the extension phase, all patients who completed the maintenance phase up to Week 54 and could benefit from continued treatment, in the opinion of the investigator, received active treatment with CT-P13 SC 120 mg via PFS from Week 56.

In the **open-label induction phase**, the patients who met all the inclusion criteria and none of the exclusion criteria were enrolled on Day 0 (Week 0). All enrolled patients received a

2-hour CT-P13 IV infusion (5 mg/kg) during on-site visits at Weeks 0, 2, and 6 as induction treatments. At Week 8, only endoscopy and biopsy for histologic assessment were performed for the evaluation of Mayo score and endoscopic-histologic mucosal improvement at Week 10. The endoscopy result at Week 8 were used for randomization at Week 10. Patients who were classified as a clinical responder at Week 10 based on modified Mayo score after receiving 3 full doses of CT-P13 via IV infusion and for whom there were no safety concerns based on the investigator's discretion were randomly assigned to receive either CT-P13 SC or Placebo SC, before treatment on Day 70 (Week 10).

A clinical responder at Week 10 was defined as a patient with a decrease in modified Mayo score from baseline of at least 2 points and at least 30%, with an accompanying decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1 point.

Figure 26. Study Design for Induction and Maintenance Phase



Abbreviations: IV, intravenous; PFS, pre-filled syringe; PK, pharmacokinetics; SC, subcutaneous.

1. Clinical remission by modified Mayo score: stool frequency subscore of 0 or 1 point, and rectal bleeding subscore of 0 point, and an endoscopic subscore of 0 or 1 point.
2. At Week 8, only endoscopy and biopsy were performed for the evaluation of Mayo score and histological assessments at Week 10. The endoscopy results at Week 8 were used for randomization at Week 10. Patients who were classified as a clinical responder at Week 10 were randomly assigned to receive either CT-P13 SC or Placebo SC at Week 10.
3. Additional PK sampling visits were conducted only on patients who agreed to collect further blood samples for population PK analysis.
4. Patients who complete the maintenance phase up to Week 54 and may benefit from continued treatment, in the opinion of investigator, will continue into the extension phase.

5. For all patients in the treatment group 1 and 2, dose adjustment to CT-P13 SC 240 mg every 2 weeks were allowed starting from Week 22, if the patients initially responded but then lost response according to the loss of response criteria.

The **double-blind maintenance phase** consisted of further doses of CT-P13 SC or Placebo SC with the last dose administered no later than Week 54.

1. Treatment Group 1, CT-P13 SC: from Week 10, CT-P13 SC 120 mg was administered every 2 weeks via PFS through Week 54
2. Treatment Group 2, Placebo SC: from Week 10, Placebo SC (matching volume to CT-P13 SC 120 mg) was administered every 2 weeks via PFS through Week 54.

From Week 22 through Week 102, dose adjustment was allowed as follows:

3. The patients who received CT-P13 SC 120 mg might increase the dose to CT-P13 SC 240 mg (double injection [2 shots] of CT-P13 SC 120 mg) every 2 weeks, if patients initially responded but then lost response according to the loss of response criteria.
4. The patients who received Placebo SC might receive CT-P13 SC 240 mg (double injection [2 shots] of CT-P13 SC 120 mg) every 2 weeks, if patients initially responded but then lost response according to the loss of response criteria.

Loss of response was defined as an increase in modified Mayo score ≥2 points and ≥30% from the Week 10 modified Mayo score with actual value of ≥5 points, and endoscopic subscore of ≥2 points. The patients whose dose was adjusted to CT-P13 SC 240 mg prior to Week 54 were considered as non-remitter or non-responder at Week 54 in the analysis of the primary endpoint and key secondary endpoints.

In the **open-label extension phase**, all patients who complete the maintenance phase up to Week 54 and may benefit from continued treatment, in the opinion of the investigator, will receive active treatment with CT-P13 SC 120 mg via PFS from Week 56. The patients who received the adjusted dose of CT-P13 SC 240 mg in the maintenance phase continued receiving the same doses of CT-P13 SC for the study treatment in the extension phase. The extension phase will continue up to Week 102. Results from the extension phase were not provided with this submission.

End of study

The EOS visit occurred 4 weeks after the last dose of study drug was received. For patients who early discontinued the study drug before administration of CT-P13 SC or Placebo SC at Week 10, the EOS visit occurred 8 weeks after the last dose of CT-P13 IV was received.

CHMP comment

This Phase 3 study was designed to evaluate the efficacy, PK, PD, and safety of the SC injection of CT-P13 (CT-P13 SC) as maintenance therapy in patients with moderately to severely active UC, after having received induction therapy with three IV-doses.

The design as such was reasonably adequate to answer the question whether maintenance therapy with SC Remsima is superior to placebo, after an initial response to induction treatment has been achieved but not the question whether a dose increase is effective.

As patients who lost response in both treatment arms were offered a switch to Remsima 240 mg Q2W from week 22 onward, comparisons of efficacy between Remsima SC 120mg Q2W and placebo beyond week 22 are compromised due to the intercurrent event. Basically, patients in the placebo group who received active treatment after loss of response are automatically counted as non-responders which may skew the results

in favour of the active arm because placebo patients are more likely to lose their response as they receive no active treatment. These patients are automatically counted as non-responders although we see from historical data and data from this study that it is possible for patients to reach "response" in the placebo arm due to the nature of the endpoint and the natural fluctuation of the disease. As loss of response after switching to placebo is very different from loss of response during maintenance treatment with 120 mg Remsima SC, we do not know whether the fluctuation back to "responder" would have occurred with equal frequency in each arm.

In the context of this variation application, study CT-P13 3.7 was submitted to support a) addition of a new induction regimen (longer induction with IV), b) addition of the possibility to increase the dose for patients with loss of initial response c) inclusion of the efficacy and safety results in Section 5.1 and 4.8.

Induction with 3 IV doses

The design as such is adequate to answer the question whether maintenance therapy with Remsima SC (CT-P13) in the treatment of UC is superior to placebo when administered with an induction regimen of 3 IV doses (5 mg/kg at Weeks 0, 2 and 6) followed by SC maintenance treatment (120 mg Q2W starting from week 10).

While the primary endpoint at week 54 is somewhat hampered by the design of study 3.7, Week 22 efficacy is considered to be a clinically relevant endpoint and acceptable by the EMA guideline on UC studies. As the new proposed induction regimen does not differ a lot from the already approved one, the W54 data is not considered crucial and the benefit-risk may be assessed based on totality of data.

Dose adjustment

The question to be answered is whether dose adjustment from SC 120 mg to 240 mg for patients with loss of response is more effective (and sufficiently safe) compared to continuing treatment with SC 120 mg. The study design is not adequate to answer this question.

As there was no randomised treatment arm where patients with a loss of response continued on the previously assigned SC 120mg treatment, it is difficult to know how the disease would have progressed without the dose escalation. As UC is a fluctuating refractory disease with sometimes long symptom free periods, some patients could have achieved remission again by week 54 after loss of response, even without dose escalation. Furthermore, as dose escalation was not mandatory for all patients who fulfilled the criteria, there is a potential for selection bias. Assessment of the BR of a dose escalation could in theory be addressed based on totality of data including PK, efficacy, safety and immunogenicity data. In this case the results need to be exceptionally compelling. The risk of higher exposure in the long term needs to be clearly overridden by the benefits.

Efficacy results in SPC 5.1

While the design is not optimal for interpretation of the results at Week 54 (primary endpoint), the increase of the dose in both arms after week 22 (i.e. in placebo arm switch to high-dose active drug, and in Remsima arm increase of the dose from 120mg to 240mg) when loss of response occurred could be seen as a *rescue therapy/ escape procedure* at intermediate time-point, which is in line with the EMA guideline on development of medicinal products for ulcerative colitis/ Crohn's disease. Subjects who initiated Remsima 240mg treatment as "rescue treatment" (placebo-group) or had a dose escalation to 240mg (Remsima SC group), were categorized as non-responders for primary efficacy analyses of co-primary endpoints. Overall, this study design was not optimal, but still considered of value if the data is presented with sufficient detail (see requests in LoQ). Similar designs have been used earlier in the same therapeutic field and have been found suitable for regulatory decision-making. However, it is noted that Remsima is already an approved maintenance therapy which was not the case for the other products. Notably, in the current submission the overall B/R of induction/maintenance treatments is not questioned, as those have already been approved

and included in the SmPC of IV and SC Remsima. The question is if these new phase 3 studies provide statistically and clinically significant and robust enough/valuable information for the prescriber to be placed into the SmPC 5.1, to replace the earlier data from the previous smaller studies in CD and UC. For these purposes, even though the design is not optimal, as discussed above, it can be agreed that the results are of value for the prescriber and could be described in SmPC 5.1 provided that satisfactory answers are given to the **LoQ**.

Updated comments (1st RSI AR)

As the MAH withdrew the initial proposal for a dose escalation in UC patients, questions related purely to the efficacy and safety of the 240mg dose are no longer relevant. However, the possibility to dose adjust is significantly intertwined in the primary endpoints as only patients who did not dose adjust had a possibility to be responders at week 54. Moreover, the intercurrent event of loss of response was handled differently for different patients and this flaw in the study design could skew the results of the primary outcome. Some patients who lost response were dose adjusted and others were not, but these different pathways were neither randomised nor based on any predefined characteristics. Therefore, week 54 results cannot be presented in the SPC without mentioning the possibility to dose adjust. However, as a dose increase is no longer proposed, this would be promoting an off label posology, which is not acceptable. Therefore, only W22 results from the UC study may be presented in the SPC.

The Final study report up to W102 was provided with the responses and the main results have been included in this AR.

Updated comments (2nd RSI AR)

The Applicant has provided the requested tables and figures.

According to study protocol, patients were offered a dose escalation if they met LoR criteria after week 22. However, based on the provided results, 29/294 patients in the infliximab group and 21/144 in the placebo group were switched to 240 mg Remsima despite not meeting LoR criteria. Hence, a total of 35% (50/144) of all patients who received a dose adjustment did not meet LoR criteria. No special criteria for these dose escalation decisions were prespecified or explained post hoc.

Out of all non-responders at W54, only 5.5% were classified as non-responders based on clinical criteria, with no difference between treatment groups, while the rest of the non-responders were due to intercurrent events, mainly dose adjustment, which did not equal LoR.

The reason for the high number of this type of protocol violations may be related to the definition of LoR. In the protocol, the LoR criteria were based on modified Mayo score (including the endoscopic subscore). However, the modified Mayo score was only recorded at weeks 10, 22 and 54. Hence, according to protocol it was not even possible to detect a LoR between W22 and 54.

As all patients randomised are included in the primary endpoint, all the aforementioned issues have a direct impact on the results of the primary endpoint.

While there is no doubt that Remsima SC is in fact more effective than placebo in the treatment of UC, the magnitude of the difference cannot be accurately estimated based on the results of this trial. The UC indication is already granted and is not put into question but no new useful information for the prescriber has been presented with this application.

To conclude, the results from study 3.7 are invalid for inclusion in the SPC.

Updated comments (3rd RSI AR)

Upon rejection of the Week 54 endpoints, the MAH proposed to include W22 results in the SPC instead. Week 22 endpoints were not pre-specified in the protocol and SAP. Generally, post-hoc analyses are included in SmPC 5.1. only in exceptional situations. There is no clinical necessity to include these results.

Furthermore, it has become apparent during the assessment that the overall study conduct and the concordance of the protocol and planned statistical analyses are not considered to produce reliable and robust results. For all the aforementioned reasons, the Week 22 results are not considered adequate for inclusion in the SmPC.

Study 3.7 in UC patients does not provide methodologically robust and clinically significant information for the prescriber. The study was not conducted according to protocol. The number and nature of the protocol violations are such that the W54 results do not provide a meaningful interpretation. Further, it would not be possible to describe the study appropriately without mentioning the possibility to increase the dose from the currently approved 120mg SC to 240mg, which would be promoting an off-label posology.

Hence the description of study 3.7 should be removed from SPC 5.1.

Updated comments (4th RSI AR)

The MAH has agreed to the assessment. No new data from study 3.7 is included in the SPC section 5.1.

CHMP/PRAC table describing current and proposed treatment regimens of IV and SC Remsima in the treatment of UC.

weeks	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Currently approved regimens																							
1. IVi + IVm		x		x				x								x							x
2. IVi + SCm		x		x	p	p	p	x		x		x		x		x		x		x		x	x
3. IVi +IVm -> SCm		x		x				x	p	p	p	p	p	p	p	x		x		x		x	x
Proposed regimens																							
4. IVi + SCm		x		x				x	p	p	p	x		x		x		x		x		x	x
5. SCi+SCm		xx	x	x	x	x		x		x		x		x		x		x		x		x	x

IVi: IV induction
IVm: IV maintenance
SCi: SC induction
SCm: SC maintenance
P: pause between IV and SC

7.1.1. Methods

Study participants

A total of 800 patients were screened and 548 patients from 92 study centers in 14 countries were enrolled in this study. Male or female patients aged 18 to 75 years old with moderately to severely active UC who had a modified Mayo score without physician global assessment (PGA) subscore of 5 to 9 points with endoscopic subscore of ≥2 points and had an inadequate response to conventional therapy were considered for enrolment. The patients had been treated for active UC but had not responded despite conventional therapy including corticosteroids alone or in combination with 6-mercaptopurine (6-MP) or azathioprine (AZA), or were intolerant to or had medical contraindications to such therapies. Detailed inclusion criteria are given in the clinical study report (CSR).

The exclusion criteria were divided into 2 categories: general exclusion criteria, TB exclusion criteria. Patients meeting any of the general and TB exclusion criteria according to their indication were excluded from this study. The main exclusion criteria were as follows:

1. Patient who had previously received 2 or more biologic agents, 2 or more JAK inhibitors, or 2 or more both biologic agents and JAK inhibitors.
2. Patient who had previously received either a TNFα inhibitor or biologic agent within 5 half-lives prior to the first administration of the study drug (Day 0).
3. Patient who had previously demonstrated inadequate response or intolerance to TNFα inhibitors for the treatment of UC.
4. Patient who had previously received infliximab for treatment of UC or other disease.
5. Patient who had received or had a plan to receive any of following prohibited medications or treatments:
    - Parenteral corticosteroids for the treatment of UC within 2 weeks prior to the first administration of the study drug (Day 0)
    - Rectally administered medications containing corticosteroids or 5-ASA for the treatment of UC within 2 weeks prior to the first administration of the study drug (Day 0)
    - JAK inhibitors including but not limited to tofacitinib and baricitinib within 4 weeks prior to the first administration of the study drug (Day 0)
    - Alkylating agents within 12 months prior to the first administration of the study drug (Day 0)
    - Cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil within 8 weeks prior to the first administration of the study drug (Day 0)

More detailed inclusion criteria are given in the clinical study report (CSR).

CHMP comment

The inclusion and exclusion criteria are in line with the target population, i.e the UC patients for whom Remsima is approved:

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.

Treatments

The dosing regimen of 3 IV induction doses of CT-P13 5 mg/kg at Weeks 0, 2, and 6 followed by maintenance doses of CT-P13 SC 120 mg every 2 weeks starting at Week 10 was selected for this study.

The dosing regimen for the IV induction period for this study was the same as the currently approved induction dosing regimen for IV infliximab, and the SC dosing started at Week 10, which was 4 weeks after the last IV induction dose at Week 6 (see assessor's table under section 7.1). According to the MAH, this timing of first SC dose was chosen to ensure trough concentration (C_{trough}) levels remained close to the steady state plasma concentration throughout the SC dosing regimen, minimizing low plasma levels and thereby preventing potential enhancement of immunogenicity.

Patients entered into open-label Induction Phase were administered three doses of CT-P13 IV 5 mg/kg at Weeks 0, 2 and 6. Patients who classified as a clinical responder at Week 10 based on modified Mayo score without PGA subscore and had no safety concerns based on the investigator's discretion were randomly assigned to either CT-P13 SC treatment arm or Placebo SC treatment arm in a 2:1 ratio for the Maintenance Phase. Dose adjustment was allowed from Week 22 if patients initially responded but then lost response according to the loss of response criteria (an increase in modified Mayo score of ≥ 2 points and ≥ 30% from the Week 10 modified Mayo score with actual value of ≥ 5 points, and endoscopic subscore of ≥ 2 points). These patients received CT-P13 SC 240 mg (double injection [2 shots] of CT-P13 SC 120 mg) every 2 weeks regardless of whether they had previously received CT-P13 SC 120 mg or Placebo SC.

Concomitant medication

Immunomodulators (such as AZA, 6-MP, or MTX) were allowed if patients maintained stable doses for at least 8 weeks prior to first administration of the study drug (Day 0) according to the inclusion criteria.

Oral corticosteroids at the equivalent dose of 20 mg/day or less of prednisone 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).

Only oral 5-ASA was allowed if patients maintained stable doses for at least 4 weeks prior to the first administration of study drug (Day 0) and the stable dose was maintained throughout Week 54. Antibiotics (such as ciprofloxacin, metronidazole) for the treatment of UC were allowed if patients maintained a stable dose for at least 4 weeks prior to the first administration of the study drug (Day 0).

CHMP comment

The timing of first SC dose was chosen to ensure trough drug concentration levels remained close to the steady state plasma concentration throughout the SC dosing regimen. This target was achieved (see PK assessment in section 6).

As discussed above in "Study design" the possibility to switch to higher dose/active treatment hampers the ability to assess the study objectives.

Objectives

Primary objective:

To demonstrate superiority of CT-P13 subcutaneous (SC) over Placebo SC based on clinical remission at Week 54

Secondary objective:

To evaluate additional efficacy, pharmacokinetics (PK), pharmacodynamics (PD), and overall safety including immunogenicity

Exploratory objective:

To evaluate additional efficacy

Outcomes/endpoints

Primary Efficacy Endpoint:

Clinical remission at Week 54, defined as the following modified Mayo score:

- Stool frequency subscore of 0 or 1 point, and

- Rectal bleeding subscore of 0 point, and
- Endoscopic subscore of 0 or 1 point Key

Key Secondary Efficacy Endpoints:

- Clinical response at Week 54, defined as a decrease in modified Mayo score from baseline of at least 2 points and at least 30%, with an accompanying decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1 point
- Endoscopic-histologic mucosal improvement at Week 54, defined as an absolute endoscopic subscore of 0 or 1 point from modified Mayo score and an absolute Robarts Histopathology Index (RHI) score of 3 points or less with an accompanying laminal propria neutrophils and neutrophils in epithelium subscore of 0 points
- Corticosteroid-free remission at Week 54, defined as being in clinical remission by modified Mayo score in addition to not requiring any treatment with corticosteroid for at least 8 weeks at Week 54, among the patients who used oral corticosteroids at baseline

Other Secondary Efficacy Endpoints:

- Clinical remission assessed at Weeks other than Week 54, by modified Mayo score
- Maintenance of clinical remission at Week 54, defined as being in clinical remission by modified Mayo score, among the patients in clinical remission by modified Mayo score at Week 10
- Sustained clinical remission at both Week 22 and Week 54, defined as a stool frequency subscore of 0 or 1, and rectal bleeding subscore of 0
- Clinical response assessed at Weeks other than Week 54, defined as a decrease in modified Mayo score from baseline of at least 2 points and at least 30%, with an accompanying decrease in rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1 point
- Endoscopic-histologic mucosal improvement assessed at Weeks other than Week 54, defined as an absolute endoscopic subscore of 0 or 1 point from modified Mayo score and an absolute RHI score of 3 points or less with an accompanying laminal propria neutrophils and neutrophils in epithelium subscore of 0 points
- The scores and change from baseline in Short Inflammatory Bowel Disease Questionnaire (SIBDQ)

Exploratory Efficacy Endpoints:

- Clinical remission with normalization of stool frequency at Week 54, defined as following modified Mayo score:
    - Stool frequency subscore of 0 point, and
    - Rectal bleeding subscore of 0 point, and
    - Endoscopic subscore of 0 or 1 point
- Total clinical remission, defined as a total Mayo score (stool frequency, rectal bleeding, endoscopic, and PGA subscores) of 2 points or lower with no individual subscore exceeding 1 point

- Total clinical response, defined as a decrease in total Mayo score from baseline of at least 3 points and at least 30%, with an accompanying decrease in rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1 point
- Partial clinical remission, defined as a partial Mayo score (stool frequency, rectal bleeding, and PGA subscores) of 1 point or lower
- Partial clinical response, 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

Pharmacokinetic Assessments:

- Trough concentration (C_{trough}) up to Week 100 (concentration before the next study drug administration)
- Observed maximum serum concentration (C_{max}) at Week 6

Pharmacodynamic Assessments:

- Faecal calprotectin (FC)
- C-reactive protein (CRP)

CHMP comment

The chosen efficacy parameters were often used in randomized clinical trials indicated for UC patients and are listed as possible endpoints in the EMA Guideline on the development of new medicinal products for the treatment of Ulcerative Colitis (CHMP/EWP/18463/2006 Rev.1) The FDA guidance (Guidance for Industry. Ulcerative Colitis [2022]), recommends using clinical remission by modified Mayo score as the primary endpoint. The modified Mayo score includes the endoscopic sub-score. According to the EMA guideline, symptomatic remission (e.g., by patient reported sub-score (Partial Mayo)) and endoscopic remission should be assessed separately as co-primary endpoints.

The primary objective of this study was to demonstrate superiority of Remsima SC over placebo in the maintenance treatment of UC patients at week 54. This is not relevant for the variation at hand as Remsima SC is already approved for maintenance treatment and it is not likely that a small adjustment of the induction regimen would render the whole treatment ineffective. However, as the MAH proposes to include the main results from study 3.7 in the SPC section 5.1, the primary endpoint also needs to be assessed.

Importantly, there is no pre-defined endpoint to assess whether high dose maintenance is effective.

Sample size

The sample size of 417 patients (278 in CT-P13 SC group and 139 in Placebo SC group) was estimated to provide 80% statistical power to detect a statistically significant effectiveness of CT-P13 SC group in comparison with Placebo SC group based on the clinical remission at Week 54 assuming a treatment difference of 15% and Placebo rate of 45% at the 1-sided significance level of 2.5%.

Considering a 32% non-responder rate of clinical response at Week 10 before randomization, a total of approximately 615 patients provided at least 90% statistical power for clinical response at Week 54, one of the key secondary endpoints, under the assumption of a treatment difference of 20% and Placebo rate

of 50% at the 1-sided significance level of 2.5%. Key secondary endpoints other than clinical response at Week 54 were not applicable for power calculation due to lack of relevant references.

CHMP comment

The sample size calculation is technically adequate for the question the study was designed to answer.

However, the protocol assumptions differ to a large degree from what was observed in the study. In the protocol a 45% response rate in the placebo arm was expected whereas the results show a response rate of 20.8%. Furthermore, in the protocol a 15% delta was expected which would have translated into 60% response rate in the active arm. This is also notably lower (43%) though the expected delta was observed. The Applicant should discuss whether the difference in the expected vs observed results is due to low number of true responders or whether the dose escalation/switch to placebo allowed in the protocol, or some other reason, explains the difference. The response may refer to the OC in the efficacy section related to categories for non-responders.

Updated comments (RSI AR)

As the MAH states, it appears that the lower absolute number of responders could be linked to the fact that patients whose dose was escalated were automatically counted as non-responders. This further confirms the impression that the impact of dose escalation in both active and placebo groups on the overall robustness of the results was not adequately considered at the planning stage of the study. This impacts the robustness of the results at Week 54.

Randomisation

For initiating the double-blind maintenance phase, an interactive web response system (IWRS) was used for the randomization. Biostatistician generated the randomization schedule for the IWRS, which linked sequential patient randomization numbers to treatment codes. Patients classified as a clinical responder by modified Mayo score at Week 10 after receiving 3 full doses of CT-P13 via IV infusion and with no safety concern based on the investigator's discretion were randomized in a 2:1 ratio to receive either CT-P13 SC or Placebo SC, before starting treatment at Day 70 (Week 10).

The randomization was stratified by previous exposure to biologic agent and/or JAK inhibitors (used or not used), use of treatment with oral corticosteroids at Week 0 (used or not used) and clinical remission at Week 10 (remitter or non-remitter by modified Mayo score).

CHMP comment

The stratification factors are adequate.

Importantly, as commented elsewhere in this report, the benefits of randomization are lost for the primary and secondary efficacy objectives at week 54 because changes based on subjective criteria in the randomized dosing regimen are allowed. Furthermore, randomization is not relevant for the question whether high dose maintenance is an option for patients with loss of response. This would have required randomization at the time of loss of response (week 22).

Blinding (masking)

This study had a double-blind maintenance phase, the treatment assignment for the maintenance phase was blinded to the investigators, patients, and predefined CELLTRION, Inc. and PPD-blinded teams until this Week 54 CSR was generated and will remain blinded until the Week 102 CSR is generated.

CHMP comment

In theory, the study is double blind. However, the investigator and patient know that if the dose was escalated, the patient received active treatment. Furthermore, the investigator knows that as a result of dose escalation the patient automatically is a non-responder in the efficacy analyses. Hence, the study cannot be considered adequately blinded.

Statistical methods

For the efficacy endpoints related remission or response, the following patients were considered as non-remitter or non-responder:

- Patients who did not meet the clinical remission or response criteria
- Patients with missing or incomplete data for the evaluation of each endpoint at their scheduled visit of interest
- Patients with dose adjustment to CT-P13 SC 240 mg prior to their scheduled visit of interest

The primary endpoint tested at the 2-sided significance level of 5% on the all-randomized population using the p-value from Cochran-Mantel-Haenszel (CMH) test stratified by previous exposure to biologic agent and/or JAK inhibitors (used or not used), use of treatment with oral corticosteroids at Week 0 (used or not used) and clinical remission at Week 10 (remitter or non-remitter by modified Mayo score). If the p-value was ≤0.05, the statistical significance of the primary endpoint was concluded. If the primary endpoint was significant, the fixed sequence procedure was used for key secondary endpoints in order to preserve the Type I error. The supportive analysis for the primary endpoint was performed in the PP population.

CHMP comment

The Applicant has outlined one intercurrent event which results into a patient counted as non-responder, namely that the patient´s dose was escalated. For patients in the placebo arm, dose escalation means that they started to receive active treatment. It is inherently difficult to assess the impact of this on study results.

The statistical test for the primary endpoint was changed late in the study based on a comment from the FDA. This is acceptable and the test is considered adequate.

Importantly, there are no pre-defined methodological aspects and endpoints to assess the impact of dose escalation which is one major focus of this submission. On the other hand, the impact of dose escalation on the primary and secondary endpoints has not been adequately prospectively considered. The number of patients with dose escalation/switch to active treatment is high (see results) and imbalanced between the arms. Though designs and endpoints similar to this study have been accepted before, the situation is different for this study because maintenance was already an approved treatment regimen at study initiation.

One analysis was included in the SAP to assess dose escalation: I*n addition, for the descriptive comparison of the treatment effect between patients with and without dose adjustment to CT-P13 SC 240 mg prior to Week 54 within CT-P13 SC treatment group, the primary endpoint was summarized by patients with and without dose adjustment in CT-P13 SC treatment group using frequency table without the statistical test. In this analysis, remitter was determined as per remission criteria regardless of dose adjustment.* This analysis is, however, not included in the submitted dossier which is rather surprising considering the intended changes to the SmPC. This analysis should be provided.

Updated comments (RSI AR)

The requested analysis was not provided but the question is no longer relevant as the dose adjustment was withdrawn for UC.

7.1.2. Results

Participant flow

A total of 800 patients were screened. There were 252 screening failures; the most frequently reported primary reason for screening failure were inclusion/exclusion criteria not met.

Out of 800 patients, 548 patients were enrolled in the study, and were treated with CT-P13 5 mg/kg via IV infusion in the open-label induction phase. Of these patients, 110 patients discontinued the study during the induction phase. The most frequently reported primary reason for discontinuation during the induction phase was non-responder at Week 10 (65/548, 11.9%).

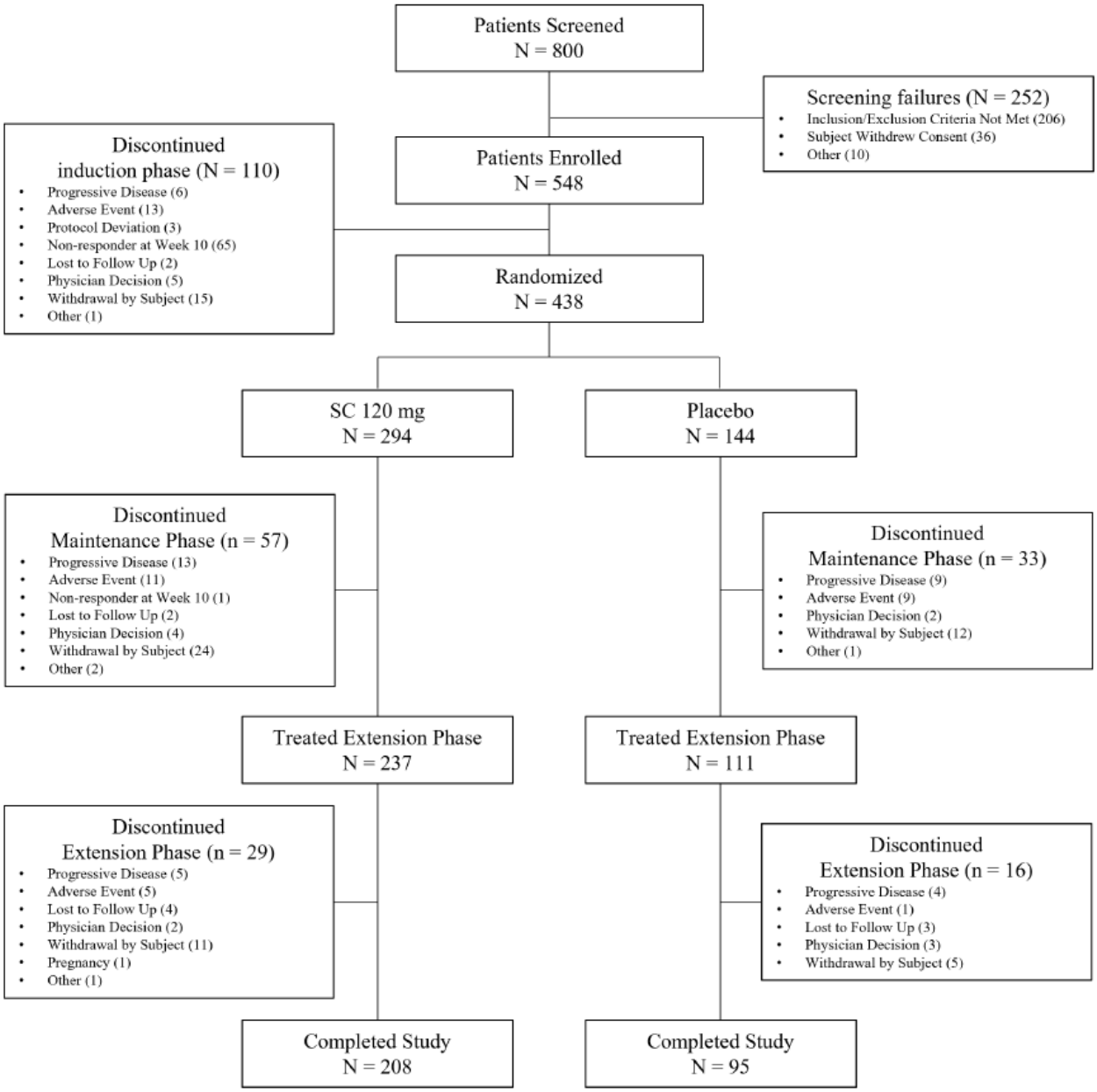
A total of 438 patients were randomly assigned to study treatment and initiated the double-blind maintenance phase at Week 10 (294 and 144 patients in the CT-P13 SC 120 mg and Placebo SC groups, respectively). Eighty-five (19.4%) patients discontinued the study during the maintenance phase (54 [18.4%] and 31 [21.5%] patients in the CT-P13 SC 120 mg and Placebo SC groups, respectively).

Overall, the most frequently reported primary reason for discontinuation during the maintenance phase was withdrawal by subject (23 [7.8%] patients in the CT-P13 SC 120 mg group and 12 [8.3%] patients in Placebo SC group, respectively). The mean (SD) time on study drug prior to discontinuation during the maintenance phase was 201.9 (95.97) and 259.5 (91.83) days in the CT-P13 SC 120 mg and Placebo SC groups, respectively.

A total of 353 (80.6%) patients (240 [81.6%] patients in the CT-P13 SC 120 mg group and 113 [78.5%] patients in Placebo SC group) were ongoing with the study at Week 54.

During maintenance, 13 (4.4%) patients in the SC 120mg arm and 9 (6.3%) in the placebo arm discontinued due to progressive disease.

Figure 27. Patient Disposition: All-Randomized Population



CHMP comment

The number of discontinuations is fairly high but balanced between the groups.

The Applicant is requested to provide a Figure of Patient Disposition which outlines for how many patients the dose was escalated at/after week 22.

It should be clarified how patients with progressive disease who discontinued the study differed from patients who received a dose increase. If possible, the differentiation should be displayed in the flow chart Figure of Patient Disposition.

Updated comments (RSI AR)

An updated flow chart of patient disposition up to W102 was provided and is presented above.

Recruitment

A total of 800 patients from 104 study centers in 15 countries were screened and 548 patients from 92 study centers in 14 countries were enrolled in this study.

01 September 2020 (first patient's first study drug administration date) to 07 July 2022 (study cut-off date: date for each patient's Week 54 visit [07 July 2022 as the last patient's Week 54 visit])

Conduct of the study

Table 30. Major Protocol Deviations: All-Randomized Population

	CT-P13 SC 120 mg (N=294)	Placebo (N=144)	Total (N=438)	Excluded Populations[1]
	Number (%) of patients			
Major protocol deviation	5 (1.7)	6 (4.2)	11 (2.5)	
Mis-randomization	0	2 (1.4)	2 (0.5)	PK, PP
Non-compliance of inclusion or exclusion criteria which affect the efficacy results	1 (0.3)	1 (0.7)	2 (0.5)	PP
Randomization without clinical response at Week 10[2]	2 (0.7)	2 (1.4)	4 (0.9)	PP
Prohibit therapy during treatment Period	2 (0.7)	1 (0.7)	3 (0.7)	PP

Abbreviations: PK, pharmacokinetic; PP, per-protocol.

1. Major protocol deviation excluded patients from the specified population(s).
2. Four patients were re-confirmed as non-responder at Week 10 after randomization.

Numbers analysed

All 548 enrolled patients were included in the ITT population.

All-randomized population consisted of 438 patients who were randomly assigned to study treatment and initiated the maintenance phase at Week 10 (294 and 144 patients in the CT-P13 SC 120 mg and Placebo SC groups, respectively).

The PP population included 421 patients (286 and 135 patients in the CT-P13 SC 120 mg and Placebo SC groups, respectively). A total of 17 patients (11 patients with major protocol deviations, 2 patients without any full dose of study drug at Week 10 or thereafter prior to Week 54 and 4 patients without any efficacy evaluation result after Week 10 study drug administration) were excluded from PP population.

CHMP comment

Major protocol deviations were few and balanced across treatment arms. No major concerns regarding GCP have emerged based on study conduct.

Updated comments (3rd RSI AR)

It has become apparent during the assessment that the overall study conduct and the concordance of the protocol and planned statistical analyses were not adequate. The number and nature of the protocol violations are such that the results do not provide a meaningful interpretation.

Baseline data

Baseline data are presented only for patients who were randomised at week 10, i.e those who responded to the induction treatment.

The mean (SD) age of patients was 38.2 (12.78) and 40.4 (13.49) years in the CT-P13 SC 120 mg and Placebo SC groups, respectively. The majority of patients were White (428 [97.7%] patients). The mean (SD) screening weight of patients was 72.40 (16.511) and 75.76 (15.011) kg in the CT-P13 SC 120 mg and Placebo SC groups, respectively and the mean (SD) screening BMI of patients was 24.160 (4.3858) and 25.091 (4.1768) kg/m^2 in the CT-P13 SC 120 mg and Placebo SC groups, respectively.

Among responders to the induction, the mean modified Mayo score at baseline was 6.6 for the CT-P13 SC 120 mg group and 6.7 for the placebo group.

Table 31. Baseline characteristics of randomised subjects in study CT-P13 3.7

Parameter Statistics	CT-P13 SC 120 mg (N=294)	Placebo (N=144)	Total (N=438)
Age (years)			
n	294	144	438
Mean (SD)	38.2 (12.78)	40.4 (13.49)	38.9 (13.04)
Median	37	39	37
Min, Max	18, 73	18, 75	18, 75
Sex, n (%)			
Male	163 (55.4)	83 (57.6)	246 (56.2)
Female	131 (44.6)	61 (42.4)	192 (43.8)
Female fertility status, n (%)[1]			
Pre-menarche	0	0	0
Surgically sterilized	4 (3.1)	1 (1.6)	5 (2.6)
Post-menopausal	22 (16.8)	17 (27.9)	39 (20.3)
Potentially able to bear children	105 (80.2)	43 (70.5)	148 (77.1)
Other	0	0	0
Race, n (%)			
American Indian or Alaska Native	6 (2.0)	4 (2.8)	10 (2.3)
Asian	0	0	0
Black or African American	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
White	288 (98.0)	140 (97.2)	428 (97.7)
Not allowed by investigator country regulations	0	0	0
Other	0	0	0
Ethnicity, n (%)			
Hispanic or Latino	7 (2.4)	4 (2.8)	11 (2.5)
Non-Hispanic or Non-Latino	285 (96.9)	140 (97.2)	425 (97.0)
Unknown	2 (0.7)	0	2 (0.5)
Screening height (cm)			

n	294	144	438
Mean (SD)	172.59(9.711)	173.43 (9.514)	172.86 (9.644)
Median	173	174	173
Min, Max	145, 208	150, 194	145, 208
Screening weight (kg)			
n	294	144	438
Mean (SD)	72.40 (16.511)	75.76 (15.011)	73.50 (16.094)
Median	70.90	76.85	72.30
Min, Max	42.1, 130.2	44.4, 108.8	42.1, 130.2
Screening body mass index (kg/m^2)			
n	294	144	438
Mean (SD)	24.160 (4.3858)	25.091(4.1768)	24.466(4.3356)
Median	23.260	24.715	23.715
Min, Max	15.09, 35.96	16.53, 34.51	15.09, 35.96
Previous exposure to biologic agent and/or JAK inhibitors, n (%)			
Used	29 (9.9)	13 (9.0)	42 (9.6)
Not used	265 (90.1)	131 (91.0)	396 (90.4)
Use of treatment with oral corticosteroids at Week 0, n (%)			
Used	120 (40.8)	61 (42.4)	181 (41.3)
Not used	174 (59.2)	83 (57.6)	257 (58.7)
Clinical remission at Week 10 by modified Mayo score, n (%)			
Remitter	143 (48.6)	66 (45.8)	209 (47.7)
Non-remitter	151 (51.4)	78 (54.2)	229 (52.3)

Abbreviations: JAK, Janus kinase; Max, maximum; Min, minimum; N, number of the patients; SC, subcutaneous; SD, standard deviation.

Note: Percentages were calculated by using the number of patients in the all-randomized population as the denominator.

1. Percentages were based on the number of female patients.

Concomitant Medications

A total of 434 (99.5%) patients had taken at least 1 concomitant medication (295 [99.7%] and 139 [99.3%] patients in the CT-P13 SC 120 mg and Placebo SC treatment groups, respectively) during the treatment period (from Week 0 through Week 54). The most commonly reported concomitant medications by drug class were antidiarrheals, intestinal anti-inflammatory/anti-infective agents (407 [93.3%]in total; 276 [93.2%] and 131 [93.6%] patients in the CT-P13 SC 120 mg group and Placebo SC group, respectively). Among them, mesalazine was the most commonly used concomitant medication by preferred term (PT) (382 [87.6%] patients in total; 254 [85.8%] and 128 [91.4%] patients in the CT-P13 SC 120 mg group and Placebo SC group, respectively).

A total 91 (20.9%) patients (64 [21.6%] and 27 [19.3%] patients in CT-P13 SC 120 mg and Placebo SC groups, respectively) had taken immunosuppressants during maintenance phase. Among them, azathioprine was the most commonly used concomitant medication by PT (90 [20.6%] patients in total; 63 [21.3%] and 27 [19.3%] patients in CT-P13 SC 120 mg and Placebo SC groups, respectively).

CHMP comment

All baseline data were presented only for patients who were randomised at week 10, i.e those who responded to the induction treatment. It is not known how non-responders differed from responders.

Among responders at week 10, demographic characteristics at baseline were balanced between CT-P13 SC 120 mg and Placebo treatment groups. The mean body weight among all subjects was 73.50 kg with a range of 42.1 to 130.2 kg. In this study, all patients received the same dose of CT-P13, regardless of weight.

No baseline characteristics were presented for the patient groups relevant for the proposed dose escalation. Baseline characteristics should be tabled for patients who required/received dose escalation and compared to those who did not.

Updated comments (RSI AR)

The baseline characteristics of dose adjusted patients are no longer relevant as the proposal for dose adjustment was withdrawn.

Outcomes and estimation

Primary Endpoint

The primary efficacy endpoint of the study was clinical remission at Week 54, by modified Mayo score.

In the All-randomized Population, at Week 54, 127 (43.2%) patients receiving CT-P13 SC 120 mg achieved clinical remission compared to 30 (20.8%) patients receiving placebo SC. The estimated difference in proportion between the treatment groups was 21.1 (95% CI: 11.8-29.3, p-value <0.0001) in favour of CT-P13 SC 120 mg.

Sensitivity analysis

Results of the primary endpoint variable were very similar in the All-Randomized Population and in the Per-Protocol population as well as in the sensitivity analyses utilizing Fisher's exact test, logistic regression model, excluding war-affected patients in Ukraine and excluding all patients in Ukraine.

To evaluate the effect of missing data on the primary endpoint, tipping point analysis was conducted on the all-randomized population. A total of 191 patients (109 [37.1%] and 82 [56.9%] patients in the CT-P13 SC and Placebo groups, respectively) were considered missing in the tipping point analysis, including 151 patients (81 [27.6%] and 70 [48.6%] patients in the CT-P13 SC and Placebo groups, respectively) who received a dose adjustment prior to Week 54 and an additional 40 patients (28 [9.5%] and 12 [8.3%] patients in the CT-P13 SC and Placebo groups, respectively) with missing or incomplete data for the evaluation of the primary efficacy assessment.

The tipping point analysis was conducted using stratified CMH test of the same method for the primary endpoint analysis. It was shown that the proportion of patients achieving the clinical remission was significantly higher in CT-P13 SC 120 mg group (p-value < 0.05) if the increased proportion of remitters in the Placebo SC group was not more than 7 percentage points higher than the increased proportion of remitters in the CT-P13 SC 120 mg group. Given that the estimated treatment effect over Placebo is 21.1%, the conclusion of the primary analysis does not seem to have been significantly impacted by missing data.

Effect of Dose Adjustment on Clinical Remission at Week 54

To evaluate the treatment effect in patients with dose adjustment to CT-P13 SC 240 mg prior to Week 54 within CT-P13 SC group, the primary endpoint was summarized for patients with and without dose adjustment in CT-P13 SC 120 mg group using a frequency table without statistical test.

A total of 81 patients with dose adjustment prior to Week 54 in the CT-P13 SC 120 mg group were assessed for clinical remission. Among the patients with dose adjustment in CT-P13 SC 120 mg group, 20/81 (24.7%) patients achieved clinical remission at Week 54.

Subgroup analyses

Table 32. Proportion of Patients Achieving Clinical Remission at Week 54 by subgroup (Subgroups – Sex, Age, and Race [White]): All-Randomized Population

	CT-P13 SC 120 mg (N=294)	Placebo (N=144)	Difference (95% CI)[1]	P-value[2]
	n/N' (%) of patients			
Subgroup by Sex				
Male				
Proportion of patients achieving clinical remission at Week 54	70/163 (42.9)	12/83 (14.5)	26.1 (14.2, 36.2)	<.0001
Female				
Proportion of patients achieving clinical remission at Week 54	57/131 (43.5)	18/61 (29.5)	14.3 (-0.7, 27.5)	0.0500
Subgroup by Age				
<35 years				
Proportion of patients achieving clinical remission at Week 54	58/129 (45.0)	11/54 (20.4)	23.7 (8.4, 36.0)	0.0017
≥35 years				
Proportion of patients achieving clinical remission at Week 54	69/165 (41.8)	19/90 (21.1)	19.1 (7.0, 29.7)	0.0014
Subgroup by Race				
White				
Proportion of patients achieving clinical remission at Week 54	124/288 (43.1)	30/140 (21.4)	20.5 (11.0, 28.9)	<.0001

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; JAK, Janus kinase; SC, subcutaneous.

Note: Clinical remission was defined as modified Mayo score with a stool frequency subscore of 0 or 1 point, rectal bleeding subscore of 0 point, and endoscopic subscore of 0 or 1 point. Analysis was stratified by previous exposure to biologic agent and/or JAK inhibitors (used or not used), use of treatment with oral corticosteroids at Week 0 (used or not used) and clinical remission at Week 10 (remitter or non-remitter by modified Mayo score). Patients with dose adjustment to CT-P13 SC 240 mg prior to Week 54 were considered as non-remitter.

N' = number of patients in the subgroup

1. The difference of proportions between 2 treatment groups was estimated using CMH weights, and the 95% stratified Newcombe CI with CMH weights were presented.
2. The nominal p-value from stratified CMH test is presented in descriptive purpose.

Key secondary endpoints

Table 33. Proportion of Patients Achieving Key Secondary Endpoints at Week 54 in Study CT-P13 3.7: All-Randomized Population

	CT-P13 SC 120 mg (N=294)	Placebo SC (N=144)	Difference (95% CI)[1]	P-value[2]
Clinical response at Week 54[3]	158 (53.7%)	45 (31.3%)	21.1 (11.2, 30.1)	<0.0001
Endoscopic-histologic mucosal improvement at Week 54[4]	105 (35.7%)	24 (16.7%)	18.0 (9.1, 25.7)	<0.0001
Corticosteroid-free remission at Week 54[5]	44/120 (36.7%)	11/61 (18.0%)	17.3 (3.1, 28.9)	0.0127

Source: CSR CT-P13 3.7 Post-text Tables 14.2.2.1, 14.2.2.2, 14.2.2.3

Note: Analysis was stratified by previous exposure to biologic agent and/or JAK inhibitors (used or not used), use of treatment with oral corticosteroids at Week 0 (used or not used) and clinical remission at Week 10 (remitter or non-remitter by modified Mayo score). Patients with dose adjustment to CT-P13 SC 240 mg prior to Week 54 were considered as non-responders or non-remitters.

[1] The difference of proportions between 2 treatment groups estimated using CMH weights, and the 95% stratified Newcombe CI with CMH weights were presented.

[2] The p-value from stratified CMH test was presented.

[3] Clinical response was defined as a decrease in modified Mayo score from baseline of at least 2 points and at least 30%, with an accompanying decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1 point.

[4] Endoscopic histologic mucosal improvement was defined as an absolute endoscopic subscore of 0 or 1 point from modified Mayo score and an absolute RHI score of 3 points or less with an accompanying lamina propria neutrophils and neutrophils in epithelium subscore of 0 point.

[5] Corticosteroid-free remission was defined as being in clinical remission by modified Mayo score in addition to not requiring any treatment with corticosteroid for at least 8 weeks at Week 54, among the patients who used oral corticosteroids at baseline. Percentages were calculated by using the number of patients who used oral corticosteroids at baseline as the denominator.

Abbreviations: CMH, Cochran-Mantel-Haenszel; CI, confidence interval; JAK, Janus kinase; SC, Subcutaneous.

Sensitivity and subgroup analyses

Results of key secondary endpoint variables were very similar in the All-Randomized Population and in the Per-Protocol population as well as in the sensitivity analyses utilizing Fisher's exact test, logistic regression model, excluding war-affected patients in Ukraine and excluding all patients in Ukraine.

Subgroup analyses of key secondary endpoints by sex are presented in the tables below.

Table 34. Proportion of Patients Achieving Clinical Response at Week 54 (Subgroup – Sex): All-Randomized Population

	CT-P13 SC 120 mg (N=294)	Placebo (N=144)	Difference (95% CI)[1]	P-value[2]
	n/N' (%) of patients			
Subgroup by Sex				
Male				
Proportion of patients achieving clinical response at Week 54	85/163 (52.1)	20/83 (24.1)	25.5 (12.6, 36.8)	<.0001
Female				

Proportion of patients achieving clinical response at Week 54	73/131 (55.7)	25/61 (41.0)	15.0 (-0.2, 29.2)	0.0437

Table 35. Proportion of Patients Achieving Endoscopic Histologic Mucosal Improvement at Week 54 (Subgroup – Sex): All-Randomized Population

	CT-P13 SC 120 mg (N=294)	Placebo (N=144)	Difference (95% CI)[1]	P-value[2]
	n/N' (%) of patients			
Subgroup by Sex				
Male				
Proportion of patients achieving endoscopic-histologic mucosal improvement at Week 54	56/163 (34.4)	10/83 (12.0)	20.2 (8.9, 29.8)	0.0004
Female				
Proportion of patients achieving endoscopic-histologic mucosal improvement at Week 54	49/131 (37.4)	14/61 (23.0)	14.6 (0.0, 27.0)	0.0379

Table 36. Proportion of Patients Achieving Corticosteroid-Free Remission at Week 54 (Subgroup – Sex): All-Randomized Population

	CT-P13 SC 120 mg (N=292)	Placebo (N=140)	Difference (95% CI)[1]	P-value[2]
	n/N' (%) of patients			
Subgroup by Sex				
Male				
Proportion of patients achieving corticosteroid-free remission at Week 54	25/70 (35.7)	3/38 (7.9)	26.3 (9.3, 39.4)	0.0017
Female				
Proportion of patients achieving corticosteroid-free remission at Week 54	19/50 (38)	8/23 (34.8)	4.2 (-19.4, 25.0)	0.7185

Effect of Dose Adjustment on Clinical Response at Week 54

A total of 81 patients with dose adjustment prior to Week 54 in the CT-P13 SC 120 mg group were assessed for clinical response at Week 54. Among the patients with dose adjustment in CT-P13 SC 120 mg group, 40/81 (49.4%) patients achieved clinical response at Week 54, 18/81 (22.2%) patients achieved endoscopic-histologic mucosal improvement at Week 54 and 13/43 (30.2%) patients achieved corticosteroid-free remission at Week 54.

Other Secondary Efficacy Endpoints

Other secondary efficacy endpoints were clinical remission assessed at weeks 10 and 22, maintenance of clinical remission at Week 54, sustained remission at both Week 22 and Week 54, clinical response assessed at weeks at weeks 10 and 22, endoscopic-histologic mucosal improvement assessed at weeks at weeks 8 and 22and scores and change from baseline in SIBDQ. The main results are summarised in tables below.

Table 37. Proportion of Patients Achieving Clinical Remission by modified Mayo score at Weeks Other Than Week 54: All-Randomized Population

	CT-P13 SC 120 mg (N=294)	Placebo SC (N=144)	Difference (95% CI)[1]	P-value[2]
Clinical remission at Week 10	143 (48.6%)	66 (45.8%)		
Clinical remission at Week 22	128 (43.5%)	41 (28.5%)	13.8 (4.1, 22.7)	0.0025
Clinical remission at Week 54	127 (43.2%)	30 (20.8%)	21.1 (11.8, 29.3)	<0.0001

Among the patients with clinical remission at Week 10, 91/143 (63.6%) patients in the CT-P13 SC 120 mg group maintained clinical remission at Week 54, compared to 18/66 (27.3) in the Placebo SC group.

Table 37 and Table 38 present the proportion of patients in the all-randomised population achieving clinical response at weeks 10, 22 and 54. At week 10 patients were per definition responders by modified Mayo score, as only responders were randomised. However, due to a few misclassifications, the responder percentages are not 100 at week 10. Of note, among patients enrolled in the induction phase, 65/548, 11.9% were non-responders at Week 10.

Table 38. Proportion of Patients Achieving Clinical Response by modified Mayo score at Weeks Other Than Week 54: All-Randomized Population

	CT-P13 SC 120 mg (N=294)	Placebo SC (N=144)	Difference (95% CI)[1]	P-value[2]
Clinical Response at Week 10	292 (99.3)	142 (98.6)		
Clinical Response at Week 22	187 (63.6)	64 (44.4)	18.3 (8.4, 27.9)	0.0002
Clinical Response at Week 54	158 (53.7)	45 (31.3)	21.1 (11.2, 30.1)	<.0001

Table 39. Proportion of Patients Achieving Total and Partial Clinical Response: All-Randomized Population

Parameter Visit	CT-P13 SC 120 mg (N=294)	Placebo (N=144)	Difference (95% CI)[1]	P-value[2]
	Number (%) of patients			
Total clinical response				
Week 10	288 (98.0)	140 (97.2)		
Week 22	188 (63.9)	68 (47.2)	16.0 (6.1, 25.6)	0.0011
Week 54	156 (53.1)	46 (31.9)	19.7 (9.8, 28.8)	<.0001
Partial clinical response				
Week 2	219 (74.5)	110 (76.4)		
Week 6	257 (87.4)	118 (81.9)		
Week 10	293 (99.7)	143 (99.3)		
Week 14	267 (90.8)	122 (84.7)	5.6 (-0.8, 13.0)	0.0812
Week 22	214 (72.8)	85 (59.0)	13.3 (3.9, 22.8)	0.0044
Week 30	194 (66.0)	68 (47.2)	17.8 (7.9, 27.4)	0.0002
Week 38	188 (63.9)	60 (41.7)	21.2 (11.3, 30.6)	<.0001
Week 46	183 (62.2)	56 (38.9)	21.9 (11.9, 31.2)	<.0001
Week 54	173 (58.8)	52 (36.1)	21.2 (11.3, 30.5)	<.0001

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; JAK, Janus kinase; SC, subcutaneous.

Note: Total clinical response was defined as decrease in total Mayo score from baseline of at least 3 points and at least 30%, with an accompanying decrease in rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1 point. Partial clinical response was 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. Analysis was stratified by previous exposure to biologic agent and/or JAK inhibitors (used or not used), use of treatment with oral corticosteroids at Week 0 (used or not used) and clinical remission at Week 10 (remitter or non-remitter by modified Mayo score).
Patients with dose adjustment to CT-P13 SC 240mg prior to their scheduled visit of interest were considered as non-responder.

1. For the results after Week 10 randomization, the difference of proportions between 2 treatment groups was estimated using CMH weights, and the 95% stratified Newcombe CI with CMH weights were presented.
2. For the results after Week 10 randomization, the nominal p-value from stratified CMH test was presented in descriptive purpose.

Endoscopic-histologic mucosal improvement at weeks 8 and 22 is described in table **39**.

Table 40. Proportion of Patients Achieving Endoscopic-Histologic Mucosal Improvement at Weeks other than Week 54: All-Randomized Population

Visit	CT-P13 SC 120 mg (N=294)	Placebo (N=144)	Difference (95% CI)[1]	P-value[2]
	Number (%) of patients			
Week 8	108 (36.7)	51 (35.4)		
Week 22	105 (35.7)	36 (25)	9.5 (0.2, 18.0)	0.0343

The mean (SD) SIBDQ score were improved in both treatment groups up to Week 10. After randomization, SIBDQ score in CT-P13 SC 120 mg group were well maintained, and slightly higher than in the Placebo SC group up to Week 54 (data not shown for brevity).

Long-term follow-up

Table 41. Proportion of Patients Achieving Clinical Remission at Week 54 and Week 102: All-Randomized Population

Visit	CT-P13 SC 120 mg (N=294)	Placebo (N=144)
	n/N' (%) of patients	
Week 54	125/224 (55.8)	30/99 (30.3)
Week 102	107/178 (60.1)	26/82 (31.7)

Note: Clinical remission was defined as modified Mayo score with a stool frequency subscore of 0 or 1 point, rectal bleeding subscore of 0 point, and endoscopic subscore of 0 or 1 point. Patients with dose adjustment to CT-P13 SC 240 mg prior to their scheduled visit of interest were considered as non-remitter. Percentages are calculated using the number of patients treated in extension phase and having modified mayo score at their scheduled visit of interest as denominator.

Among patients originally randomised to placebo 26/144 (18.1%) were in clinical remission two years after a successful induction treatment with infliximab IV, despite no active treatment after week 10.

CHMP comment

As discussed in the methods section, the study´s ability to provide meaningful results at Week 54 is inherently compromised due to dose escalation/switch to active treatment allowed in the protocol.

The proportion of patients who achieved a clinical remission by modified Mayo at Week 54 was significantly higher in the CT-P13 SC 120 mg treatment group (127 [43.2%]) than in the Placebo SC treatment group (30 [20.8%]). All sensitivity analyses showed similar results.

There are no tables depicting the details of the non-responder category at Week 54. The MAH should provide tables outlining the number of patients who were: a) non-responder according to the clinical criteria b) dose was escalated/switch to active c) discontinuation before Week 54 d) missing data e) incomplete data f) any other reason and corresponding combination categories.

The difference between placebo and CT-P13 SC 120 mg treatment was notable also for all secondary efficacy endpoints. At week 22, clinical remission by modified Mayo score was achieved by 128 (43.5%) and 41 (28.5%) patients in the CT-P13 SC 120 mg treatment group and in the Placebo SC treatment group, respectively. A small difference between treatment arms was seen in measured clinical parameters already at week 14, i.e four weeks (two SC doses) after the switch from IV Remsima. The actual values of endoscopic scores continued to improve throughout the study in the treatment arm while improvement was much less pronounced in the placebo arm, although also present throughout the study.

Subgroup analyses were performed for efficacy endpoints at week 54 by sex, age, and race. There were no differences in efficacy at week 54 between patients <35 or >35 years of age. Subgroup analysis by race was not feasible as 98% of participants were white. Male and female patients achieved remission and response at week 54 with equal frequency in the CT-P13 SC 120 mg treatment arm. However, in the placebo arm, women seemed to achieve response almost twice as often as men and the difference between treatment and placebo was not as pronounced. According to corticoid-free remission, there was no clear difference between Remsima and placebo among women (38% of women in the treatment arm and 35%

in the placebo arm were remitters at 54 weeks). The MAH should discuss whether this reflects a true gender difference in placebo response or if the different criteria leading to classification as a non-responder (corticosteroid use, dose increase, missing value) could have caused a discrepancy between sexes. **(OC)** Although this question might not affect the outcome of the procedure, it is considered relevant for the overall understanding of study outcome.

The tipping point analyses demonstrate that the results are fairly robust. However, in light of the 1:2 randomization the results in the placebo arm are more sensitive to changes in absolute number of patients counted as responders. It remains unclear whether all patients who switched to active treatment in the placebo arm before week 54 would have been clinical non responders at week 54. For example, if 10 patients of the ones who switched to active treatment would have been responders at Week 54, the observed efficacy effect would have been only around 15%.

Proposed induction regimen

The currently approved induction regimen for IV Remsima is identical to the one proposed now and used in study 3.7. Instead of continuing with SC 120mg Q2W from week 10 onward (as proposed now) the approved regimen is to continue with IV 5 mg/kg Q8W from week 14. Before evaluation at week 14 (as advised in the SPC) patients on this new regimen will have received two doses with Remsima SC 120mg while patient on the approved regimen will have received none. Otherwise, the posology is identical. Hence, at week 14 efficacy of the newly proposed regimen cannot be worse than the one already approved.

It has already been shown that a switch to SC Remsima from IV Remsima does not attenuate efficacy after an initial induction of 6 weeks and a switch to SC Remsima is approved at any time during maintenance, starting 8 weeks after the last IV dose. Therefore, the switch to SC Remsima at week 10, starting only 4 weeks after the last IV dose, as proposed now, does not introduce any new efficacy issues compared to already approved regimens.

Also PK analyses showed that trough drug concentration levels remained close to the steady state plasma concentration throughout the SC dosing regimen without any concentration falls due to the switch (see PK assessment in section 6).

To conclude, based on pharmacokinetic reasoning and previously established positive benefit-risk for very similar dosing regimens, introduction of the 3-IV induction dosing regimen (5 mg/kg at Weeks 0, 2 and 6) followed by SC maintenance treatment (120 mg Q2W from week 10) is acceptable from the efficacy point of view. However, as results are intended to be included in the SPC, some scrutiny of the numbers is warranted (see LoQ). Please see section 8 for safety assessment.

According to the label, available data suggest that clinical response is usually achieved within 14 weeks in the treatment of UC. This recommendation stems from the initial IV formulation and dosing intervals. The MAH is invited to discuss, whether another time point could be introduced with the current and newly proposed SC regimen.

Effect of dose adjustment

Responders at week 10 who lost response were allowed a dose increase from week 22 onward. UC is a fluctuating refractory disease with sometimes long symptom free periods. Therefore, some patients could have achieved remission again by week 54 after loss of response, even without dose escalation. Hence, the effect of dose escalation is difficult to contextualize due to the lack of an adequate control group.

Moreover, the MAH has provided a minimal amount of data to support the intended update in SPC section 4.2 to allow dose escalation. 81 [27.6%] and 70 [48.6%] patients in the CT-P13 SC and Placebo groups, respectively received a dose adjustment prior to Week 54. Among the patients with dose adjustment in the CT-P13 SC 120 mg group 40/81 (49.4%) patients regained clinical response by Week 54. Patients in the

placebo arm and patients who stayed on the initial dose of CT-P13 were not described at all. It is not clear how many patients were eligible for dose increase, how many got it, how many of these had missing data at week 54, and how the disease progressed in patients who stayed on the initial dose.

Approximately 20% of patients in active arm who underwent dose escalation were responders at Week 54 which is approximately the same number as the percentage of responders in the placebo arm. The interpretation of this result is not straight forward but it illustrates how difficult definitive interpretations of the results are in the absence of a properly designed study.

As the study design is inadequate to answer the relevant questions regarding the benefit/risk of a dose increase and the MAH provided virtually no details to enable assessment of the totality of data, the benefit-risk of a dose increase is unknown. To enable any assessment of the impact of a dose increase in UC patients, the MAH should address the following questions:

a) How many patients in each treatment arm were eligible for a dose increase before Week 54 and how many got it? The data should be presented by sex, body weight, disease severity, drug concentration and ADA status. It should also be clarified which weeks the dose increase was initiated at, i.e for how long the patients were exposed to the higher dose.

b) How did the disease progress among those who stayed on initial treatment regimen versus those who had a dose escalation? The analysis should be conducted for patients for whom dose was escalated/not escalated and patients who were eligible for dose escalation but did not escalate/did escalate. Did regain of response occur in patients who continued on placebo? Spontaneous fluctuation of the disease should be discussed and comparison should be made to patients who did not escalate and to historical controls. The MAH should provide spaghetti plots (overlay and individual) where time point of dose escalation is standardized in the middle of the graph and 4 visits before and after dose escalation are included.

c) Tha MAH claims that for patients who adjusted the dose, the reduction in the efficacy scores was observed from their following scheduled visit after the first dose adjustment. Appropriate data should be provided to support this claim.

d) Did the groups (i.e., patients for whom dose was escalated/not escalated and patients who were eligible for dose escalation but did not escalate/did escalate) differ in terms of compliance with the protocol or other parameters which could describe their well-being in addition to the primary endpoint?

e) Did loss of response or regain of response correlate with PK and/or ADA titres? Did the subjects needing dose escalation have lower concentrations of CT-P13 during the induction treatment (placebo group) and during induction and maintenance treatment (CT-P13 group)? Did the subjects who regained response have higher concentrations of CT-P13 compared to those who did not? Was the need for dose escalation or failure to regain response associated with high ADA titres? Were high ADA titres associated with low drug concentrations?

f) The MAH should provide analysis according to principal stratum estimand.

g) The MAH should discuss how the fact that patients and investigators were effectively unblinded at the time of dose escalation impacts the results.

It should be noted that the results will be based on post-hoc analyses that were not pre-defined in the protocol.

The benefit-risk balance of a dose escalation from 120mg SC Q2W to 240mg SC Q2W is very uncertain. With this initial submission, efficacy cannot be determined since very limited data was provided. Moreover, the safety of the higher dose is not known. It seems that 157 UC patients were exposed to the 240mg dose but exposure time is not known. In light of the fact that trough drug concentrations are much higher with SC dosing than with IV dosing, the dose escalation becomes even more problematic. In previous studies

on UC, the steady state C_{trough} of infliximab has been around 8 microg/l with the double IV dose of 10 mg/kg. In study 3.7, the normal SC dose of 120mg gave median C_{trough} concentrations of 13.3 microg/l. Hence, already the 120mg SC dose gives rise to considerably higher drug concentrations than those achieved with the highest approved IV dosing. Sufficient safety data with long-time exposure to such high drug concentrations has not been provided.

Of note, in the assessment report of the initial MA of Remsima SC in the treatment of UC and CD (EMEA/H/C/002576/II/0082), it was concluded based on data from Study CT-P13 1.6, that loss of response was not driven by low drug concentrations. After a dose increase from 120mg SC to 240mg SC 7/14 patients showed some sign of improvement but evidence for causality between improvement and dose increase was lacking. Moreover, the follow-up time was very limited and, therefore, the duration of the renewed response as well as the long-term safety of the high dos remained uncertain.

Updated comments (RSI AR)

Detailed characteristics of dose adjusted patients are no longer relevant as the proposal for dose adjustment was withdrawn. Since dose escalation is thus off-label, it should not be mentioned in the SPC.

7.2. Study CT-P13 3.8

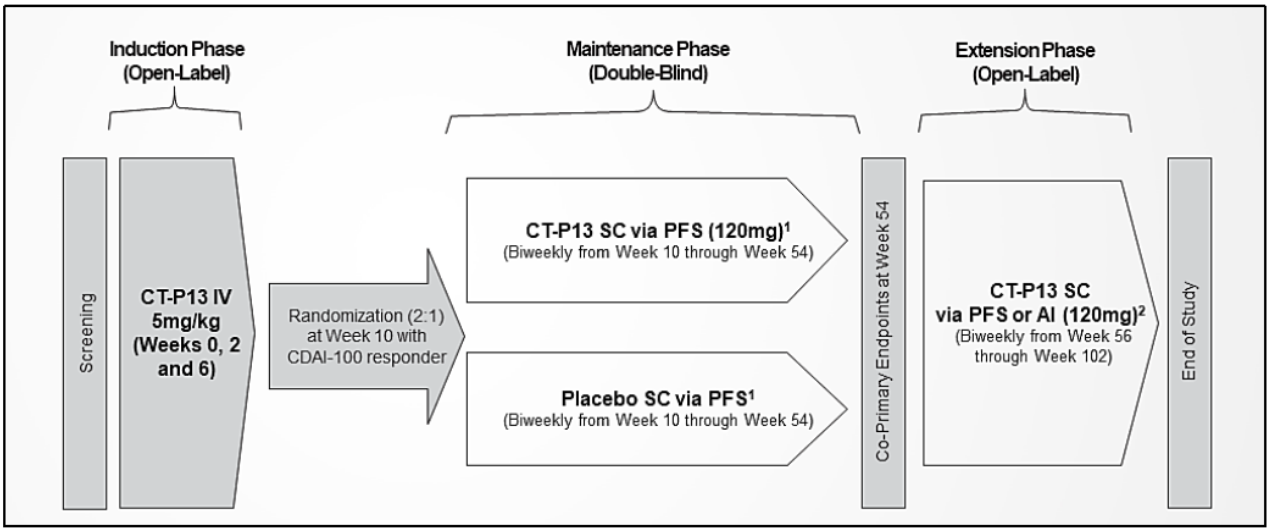
7.2.1. Study design

Study CT-P13 3.8 was a randomised, placebo-controlled, double-blind, Phase 3 study to evaluate the efficacy and safety of the CT-P13 SC as maintenance therapy in patients with moderately to severely active CD.

This study comprises of 3 study periods including screening, treatment period (Induction Phase, Maintenance Phase, and Extension Phase), and EOS visit. The schematic outline of Study CT-P13 3.8 design is illustrated in Figure 28.

This study is ongoing. The total duration of the study will be up to 112 weeks, which included screening (up to 6 weeks) and treatment period (up to the last dosing visit of study drug at Week 102) followed by EOS visit (after 4 weeks off dose period).

Figure 28. Schematic Diagram of Study CT-P13 3.8 Design



[1] From Week 22 through Week 54, dose adjustment was allowed. The patients who received CT-P13 SC 120 mg could increase the dose to CT-P13 SC 240 mg Q2W and the patients who received Placebo SC could receive CT-P13 SC 240 mg Q2W, if they initially responded but then lost response according to the loss of response criteria. Loss of Response was defined as an increase in CDAI of ≥100 points from Week 10 CDAI score with a total score ≥220.

[2] In the open-label Extension Phase, all patients who completed the Maintenance Phase up to Week 54 and who, in the opinion of the investigator, may benefit from continued treatment, will receive active treatment with CT-P13 SC 120 mg via PFS or AI from Week 56. The patients who received the adjusted dose of CT P13 SC 240 mg (double injection [2 shots] of CT-P13 SC 120 mg) Q2W in the Maintenance Phase will continue receiving the same doses of CT-P13 SC for the study treatment in the Extension Phase.

CHMP comment

This Phase 3 study was designed to evaluate the efficacy, PK, PD, and safety of the SC injection of CT-P13 (CT-P13 SC) as maintenance therapy in patients with moderately to severely active CD, after having received induction therapy with three IV-doses.

The design as such was reasonably adequate to answer the question whether maintenance therapy with SC Remsima is superior to placebo, after an initial response to induction treatment has been achieved but not the question whether a dose increase is effective. Please see further reasoning in section 7.1.1. As the design of study 3.8 was very similar to that of study 3.7, the critique will not be repeated here if the issues are identical.

Of note, for CD a dose increase is already approved for the IV maintenance regimen, but it is not comparable to the SC regimen since the PK of SC Remsima is very different. The target concentration of ≥5 µg/mL is often not reached when treating patients with IV infliximab with the 5mg/kg dosing and therefore, a dose increase may be beneficial for some patients, as stated in the approved SPC of the IV product. However, the target concentration is usually well exceeded with SC 120 mg and therefore, it is on one hand not clear whether a dose increase from Remsima SC 120mg can add efficacy and on the other hand, the safety profile cannot be extrapolated from the IV dose.

7.2.2. Methods

Study participants

The study population consisted of patients aged 18 to 75 years old, inclusive, with moderately to severely active CD who had a Crohn's disease activity index (CDAI) score between 220 and 450 points and had an inadequate response to conventional therapy.

The exclusion criteria were divided into 2 categories: general and TB exclusion criteria. Patients meeting any of the general and TB exclusion criteria were excluded from this study.

Main general Exclusion Criteria

1. Patient who had previously received 2 or more biologic agents, 2 or more JAK inhibitors, or 2 or more of both biologic agents and JAK inhibitors.
2. Patient who had previously received either a TNFα inhibitor or biologic agent within 5 half-lives prior to the first administration of the study drug (Day 0).
3. Patient who had previously demonstrated inadequate response or intolerance to TNFα inhibitors for the treatment of CD.
4. Patient who had previously received infliximab for treatment of CD or other disease.
5. Patient who had allergies to any of the excipients of infliximab or any other murine and/or human proteins or had a hypersensitivity to immunoglobulin products.
6. Patient who had received or had a plan to receive any of following prohibited medications or treatments:

- Parenteral corticosteroids for the treatment of CD within 2 weeks prior to the first administration of the study drug (Day 0)
- JAK inhibitors including but not limited to tofacitinib and baricitinib within 4 weeks prior to the first administration of the study drug (Day 0)
- Alkylating agents within 12 months prior to the first administration of the study drug (Day 0)
- Cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil within 8 weeks prior to the first administration of the study drug (Day 0)
- Live or live-attenuated vaccine within 4 weeks prior to the first administration of the study drug (Day 0)
- Abdominal surgery for, including but not limited to, active gastrointestinal bleeding, peritonitis, intestinal obstruction, gastrointestinal resection, or intra-abdominal or pancreatic abscess requiring surgical drainage within 6 months prior to the first administration of the study drug (Day 0)
- Nonautologous stem cell therapy (e.g., Prochymal) within 12 months prior to the first administration of the study drug (Day 0)
- Apheresis (e.g., Adacolumn apheresis) for the treatment of CD within 3 weeks prior to the first administration of the study drug (Day 0)
- Use of total parenteral nutrition within a month prior to the first administration of the study drug (Day 0)

- Use of exclusive enteral nutrition for more than 3 consecutive days within a month or any single day of exclusive enteral nutrition within 2 weeks prior to the first administration of the study drug (Day 0)

Patients with a history of certain serious infections and medical conditions were also excluded. For example: Active entero-vesical, entero-retroperitoneal, entero-cutaneous, or entero-vaginal fistulae within 6 months prior to the first administration of the study drug (Day 0). Entero-enteral fistulae without clinically significant symptoms in the investigator's opinion and anal fistulae without draining problems were allowed.

CHMP comment

The inclusion and exclusion criteria are only partly in line with the target population for this variation, i.e the CD patients for whom Remsima is approved:

- 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).

Only patients with anal fistulae were included (11 (4.8%) and 7 (6.3%) patients in the CT-P13 and placebo arms, respectively), while patients with entero-vesical, entero-retroperitoneal, entero-cutaneous, or entero-vaginal fistulae within 6 months prior to the trial were excluded. It is not clear how well the current study results are applicable to patients with active fistulising CD. According to the EMA guideline on the development of new medicinal products for the treatment of Crohn's Disease (CPMP/EWP/2284/99 Rev. 2), the therapeutic goals of management of fistulising CD are to close fistulas and maintain their closure, to reduce the incidence of infections in persisting fistulas, and to limit the need for surgical interventions. These endpoints have not been assessed in study 3.8.

The proposed update of section 4.2 for Remsima SC includes a harmonisation of posologies between active Crohn's disease and fistulising active Crohn's disease but many patients with active fistulising CD were excluded from the study. Taking into account the exclusion criteria, the MAH should discuss how well the current study results and resulting amendments to the SPC are applicable to patients with active fistulising CD.

Updated comments (RSI AR)

After the first RSI the MAH withdrew the proposal to harmonise posologies between active Crohn's disease and fistulising active Crohn's disease regarding timing of decision on continuation.

The newly included possibility to use a 3 IV induction regimen in addition to the 2 IV induction regimen is a minor amendment for which the small differences in the indications are not relevant. Therefore, the 3 IV regimen can be applied also to the fCD although such patients were not included in the clinical study.

Although there is no data available on the effect of dose escalation in fistulising CD, it can be assumed that the benefit is not significantly different from that seen in CD and with IV Remsima, for which a dose escalation is approved in fCD. Hence, the OC on inclusion criteria is resolved.

Treatments

In the **open-label induction phase**, the patients who met all the inclusion criteria and none of the exclusion criteria were enrolled on Day 0 (Week 0). All enrolled patients received a 2-hour CT-P13 IV infusion (5 mg/kg) during onsite visits at Weeks 0, 2, and 6 as induction treatments. Patients who were classified as a Crohn's disease activity index (CDAI)-100 responder at Week 10 after receiving 3 full doses of CT-P13 via IV infusion and for whom there were no safety concerns based on the investigator's discretion were randomly assigned to receive either CT-P13 SC or placebo SC, before treatment on Week 10.

The **double-blind maintenance phase** consisted of further doses of CT-P13 SC or placebo SC with the last dose administered no later than Week 54.

1. Treatment Group 1, CT-P13 SC: from Week 10, CT-P13 SC 120 mg was administered every 2 weeks via PFS through Week 54
2. Treatment Group 2, placebo SC: from Week 10, placebo SC (matching volume to CT-P13 SC 120 mg) was administered every 2 weeks via PFS through Week 54

In the **open-label extension phase**, all patients who complete the maintenance phase up to Week 54 and may benefit from continued treatment, in the opinion of the investigator, will receive active treatment with CT-P13 SC 120 mg via PFS or AI from Week 56. The patients who received the adjusted dose of CT-P13 SC 240 mg in the maintenance phase continued receiving the same doses of CT-P13 SC for the study treatment in the extension phase. The extension phase will continue up to Week 102.

From Week 22 through Week 102, dose adjustment was allowed as follows:

1. The patients who received CT-P13 SC 120 mg may increase the dose to CT-P13 SC 240 mg (double injection [2 shots] of CT-P13 SC 120 mg) every 2 weeks, if patients initially responded but then lost response according to the loss of response criteria

2. The patients who received placebo SC may receive CT-P13 SC 240 mg (double injection [2 shots] of CT-P13 SC 120 mg) every 2 weeks, if patients initially responded but then lost response according to the loss of response criteria

Loss of response was defined as an increase in CDAI of ≥100 points from the Week 10 CDAI score with a total score of ≥220.

CHMP comment

All patients received the same induction treatment with Remsima IV infusion (5 mg/kg) at Weeks 0, 2, and 6. After randomisation at week 10, only responders continued and received Remsima SC 120 mg or placebo every 2 weeks.

From Week 22 a dose adjustment was allowed but not mandatory and not randomised. As discussed above in section 7.1.1 the possibility to switch to higher dose/active treatment hampers the ability to assess the study objectives.

There are slight differences in the posology for CD and fistulising CD which are now proposed to be harmonised:

In the currently approved posology for CD, treatment should not be continued beyond 6 weeks if no response is seen. In fistulising CD, the decision on continuation of treatment should be made at week 14. In all other aspects the posology in CD and fistulising CD are identical.

This difference has its origin in the IV posology of the originator infliximab (Remicade) and it is assumed that there is clinical data to support it. Although it is acknowledged that the amount of weeks needed before

response is assessed is dictated by the actual dosing/visit interval more than the exact time to response and that there is no clinical data available on fistulising CD with the SC presentation, it seems evident based on the approved wording for the IV originator that response is reached slower in fistulising CD than in CD.

With the current variation, the MAH proposes to change the timing for decision on continuation of treatment to 10 weeks for both CD and fistulising CD. Since patients with active fistulising CD were excluded, Study CT-P13 3.8 cannot support this change for all fistulising CD. Furthermore, no discussion on this aspect of the amended wording was provided in the dossier.

Updated comments (RSI AR)

The Applicant has withdrawn the changes to the PI regarding timing of decision on continuation.

Objectives

Primary objective:

To demonstrate superiority of CT-P13 subcutaneous (SC) over Placebo SC based on clinical remission and endoscopic response at Week 54

Secondary objective:

To evaluate additional efficacy, pharmacokinetics (PK), pharmacodynamics (PD), usability, and overall safety including immunogenicity

Outcomes/endpoints

Co-Primary Efficacy Endpoints:

In Study CT-P13 3.8, co-primary endpoints were:

- Clinical remission at Week 54, defined as an absolute CDAI score of <150 points
- Endoscopic response at Week 54, defined as a 50% decrease in SES-CD score from the baseline value

Key Secondary Efficacy Endpoints:

- CDAI-100 response at Week 54, defined as a decrease in CDAI score of 100 points or more from the baseline value
- Clinical remission (based on AP [abdominal pain] and SF [stool frequency]) at Week 54, defined as an average worst daily AP score of ≤1 (using 4-point scale), and an average loose/watery SF score of ≤3 (of Type 6 or Type 7 on Bristol stool form scale [BSFS]) with no worsening in either score compared to the baseline value
- Endoscopic remission at Week 54, defined as an absolute SES-CD score of ≤4 and at least 2-point reduction from the baseline value with no sub-score of >1
- Corticosteroid-free remission at Week 54, defined as being in clinical remission (by an absolute CDAI score of <150) in addition to not receiving any corticosteroids for at least 8 weeks prior to Week 54, among the patients who used oral corticosteroids at baseline

Other Secondary Efficacy Endpoints:

- Clinical remission, defined as an absolute CDAI score of <150 points

- Maintenance of clinical remission at Week 54, defined as being in clinical remission by CDAI score of <150 points, among the patients in clinical remission at Week 10
- Sustained clinical remission at both Week 22 and Week 54, defined as an average worst daily AP score of ≤1 (using 4-point scale), and an average loose/watery SF score of ≤3 (of Type 6 or Type 7 on BSFS) at both Week 22 and Week 54 with no worsening in either score compared to the baseline value
- 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
- Maintenance of clinical response at Week 54, defined as being in CDAI-100 response at Week 54, among the patients in CDAI-100 response at Week 10
- Sustained clinical response at both Week 22 and Week 54, defined as a reduction from the baseline value in average worst daily AP score (using 4-point scale) and/or in average daily loose/watery SF (of Type 6 or Type 7 on BSFS) at both Week 22 and Week 54
- Endoscopic remission, defined as an absolute SES-CD score of ≤4 and at least 2-point reduction from the baseline value with no sub-score of >1
- Endoscopic response, defined as a 50% decrease in SES-CD score from the baseline value
- Patient global scale, defined as a question that asked a patient's position on achieving remission from his or her CD symptoms (Yes or No)
- SIBDQ

CHMP comment

The chosen efficacy parameters are in line with the EMA guideline on the development of new medicinal products for the treatment of Crohn's Disease (CPMP/EWP/2284/99 Rev. 2).

The primary objective of this study was to demonstrate superiority of Remsima SC over placebo in the maintenance treatment of CD patients at week 54. This is not relevant for the variation at hand as Remsima SC is already approved for maintenance treatment and it is not likely that a small adjustment of the induction regimen would render the whole treatment ineffective. However, as the MAH proposes to include the main results from study 3.8 in the SPC section 5.1, the primary endpoints also need to be assessed.

Importantly, there is no pre-defined endpoint to assess whether high dose maintenance is effective.

Sample size

The sample size of 360 patients (240 in CT-P13 SC 120 mg group and 120 in placebo SC group) was estimated to provide at least 90% statistical power to detect a statistically significant clinical effectiveness of CT-P13 SC in comparison with placebo SC in the following co-primary endpoints at the one-sided significance level of 2.5%.

- Clinical remission at Week 54, defined as an absolute CDAI score of <150 points, assuming a treatment difference of 18% and placebo rate of 19%
- Endoscopic response at Week 54 assuming a treatment difference of 26% and placebo rate of 2%

Considering a 40% non-responder rate of CDAI-100 at Week 10 before randomization, a total of approximately 600 patients were to be enrolled at Week 0. The number

CHMP comment

The study includes co-primary endpoints and the sample size has been set up to test both at alpha-level 2.5%, one sided. Study success is only to be concluded if both endpoints are positive. This is appropriate.

In the protocol, a 2% response rate in placebo has been assumed for endoscopic response at Week 54. In the end 17.9% response rate was observed. The difference between the assumed (basically no responders) and observed (a meaningful proportion of responders) cannot be neglected because it reflects that either the study population or the behavior of the endpoint (potentially including data analysis), or something else, is not as expected. The MAH should elaborate on the potential root cause(s) for this finding.

The comments outlined for study CT-P13.3.7. are relevant also here.

Updated comments (RSI AR)

The issue on discrepant response rate is not pursued further.

Randomisation

For initiating the double-blind maintenance phase, an interactive web response system (IWRS) was used for the randomization. A biostatistician generated the randomization schedule for the IWRS, which linked sequential patient randomization numbers to treatment codes. Patients classified as a CDAI-100 responder at Week 10 after receiving 3 full doses of CT-P13 via IV infusion and have no safety concern based on the investigator's discretion were randomized in a 2:1 ratio to receive either CT-P13 SC or Placebo SC, before treatment on Week 10.

The randomization was stratified by previous exposure to biologic agent and/or JAK inhibitors (used or not used), use of treatment with oral corticosteroids at Week 0 (used or not used), and clinical remission at Week 10 (remitter or non-remitter by CDAI score). Permuted block design was used to randomize patients to treatment groups, where within each block the same pre-specified ratio of patients was allocated to the treatment groups. The block size was not revealed.

CHMP comment

The stratification factors are adequate.

Importantly, as commented elsewhere in this report, the benefits of randomization are lost for the primary and secondary efficacy objectives at week 54 because changes based on subjective criteria in the randomized dosing regimen are allowed. Furthermore, randomization is not relevant for the question whether high dose maintenance is an option for patients with loss of response. This would have required randomization at the time of loss of response (week 22).

Blinding (masking)

This study had a double-blind maintenance phase, the treatment assignment for the maintenance phase was blinded to the investigators, patients, and predefined CELLTRION, Inc. and PPD-blinded teams until this Week 54 CSR was generated and will remain blinded until the Week 102 CSR is generated.

CHMP comment

In theory, the study is double blind. However, the investigator and patient know that if the dose was escalated, the patient received active treatment. Furthermore, the investigator knows that as a result of

dose escalation the patient automatically is a non-responder in the efficacy analyses. Hence, the study cannot be considered adequately blinded.

Statistical methods

For the efficacy endpoints related remission or response, the following patients were considered as non-remitter or non-responder:

- Patients who did not met the remission or response criteria
- Patients with missing or incomplete data for the evaluation of each endpoint at their scheduled visit of interest, even after applying the data handling rule
- Patients with dose adjustment to CT-P13 SC 240 mg prior to their scheduled visit of interest

The following efficacy parameters were determined as the co-primary efficacy endpoints:

- Clinical remission at Week 54, defined as an absolute CDAI score of <150 points
- Endoscopic response at Week 54, defined as a 50% decrease in SES-CD score from the baseline value

The co-primary endpoints were tested at the two-sided significance level of 5% on the all-randomized population using the p-value from Cochran-Mantel-Haenszel (CMH) test stratified by previous exposure to biologic agent and/or JAK inhibitors (used or not used), use of treatment with oral corticosteroids at Week 0 (used or not used) and clinical remission at Week 10 (remitter or non-remitter by CDAI score). If both p-values were ≤0.05, the statistical significance of both co-primary endpoints was planned to be concluded.

CHMP comment

The assessment of statistical methods is as for study CT-P13 3.7.

7.2.3. Results

Participant flow

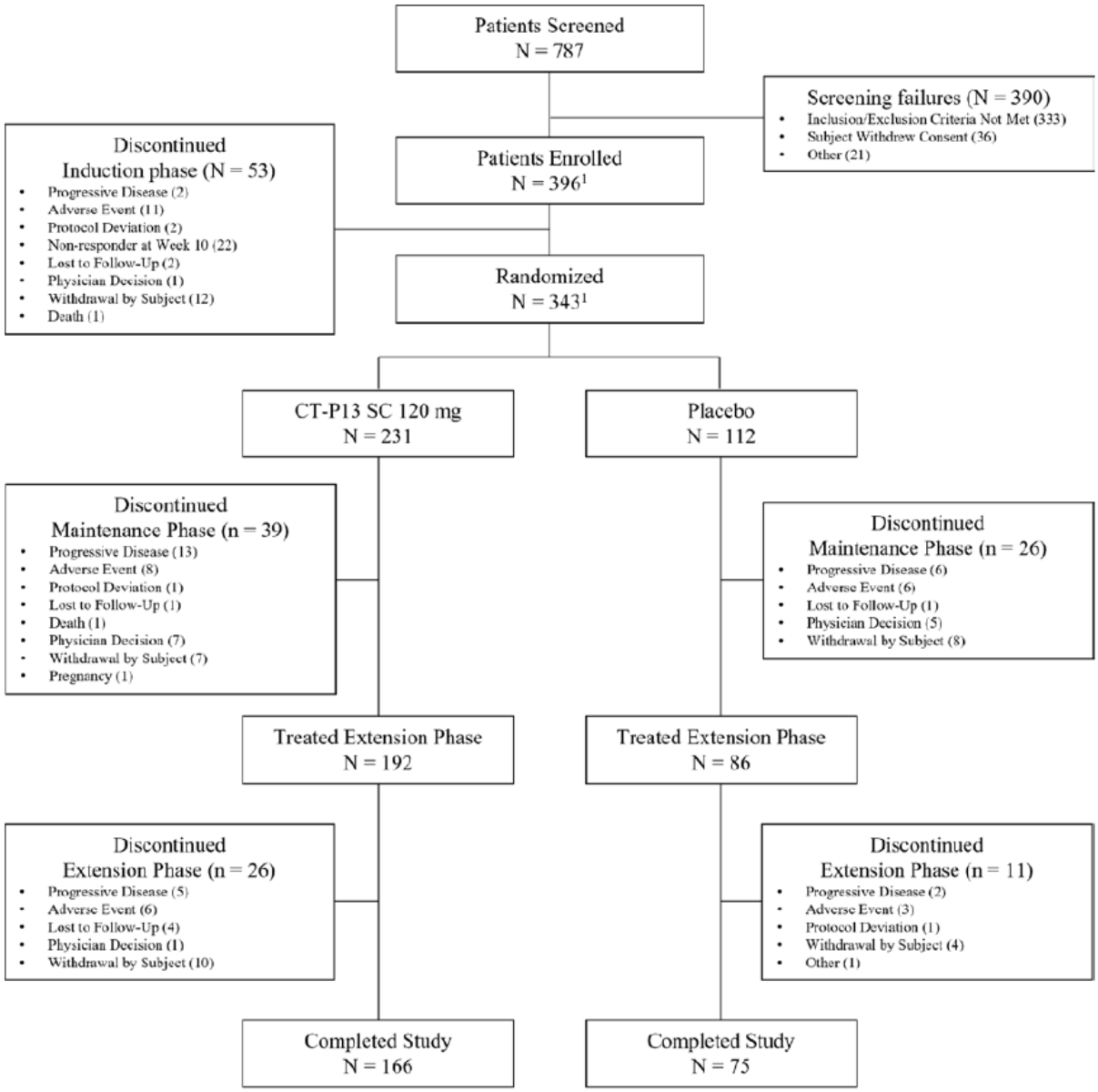
A total of 787 patients were screened. Out of 787 patients, 396 patients were enrolled in the study in which, all-randomized patients were treated with CT-P13 5 mg/kg via IV infusion in the open-label induction phase. Of these patients, 53 patients discontinued the study during the induction phase. The most frequently reported primary reason for discontinuation during the induction phase was non-responder at Week 10 (22 patients). The mean (SD) time on CT-P13 5 mg/kg via IV infusion prior to discontinuation in the induction phase was 36.5 (14.97) days.

A total of 343 patients were randomly assigned to study treatment and initiated the double-blind maintenance phase at Week 10 (231 and 112 patients in the CT-P13 SC 120 mg and placebo SC groups, respectively). All randomly assigned patients were treated in the maintenance phase (231 and 112 patients in the CT-P13 SC 120 mg and placebo SC groups, respectively). Sixty (17.5%) patients discontinued the study during the maintenance phase (35 [15.2%] and 25 [22.3%] patients in the CT-P13 SC 120 mg and placebo SC groups, respectively).

Overall, the most frequently reported primary reason for discontinuation during the maintenance phase was progressive disease (12 [5.2%] patients in the CT-P13 SC 120 mg group and 6 [5.4%] patients in placebo SC group). The mean (SD) time on study drug prior to discontinuation during the maintenance

phase was 235.7 (96.90) and 256.7 (106.90) days in the CT-P13 SC 120 mg and placebo SC groups, respectively.

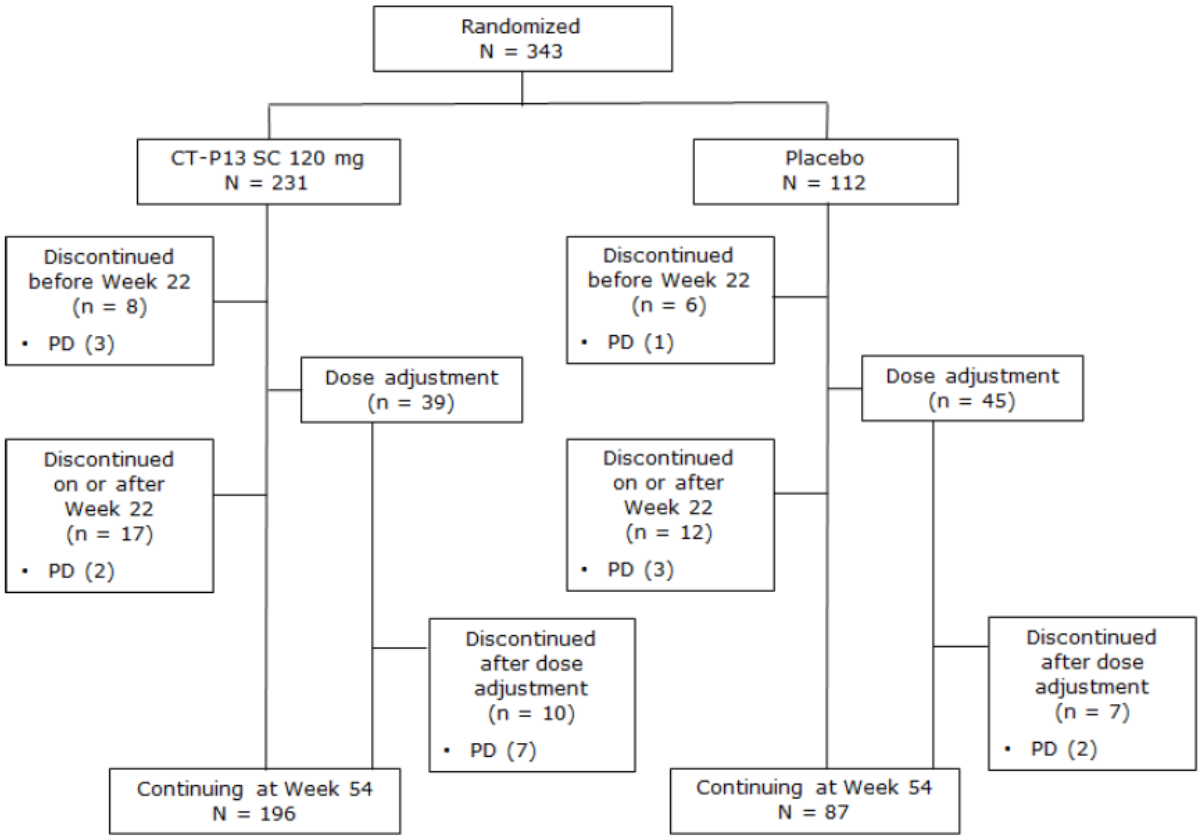
Figure 29. Patient Disposition: All-Randomized Population



Abbreviation: SC, subcutaneous.

1. A patient in CT-P13 SC 120 mg group was excluded from all analysis populations due to significant GCP non-compliance of the study EMA: deletion agreed, but pleacenter 3001.

Source: Post-text Table 14.1.1.



CHMP comment

The Applicant is requested to provide a Figure of Patient Disposition which outlines for how many patients the dose was escalated at/after week 22.

It should be clarified how patients with progressive disease who discontinued the study differed from patients who received a dose increase. If possible, the differentiation should be displayed in the flow chart Figure of Patient Disposition.

Updated comments (RSI AR)

The number of patients with dose adjustment has been clarified (see section 13 for assessment of responses).

The MAH has explained that dose adjustment and disease progression had different indicators and were independently decided. Only two patients in each treatment arm had disease progression but did not receive a dose escalation and were discontinued instead.

The final flow chart has been added with data up to W102.

Recruitment

A total of 787 patients from 148 study centers in 26 countries were screened and 396 patients from 114 study centers in 26 countries were enrolled in this study.

28 October 2019 (first patient's first drug administration date) to 23 August 2022 (Date for last patient's Week 54 visit).

Conduct of the study

The most frequently reported major protocol deviations were patients who were non-compliance with inclusion or exclusion criteria which affect the efficacy result (4 [1.7%] patients and 2 [1.8%] patients in the CT-P13 SC and placebo SC groups, respectively). Patients with major protocol deviations were excluded from the PP population or PP and PK populations.

There was a site () with significant GCP non-compliance. The site failed to conduct the study in accordance with ICH GCP guidelines based on the findings detected during the on-site monitoring visit. A patient, who was the only one enrolled in this study from the site, was excluded from all analysis population analysis in accordance with the Statistical Analysis Plan (SAP) version 1.0.

Table 42. Major Protocol Deviations: All-Randomized Population

	CT-P13 SC 120 mg (N=231)	Placebo SC (N=112)	Total (N=343)	Excluded Populations[1]
	Number (%) of patients			
Major protocol deviation	7 (3.0%)	4 (3.6%)	11 (3.2%)	
Mis-randomizations	2 (0.9%)	1 (0.9%)	3 (0.9%)	PP, PK
Non-compliance of inclusion or exclusion criteria which affect the efficacy result	4 (1.7%)	2 (1.8%)	6 (1.7%)	PP
Randomization without CDAI-100 response at Week 10[2]	2 (0.9%)	0	2 (0.6%)	PP
Other deviation which affects the efficacy results[3]	1 (0.4%)	1 (0.9%)	2 (0.6%)	PP

Numbers analysed

All 396 enrolled patients were included in the ITT population.

All-randomized population consisted of 343 patients who were randomly assigned to study treatment and initiated the maintenance phase at Week 10 (231 and 112 patients in the CT-P13 SC 120 mg and placebo SC groups, respectively).

The PP population included 332 patients (230 and 102 patients in the CT-P13 SC 120 mg and placebo SC groups, respectively). Among the randomized patients, 11 patients with major protocol deviation were excluded from the PP population.

CHMP comment

The reported major protocol deviations were few and balanced across treatment arms.

However, there is a discrepancy in the reported number of patients analysed per protocol. It is stated that 11 patients with major protocol deviation were excluded from the PP population, only one of whom was in the CT-P13 arm. However, in Table 7.2.3.1 it is stated that 7 major protocol deviations occurred in the CT-P13 arm and 4 in the placebo arm. The numbers should be clarified and aligned.

No other concerns regarding GCP or validity of the results have emerged based on study conduct. Exclusion of the GCP non-compliant site is endorsed.

Updated comments (RSI AR)

The discrepancies have been clarified.

Baseline data

Baseline data are presented only for patients who were randomised at week 10, i.e those who responded to the induction treatment.

The mean (SD) age of patients was 36.0 (12.53) and 32.3 (11.53) years in the CT-P13 SC 120 mg and placebo SC groups, respectively. In total, there was a slightly higher proportion of male patients than female patients (203 [59.2%] male and 140 [40.8%] female patients). Most patients were White (312 [91.0%] patients). The mean (SD) screening weight of patients was 68.88 (15.584) and 67.32 (15.241) kg in the CT-P13 SC 120 mg and placebo SC groups, respectively. The mean (SD) screening BMI of patients was 23.272 (4.3960) and 22.549 (4.3786) kg/m^2 in the CT-P13 SC 120 mg and placebo SC groups, respectively.

Overall, the mean (SD) time since active CD diagnosis was 4.38 (5.375) years and similar between the 2 groups (4.34 [5.183] and 4.45 [5.775] years for the CT-P13 SC 120 mg and placebo SC groups, respectively).

Among responders to the induction, the mean CDAI score at baseline was 312 for the CT-P13 SC 120 mg group and 310 for the placebo group.

Table 43. Baseline characteristics

Parameter Statistics	CT-P13 SC 120 mg (N=231)	Placebo SC (N=112)	Total (N=343)
Age (years)			
n	231	112	343
Mean (SD)	36.0 (12.53)	32.3 (11.53)	34.8 (12.32)
Median	36.0	29.0	33.0
Min, Max	18, 75	18, 66	18, 75
Gender, n (%)			
Male	134 (58.0%)	69 (61.6%)	203 (59.2%)
Female	97 (42.0%)	43 (38.4%)	140 (40.8%)
Female fertility status, n (%)[1]			
Surgically sterilized	1 (1.0%)	2 (4.7%)	3 (2.1%)
Post-menopausal	21 (21.6%)	4 (9.3%)	25 (17.9%)
Potentially able to bear children	75 (77.3%)	37 (86.0%)	112 (80%)
Race, n (%)			
American Indian or Alaska Native	8 (3.5%)	5 (4.5%)	13 (3.8%)
Asian	9 (3.9%)	4 (3.6%)	13 (3.8%)
Black or African American	1 (0.4%)	0	1 (0.3%)
White	211 (91.3%)	101 (90.2%)	312 (91.0%)
Other	2 (0.9%)	2 (1.8%)	4 (1.2%)
Ethnicity, n (%)			
Hispanic or Latino	12 (5.2%)	7 (6.3%)	19 (5.5%)
Non-Hispanic or Non-Latino	219 (94.8%)	105 (93.8%)	324 (94.5%)
Unknown	0	0	0
Screening height (cm)			
n	231	112	343
Mean (SD)	171.63 (8.902)	172.41 (10.585)	171.89 (9.476)
Median	172.00	173.00	172.00
Min, Max	148, 194	145, 203	145, 203
Screening weight (kg)			

Parameter Statistics	CT-P13 SC 120 mg (N=231)	Placebo SC (N=112)	Total (N=343)
n	231	112	343
Mean (SD)	68.88 (15.584)	67.32 (15.241)	68.37 (15.467)
Median	66.00	65.00	65.60
Min, Max	41, 126	40, 101.5	40, 126
Screening BMI (kg/m^2)			
n	231	112	343
Mean (SD)	23.272 (4.3960)	22.549 (4.3786)	23.036 (4.3970)
Median	22.700	21.755	22.280
Min, Max	14.2, 34.61	15.93, 34.72	14.2, 34.72
Previous exposure to biologic agent and/or JAK inhibitors, n (%)			
Used	26 (11.3%)	9 (8.0%)	35 (10.2%)
Not used	205 (88.7%)	103 (92.0%)	308 (89.8%)
Use of treatment with oral corticosteroids at Week 0, n (%)			
Used	99 (42.9%)	43 (38.4%)	142 (41.4%)
Not used	132 (57.1%)	69[2] (61.6%)	201 (58.6%)
Clinical remission at Week 10 by CDAI score, n (%)			
Remitter	174 (75.3%)	91 (81.3%)	265 (77.3%)
Non-remitter	57 (24.7%)	21 (18.8%)	78 (22.7%)

Abbreviations: BMI, body mass index; CDAI, Crohn's disease activity index; JAK, Janus kinase; Max, maximum; Min, minimum; SC, subcutaneous; SD, standard deviation.

Note: Percentages were calculated by using the number of patients in the all-randomized population as the denominator.

1. Percentages were based on the number of female patients.
2. A patient was reported 'Not used' of the use of treatment with oral corticosteroids at Week 0 in the stratification factor at the first Week 54 CSR. However, the use of oral corticosteroid was recorded at Week 0 in concomitant medication page and was confirmed by the investigator. As a result, the patient was corrected as used patient for the treatment with oral corticosteroids at Week 0 in this final CSR. The analysis for this correction had been included in the first Week 54 CSR.

Prior and Concomitant Medications

A total of 325 (94.8%) patients had taken at least 1 prior medication (225 [94.5%] and 100 [95.2%] patients in the CT-P13 SC 120 mg and placebo SC groups, respectively). The most commonly reported prior medications by drug class was drugs for constipation (251 [73.2%] patients in total; 173 [72.7%] and 78 [74.3%] patients in the CT-P13 SC 120 mg and placebo SC groups, respectively), and the second was antidiarrheals, intestinal anti- inflammatory/anti-infective agents (186 [54.2%] patients in total; 129 [54.2%] and 57 [54.3%] patients in the CT-P13 SC 120 mg and placebo SC groups, respectively).

A total of 339 (98.8%) patients had taken at least 1 concomitant medication (235 [98.7%] and 104 [99.0%] patients in the CT-P13 SC 120 mg and placebo SC groups, respectively) during the treatment period (from Week 0 through Week 54). The most commonly reported concomitant medications by drug class was antidiarrheals, intestinal anti-inflammatory/anti- infective agents (180 [75.6%] and 71 [67.6%] patients in the CT-P13 SC 120 mg and placebo SC groups, respectively). Among them, mesalazine was the most

commonly used concomitant medication by PT (142 [59.7%] and 57 [54.3%] patients in the CT-P13 SC 120 mg and placebo SC groups, respectively).

CHMP comment

All baseline data were presented only for patients who were randomised at week 10, i.e those who responded to the induction treatment. It is not known how non-responders differed from responders.

Among responders at week 10, demographic characteristics at baseline were balanced between the treatment groups. The mean body weight among all subjects was 68.4 kg with a range of 40 to 126 kg. In this study, all patients received the same dose of CT-P13, regardless of weight.

No baseline characteristics were presented for the patient groups relevant for the proposed dose escalation. Baseline characteristics should be tabled for patients who required/received dose escalation and compared to those who did not.

Updated comments (RSI AR)

Among patients who received a dose escalation the use of oral corticosteroids was more frequent at baseline compared to those who did not require a dose increase (see section 13 Q28 for details). This could possibly reflect a more severe form of disease among those who lost response.

Outcomes and estimation

Primary Endpoint

The results of the co-primary endpoints (clinical remission based on CDAI at Week 54 and endoscopic response based on central SES-CD at Week 54) are presented in Table 43.

Table 44. Proportion of Patients Achieving Clinical Remission (Based on CDAI) at Week 54 and Endoscopic Response (Based on Central SES-CD) at Week 54 in Study CT-P13 3.8: All-randomized Population

	CT-P13 SC 120 mg (N=231)	Placebo SC (N=112)	Difference (95% CI)[1]	P-value[2]
Clinical remission based on CDAI at Week 54	144 (62.3%)	36 (32.1%)	32.1 (20.9, 42.1).	<0.0001
Endoscopic response based on central SES-CD at Week 54	118 (51.1%)	20 (17.9%)	34.7 (24.2, 43.5)	<0.0001

Source: CSR CT-P13 3.8 Post-text Table 14.2.1.1 and Table 14.2.1.2

Note: Clinical remission was defined as an absolute CDAI score of <150 points. Analysis was stratified by previous exposure to biologic agents and/or JAK inhibitors (used or not used), use of treatment with oral corticosteroids at Week 0 (used or not used) and clinical remission at Week 10 (remitter or non-remitter by CDAI score). Patients with dose adjustment to CT-P13 SC 240 mg prior to Week 54 were considered as non-remitters.

Endoscopic response was defined as a 50% decrease in SES-CD score from the baseline value. Analysis was stratified by previous exposure to biologic agents and/or JAK inhibitors (used or not used), use of treatment with oral corticosteroids at Week 0 (used or not used) and clinical remission at Week 10 (remitter or non-remitter by CDAI score). Patients with dose adjustment to CT-P13 SC 240 mg prior to Week 54 were considered as non-responders

[1] The difference of proportions between 2 treatment groups estimated using CMH weights, and the 95% stratified Newcombe CI with CMH weights are presented.

[2] The p-value from stratified CMH test is presented.

Abbreviations: CDAI, Crohn's disease activity index; CMH, Cochran-Mantel-Haenszel; CI, confidence interval; JAK, Janus kinase; SES-CD, Simplified endoscopic activity score for Crohn's disease; SC, Subcutaneous.

Sensitivity analysis

Results of the primary endpoint variable were very similar in the All-Randomized Population and in the Per-Protocol population as well as in the sensitivity analyses utilizing Fisher's exact test, logistic regression model, excluding war-affected patients in Ukraine and excluding all patients in Ukraine.

The subgroup analysis for clinical remission and endoscopic response based on gender, age and race in all-randomized population showed that gender and age generally did not have a major impact on the response at Week 54. For the subgroup based on race, only the white subgroup was analyzed since the other race subgroups were less than 5% of the all- randomized population according to SAP (results not shown here for brevity).

Effect of dose adjustment on clinical remission and endoscopic response *at week 54*

Thirty-nine patients with dose adjustment prior to Week 54 in the CT-P13 SC 120 mg group were assessed for clinical remission at Week 54. Among 39 patients with dose adjustment, 21 (53.8 %) patients achieved clinical remission and 11 (28.2 %) patients achieved endoscopic response at Week 54.

Key secondary efficacy endpoints

A summary of the key secondary efficacy endpoints is presented for the All-randomized Population in Table 44.

Table 45. Key secondary efficacy outcome in study CT-P13 3.8

	CT-P13 SC 120 mg (N=231)	Placebo SC (N=112)	Difference (95% CI)[1]	P-value[2]
	Number (%) of patients			
CDAI-100 response at Week 54	152 (65.8%)	43 (38.4%)	29.0 (17.7, 39.3)	<0.0001
Clinical remission based on AP and SF at Week 54	131 (56.7%)	35 (31.3%)	27.0 (15.8, 37.1)	<0.0001
Endoscopic remission at Week 54	80 (34.6%)	12 (10.7%)	24.9 (15.4, 32.8)	<0.0001
Corticosteroid-free remission based on CDAI at Week 54	39/98 (39.8%)	10/44 (22.7%)	17.1 (-0.4, 31.5)	0.0434

Source: CSR CT-P13 3.8 Post-text Tables 14.2.2.1, 14.2.2.2, 14.2.2.3, 14.2.2.4

Note: CDAI-100 response is defined as a decrease in CDAI score of 100 points or more from the baseline value. Clinical remission based on AP and SF was defined as an average worst daily AP score of ≤1 (using 4-point scale) and an average daily loose/watery SF score of ≤3 (of Type 6 or Type 7 on BSFS) with no worsening in either average score compared with the baseline value. Endoscopic remission is defined as an absolute SES-CD score of ≤4 and at least 2-point reduction from the baseline value with no segment sub-score of >1. Corticosteroid-free remission at Week 54 is defined as being in clinical remission (by an absolute CDAI score of <150) in addition to not receiving any corticosteroids for at least 8 weeks prior to Week 54, among the patients who used oral corticosteroids at baseline. Percentages are calculated by using the number of patients who used oral corticosteroids at baseline as the denominator. Analysis is stratified by Previous exposure to biologic agents and/or JAK inhibitors (used or not used), Use of treatment with oral corticosteroids at Week 0 (used or not used) and Clinical remission at Week 10 (remitter or non-remitter by CDAI score). Patients with dose adjustment to CT-P13 SC 240 mg prior to Week 54 are considered as non-remitter/non-responder.

[1] The difference of proportions between 2 treatment groups estimated using CMH weights, and the 95% stratified Newcombe CI with CMH weights are presented.

[2] The p-value from stratified CMH test is presented.

Abbreviations: AP, Abdominal pain; CDAI, Crohn's disease activity index; CI, confidence interval; JAK, Janus kinase; SC, Subcutaneous; SF, Stool frequency.

Clinical remission based on abdominal pain and stool frequency at Week 54 was defined as an average worst daily AP score of ≤1 (using 4-point scale) and an average daily loose/watery SF score of ≤3 (of Type 6 or Type 7 on BSFS) with no worsening in either average score compared with the baseline value.

In all-randomized population, the proportion of patients who achieved clinical remission based on AP and SF at Week 54 was higher in the CT-P13 SC 120 mg group (131 [56.7 %]) than in the placebo SC group (35 [31.3%]).

Sustained clinical remission at both Week 22 and Week 54 was defined as an average worst daily AP score of ≤1 (using 4-point scale) and an average loose/watery SF score of ≤3 (of Type 6 or Type 7 on BSFS) at both Week 22 and Week 54 with no worsening in either average score compared with the baseline value. Sustained clinical remission at both Week 22 and Week 54 was achieved by 120 (51.9%) and 33 (29.5%) patients in the CT-P13 and placebo arms, respectively.

Clinical remission defined as an absolute CDAI score of <150 points was assessed at all scheduled visits at all scheduled visits for the all-randomized population is presented in Table 45.

Table 46. Proportion of Patients Achieving Clinical Remission (Based on CDAI): All-Randomized Population

	CT-P13 SC 120 mg (N=231)	Placebo SC (N=112)	Difference (95% CI)[1]	P-value[2]
	Number (%) of patients			
Week 2	83 (35.9)	32 (28.6)		
Week 6	132 (57.1)	61 (54.5)		
Week 10	174 (75.3)	91 (81.3)		
Week 14	181 (78.4)	89 (79.5)	2.4 (-6.2, 12.0)	0.5663
Week 22	181 (78.4)	62 (55.4)	25.5 (14.9, 35.9)	<.0001
Week 30	171 (74.0)	51 (45.5)	30.5 (19.5, 40.8)	<.0001
Week 38	155 (67.1)	48 (42.9)	25.9 (14.7, 36.4)	<.0001
Week 46	145 (62.8)	42 (37.5)	27.2 (15.9, 37.5)	<.0001
Week 54	144 (62.3)	36 (32.1)	32.1 (20.9, 42.1)	<.0001

Abbreviations: CDAI, Crohn's disease activity index; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; JAK, Janus kinase; SC, subcutaneous.

Note: Clinical remission was defined as an absolute CDAI score of <150 points. Analysis was stratified by previous exposure to biologic agent and/or JAK inhibitors (used or not used), use of treatment with oral corticosteroids at Week 0 (used or not used) and clinical remission at Week 10 (remitter or non-remitter by CDAI score). Patients with dose adjustment to CT-P13 SC 240 mg prior to their scheduled visit of interest were considered as non-remitter.

1. For the results after Week 10 randomization, the difference of proportions between 2 treatment groups estimated using CMH weights, and the 95% stratified Newcombe CI with CMH weights are presented.
2. For the results after Week 10 randomization, the nominal p-value from stratified CMH test is presented in descriptive purpose.

In the open label extension phase 192 patients on CT-P13 and 86 patients on placebo continued the study after week 54. The proportion of patients who achieved clinical remission was well maintained at Week 102 compared to Week 54 in both CT-P13 and placebo groups (Table 46).

Table 47. Proportion of Patients Achieving Clinical Remission (Based on CDAI) at Week 54 and Week 102: All-Randomized Population

Visit	CT-P13 SC 120 mg (N=231)	Placebo SC (N=112)
	Number (%) of patients	
Week 62	137 (59.3)	36 (32.1)
Week 70	132 (57.1)	36 (32.1)
Week 78	131 (56.7)	34 (30.4)

Visit	CT-P13 SC 120 mg (N=231)	Placebo SC (N=112)
	Number (%) of patients	
Week 86	129 (55.8)	32 (28.6)
Week 94	126 (54.5)	33 (29.5)
Week 102	122 (52.8)	31 (27.7)

Abbreviations: CDAI, Crohn's disease activity index; SC, subcutaneous.
Note: Clinical remission is defined as an absolute CDAI score of less than 150 points. Patients with dose adjustment to CT-P13 SC 240 mg prior to their scheduled visit of interest were considered as non-remitter.

CHMP comment

The proportion of patients who achieved clinical remission by CDAI at Week 54 was higher in the CT-P13 SC 120 mg group than Placebo SC group (144 [62.3%] and 36 [32.1%] patients in CT-P13 SC 120 mg and Placebo SC groups, respectively). The estimated difference (95% CI) in proportion between the treatment groups was 32.1 (20.9, 42.1).

The proportion of patients who achieved endoscopic response (defined as a 50% decrease in SES-CD score) at Week 54 was 118 [51.1%] and 20 [17.9%] in CT-P13 SC 120 mg and Placebo SC groups, respectively. The estimated difference (95% CI) in proportion between the treatment groups was 34.7 (24.2, 43.5).

All sensitivity analyses and subgroup analyses of the primary endpoints showed similar results. All secondary endpoints supported the finding that CT-P13 SC 120mg is superior to placebo in the maintenance treatment of patients with moderately to severely active CD.

However, as discussed in the methods section, the study´s ability to provide meaningful results at Week 54 is inherently compromised due to dose escalation/switch to active treatment allowed in the protocol.

There are no tables depicting the details of the non-responder category at Week 54. The MAH should provide tables outlining the number of patients who were: a) non-responder according to the clinical criteria b) dose was escalated/switch to active c) discontinuation before Week 54 d) missing data e) incomplete data f) any other reason and corresponding combination categories.

Proposed induction regimen

Based on pharmacokinetic reasoning (see section 7.1.3) and previously established positive benefit-risk for very similar dosing regimens, introduction of the 3-IV induction dosing regimen (5 mg/kg at Weeks 0, 2 and 6) followed by SC maintenance treatment (120 mg Q2W from week 10) is acceptable from the efficacy point of view. However, as efficacy results are intended to be included in the SPC, some scrutiny of the numbers is warranted.

According to the current label, available data suggest that clinical response is usually achieved within 6 weeks in the treatment of CD and 14 weeks in the treatment of fistulising CD. With the current variation, the MAH proposes to change the timing for decision on continuation of treatment to 10 weeks for both CD and fistulising CD. Since patients with active fistulising CD were excluded, Study CT-P13 3.8 cannot support this change for all fistulising CD. Furthermore, no discussion on this aspect of the amended wording was provided in the dossier.

The MAH should provide scientific justification for the newly proposed time frame for decision making in both CD and fistulising CD. It should also be noted that decision after 6 weeks of treatment is still recommended with IV Remsima in CD and that this wording for IV is bound by the originator wording.

Effect of dose adjustment

Responders at week 10 who later lost response were allowed a dose increase from week 22 onward. CD is a fluctuating refractory disease with sometimes long symptom free periods. Therefore, some patients could have achieved remission again by week 54 after loss of response, even without dose escalation. Hence, the effect of dose escalation is difficult to contextualize due to the lack of an adequate control group.

Moreover, the MAH has provided a minimal amount of data to support the intended update in SPC section 4.2 to allow dose escalation. 84 patients (39 [16.9%] and 45 [40.2%] patients in the CT-P13 SC 120 mg and placebo SC groups, respectively) received a dose adjustment prior to Week 54. Among the 39 patients with dose adjustment in the CT-P13 SC 120 mg group 21 (53.8 %) patients achieved clinical remission by CDAI and 11 (28.2 %) patients achieved endoscopic response at Week 54. Patients who stayed on the initial dose of CT-P13 were not described at all, and neither were the 45 patients originally in the placebo arm who later switched to the double dose of CT-P13. It is not clear how many patients were eligible for dose increase, how many got it, how many of these had missing data at week 54, and how the disease progressed in patients who stayed on the initial dose.

As the study design is inadequate to answer the relevant questions regarding the benefit/risk of a dose increase and the MAH provided virtually no details to enable assessment of the totality of data, the benefit-risk of a dose increase is unknown. To enable any assessment of the impact of a dose increase in CD patients, the MAH should address the following questions:

a) How many patients in each treatment arm were eligible for a dose increase before Week 54 and how many got it? The data should be presented by sex, body weight, disease severity, drug concentration and ADA status. It should also be clarified which weeks the dose increase was initiated at, i.e for how long the patients were exposed to the higher dose.

b) How did the disease progress among those who stayed on initial treatment regimen versus those who had a dose escalation? The analysis should be conducted for patients for whom dose was escalated/not escalated and patients who were eligible for dose escalation but did not escalate/did escalate. Did regain of response occur in patients who continued on placebo? Spontaneous fluctuation of the disease should be discussed and comparison should be made to patients who did not escalate and to historical controls. The MAH should provide spaghetti plots (overlay and individual) where time point of dose escalation is standardized in the middle of the graph and 4 visits before and after dose escalation are included.

c) The MAH claims that for patients who adjusted the dose, the reduction in the efficacy scores was observed from their following scheduled visit after the first dose adjustment. Appropriate data should be provided to support this claim.

d) Did the groups (i.e., patients for whom dose was escalated/not escalated and patients who were eligible for dose escalation but did not escalate/did escalate) differ in terms of compliance with the protocol or other parameters which could describe their well-being in addition to the primary endpoint?

e) Did loss of response or regain of response correlate with PK and/or ADA titres?

f) The MAH should provide analysis according to principal stratum estimand.

g) The MAH should discuss how the fact that patients and investigators were effectively unblinded at the time of dose escalation impacts the results.

It should be noted that the results will be based on post-hoc analyses that were not pre-defined in the protocol.

The benefit-risk balance of a dose escalation from 120mg SC Q2W to 240mg SC Q2W is very uncertain. With this initial submission, efficacy cannot be determined since very limited data was provided. Moreover, the safety of the higher dose is not known. It seems that 93 CD patients were exposed to the 240mg dose but exposure time is not known. In light of the fact that trough drug concentrations are much higher with SC dosing than with IV dosing, the dose escalation becomes even more problematic. In previous studies on CD, the steady state C_{trough} of infliximab has been around 6 microg/l with the double IV dose of 10 mg/kg. In study 3.8, the normal SC dose of 120mg gave median C_{trough} concentrations of 16 microg/l. Hence, already the 120mg SC dose gives rise to considerably higher trough concentrations than those achieved with the highest approved IV dosing. Sufficient safety data with long-time exposure to such high drug concentrations has not been provided.

Of note, in the assessment report of the initial MA of Remsima SC in the treatment of UC and CD (EMEA/H/C/002576/II/0082), it was concluded based on data from Study CT-P13 1.6, that loss of response was not driven by low drug concentrations. After a dose increase from 120mg SC to 240mg SC 7/14 patients showed some sign of improvement but evidence for causality between improvement and dose increase was lacking. Moreover, the follow-up time was very limited and, therefore, the duration of the renewed response as well as the long-term safety of the high dos remained uncertain.

Updated comments (RSI AR)

- The requested additional information has been provided and is discussed in sections 7.4 and 13. Some additional clarifications are requested before a possibility for dose escalation could be approved.
- The MAH proposed to keep the approved wording unchanged regarding the time point for decision on maintenance in both CD (6 weeks) and fCD (14 weeks). This is endorsed.
- New data from the open label extension phase were submitted. The proportion of patients who achieved clinical remission and the improved mean CDAI scores were more or less maintained at Week 102 compared to Week 54 in both CT-P13 and placebo groups. Of patients originally randomised to placebo 27/112 were in clinical remission two years after a successful induction treatment with infliximab IV despite no active treatment after week 10.

7.2.4. Usability

Study background

One of the secondary objectives of the Study CT-P13 3.8 was to evaluate usability.

The CT-P13 SC or placebo SC via PFS was injected by the investigator or designee at Weeks 10 and 12, or until the patient (or caregiver, if needed) was properly trained and confident to administer the study drug at home or the study center at Weeks 14, 16, 18, 20, and 22. If needed, the patient or caregiver were retrained during the study on how to perform the injection of the study drug.

The usability population for PFS was defined as all randomly assigned patients who self-injected at least one (partial or full) dose of study drug via PFS from Week 14 to 22 and who had at least one usability assessment in maintenance phase.

Self-injection training was provided at Week 56 prior to the first AI injection. After proper training in AI injection technique, patient will self-inject with CT-P13 SC via AI at Weeks 56, 58, 60, and 62. If the patient requested it, additional training could be provided during the visits to the study center.

The usability population for AI was defined as all randomly assigned patients who self-injected at least one (partial or full) dose of study drug via AI from Week 56 to 62 and who had at least one usability assessment in extension phase.

From Week 22 through Week 102, dose adjustment was allowed. The patients who received CT-P13 SC 120 mg could increase the dose to CT-P13 SC 240 mg (double injection [2 shots] of CT-P13 SC 120 mg) every 2 weeks, if patients initially responded but then lost response according to the loss of response criteria. The patients who received placebo could also receive CT-P13 SC as described above.

Assessment

The following usability endpoints for PFS or AI were assessed as secondary endpoints only for self-injected patients.

• Usability for PFS as assessed by patient rating using PRE- and POST-self-injection assessment questionnaire (SIAQ) at Weeks 14, 16, 18, 20, and 22

• Usability for AI as assessed by patient rating using PRE- and POST-SIAQ at Weeks 56, 58, 60, and 62

• The observer rating of successful self-injection for PFS, indicated by complete dose delivery, using P8, P9, and P10 of the self-injection assessment checklist at Weeks 14 and 22

• The observer rating of successful self-injection for AI, indicated by complete dose delivery, using P8, P9, P10, and P11 of the self-injection assessment checklist at Weeks 56 and 62

• The observer rating of completion of all instructions in the self-injection assessment checklist for PFS at Weeks 14 and 22

• The observer rating of completion of all instructions in the self-injection assessment checklist for AI at Weeks 56 and 62

• Device integrity for used PFS at Weeks 14 and 22

• Device integrity for used AI at Weeks 56 and 62

Study design

Printed instructions for use (IFU) of PFS and AI, and the patient's self-injection diary for PFS or AI were provided to the patient that served as a guide while administering the study drug.

During a study center visit, the investigator or designee observed the patient how they performed the injection without assistance or guidance provided from the investigator or designee.

At each instance of CT-P13 SC or placebo SC self-injection, each patient recorded details of the injection in their patient diary including the date and time of injection, kit number of each syringe, the number of

syringes administered, and administration sites. At each visit date, the investigator or designee reviewed the patient diary and checked the number of returned syringes (unused), to judge the patient's dosing compliance and the source data was recorded in the eCRF.

The PRE-SIAQ module is a 7-item questionnaire that assessed feelings about injections, self-confidence (regarding self-injection), and satisfaction with self-injection. The patients completed the PRE-SIAQ immediately (not exceeding 1 hour) before the administration of the study drug.

The POST-SIAQ module is a 27-item questionnaire that assessed feelings about injections, self-image, self-confidence (regarding self-injection), pain and skin reactions during or after the injection (localized injection site reactions), ease of use of PFS or AI, and satisfaction with self-injection. The patients completed the POST-SIAQ immediately (not exceeding 1 hour) after the administration of the study drug.

Item score was transformed to obtain a score ranging from 0 (worst experience) to 10 (best experience) for each item.

The patient's ability to successfully follow the steps in the printed instruction for use to self-administer the study drugs was assessed using the self-injection assessment checklist. The self-injection assessment for PFS was coded as successful if instructions (P8, P9, and P10), which ask complete dose delivery in the self-injection assessment checklist, were checked as Yes. The self-injection assessment for AI was coded as successful if instructions (P8, P9, P10, and P11), which ask complete dose delivery in the self-injection assessment checklist, were checked as Yes. The investigator or designee observed the patient's self-injection and completed the checklist within 15 minutes after patient's self-injection.

The structural or mechanical integrity issues of used PFS and AI after the completion of the self-injection was assessed by the observer using a question that asked clear evidence of damage and/or compromised structural or mechanical integrity based on a visual examination (Yes or No).

Results

The CT-P13 SC 120 mg (N= 142) and placebo (N=61) SC PFS self-injection groups had totally 203 patients.

For PFS, the mean PRE-SIAQ scores (feelings about injections, self-confidence [regarding self-injection], and satisfaction with self-injection) and POST-SIAQ scores (feelings about injections, self-image, self-confidence [regarding self-injection], ease of use) for all the domains were high in both treatment groups from Week 14 to Week 22 (PRE-SIAQ mean values: 7.27 - 8.16 out of 10 and POST-SIAQ mean values: 7.38 - 8.44 out of 10). Mean POST-SIAQ scores for pain and skin reactions during or after the injection (localized injection site reactions), were 9.16 - 9.30 out of 10.

The CT-P13 SC 120 mg (N= 42) and placebo (N=19) SC AI self-injection groups had totally 61 patients.

For AI, the mean PRE-SIAQ scores and POST-SIAQ scores for all the domains were high in all patients with CT-P13 AI administration from Week 56 to Week 62 (PRE-SIAQ mean values: 7.30 - 8.00 out of 10 and POST-SIAQ mean values: 7.26 - 8.26 out of 10). Mean POST-SIAQ scores for pain and skin reactions during or after the injection (localized injection site reactions), were 8.76 - 8.88 out of 10.

For PFS, at both Week 14 and Week 22, most patients in both treatment groups successfully self-injected (completing P8, P9, and P10) and completed all instructions. A total of 203 patients were in usability population for PFS and 176 patients performed self-injection assessment checklist with self-injection at Week 14. Among 176 patients, 175 patients in both groups successfully self-injected (completing P8, P9, and P10) and completed all instruction (120/121 and 55/55 patients in CT-P13 SC 120 mg and placebo SC groups, respectively) at Week 14. At Week 22, 171 patients performed self-injection assessment checklist

with self-injection. Among 171 patients who performed self-injection assessment checklist with self-injection at Week 22, all patients successfully self-injected (completing P8, P9, and P10) and completed all instruction in both treatment groups (121/121 and 50/50 patients in CT-P13 SC 120 mg and placebo SC groups, respectively).

For AI, at both Week 56 and Week 62, most of patients in both treatment groups successfully self-injected (completing P8, P9, P10, and P11) and completed all instructions. A total of 61 patients were in usability population for AI and 58 patients performed self-injection assessment checklist with self-injection at Week 56. Among 58 patients, all patients successfully self-injected (completing P8, P9, and P10) and completed all instruction. Among 57 patients who performed self-injection assessment checklist with self-injection at Week 62, all patients successfully self-injected (completing P8, P9, and P10) and completed all instruction in both treatment groups.

No structural or mechanical integrity issues for PFS (CT-P13 SC 120 mg, N= 142 and placebo, N=61, total N=203) and AI (CT-P13 SC 120 mg, N= 42 and placebo, N=19, total N=61) after the completion of the self-injection in both the CT-P13 SC 120 mg and placebo SC groups were reported.

CHMP comment

The protocol to study usability was well-designed. The assessment and methodology to verify usability was appropriately planned and performed.

Summaries of the self-injection assessment checklist results could have been also presented as tabular format.

As a conclusion, based on the results, the usability of the PFS and AI in clinical use has been demonstrated and is acceptable.

7.3. REMSWITCH

The REMSWITCH Study was designed to assess the effectiveness of switching from intravenous to subcutaneous infliximab in patients with inflammatory bowel diseases (IBDs) treated with or without intensified intravenous regimen.

This summary is based only on a published peer reviewed article and no complete CSR was available. The study was independent but received a grant from Celltrion Healthcare.

Study design

The REMSWITCH Study was a multicenter observational study performed in 3 IBD referral centers in France.

A switch from IV infliximab to SC Remsima was proposed to all Crohn's disease and ulcerative colitis patients treated with IV infliximab who were in steroid-free clinical remission (partial Mayo score ≤ 2 or Harvey-Bradshaw index ≤ 4). All the patients who were considered for switching between February and August 2021 were included.

It was decided that all the patients would be switched at a SC dose of 120 mg every other week regardless of the initial IV regimen, which could be 5 mg/kg every 8 weeks or 10 mg/kg every 4 weeks, 6 weeks, or 8 weeks. Dose escalation to 240 mg every 2 weeks was applied in case of relapse. The theoretical date of next IV infusion was considered as baseline or visit 0 (V0), and data were collected at V1 (between 4 and

8 weeks after the switch), V2 (between 8 and 16 weeks after the switch), and V3 (between 16 and 24 weeks after the switch).

Endpoints

Clinical and pharmacological outcomes were assessed at baseline or visit 0 (V0), V1 (between 4 and 8 weeks after the switch), V2 (between 8 and 16 weeks after the switch), and V3 (between 16 and 24 weeks after the switch).

Rate of relapse after switching was the primary focus. Relapse was defined as a clinical recurrence (partial Mayo score >2 or Harvey-Bradshaw index >4) leading to therapeutic escalation or an increase of fecal calpro- tectin value of more than 150 mg/g compared with baseline (V0).

Median trough concentrations of infliximab were measured at each visit to assess the equivalence of serum levels between IV and SC infliximab. Three categories of patients were distinguished based on the variation of infliximab serum levels from baseline to first visit after the switch: increased (increase >1 mg/mL), stable (variation ≤±1 mg/mL), and reduced (decrease >1 mg/mL) levels.

Acceptability of both IV and SC infliximab administration was evaluated with a numerical 10-points scale.

Results

Among 184 eligible patients, 72.3% (n=133 of 184) agreed to switch to subcutaneous infliximab.

The participant flow is described in Figure 30 and the baseline characteristics, including dosing regimens are described in table 47. In this cohort, 25.6% (n=34 of 133) of them were treated with concomitant immunosuppressive therapy.

Figure 30. Flow chart illustrating the selection of the patients included into the effectiveness of switching from intravenous to subcutaneous infliximab in patients with inflammatory bowel diseases treated with intensified doses (REMSWITCH) study.

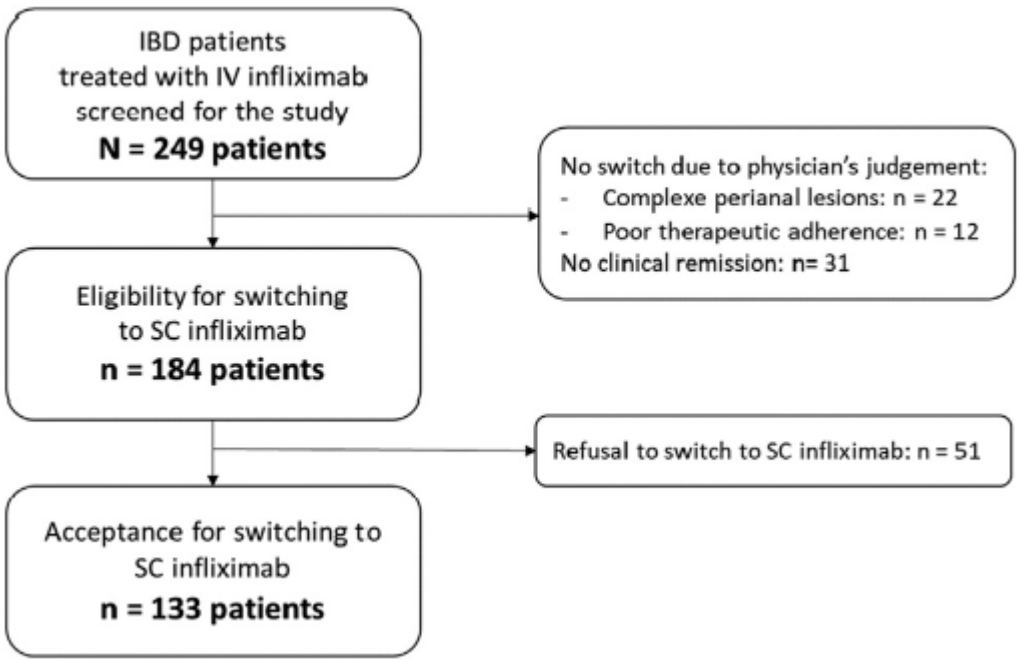


Table 48. Baseline Characteristics of the 133 Patients With IBD Included in the REMSWITCH Study

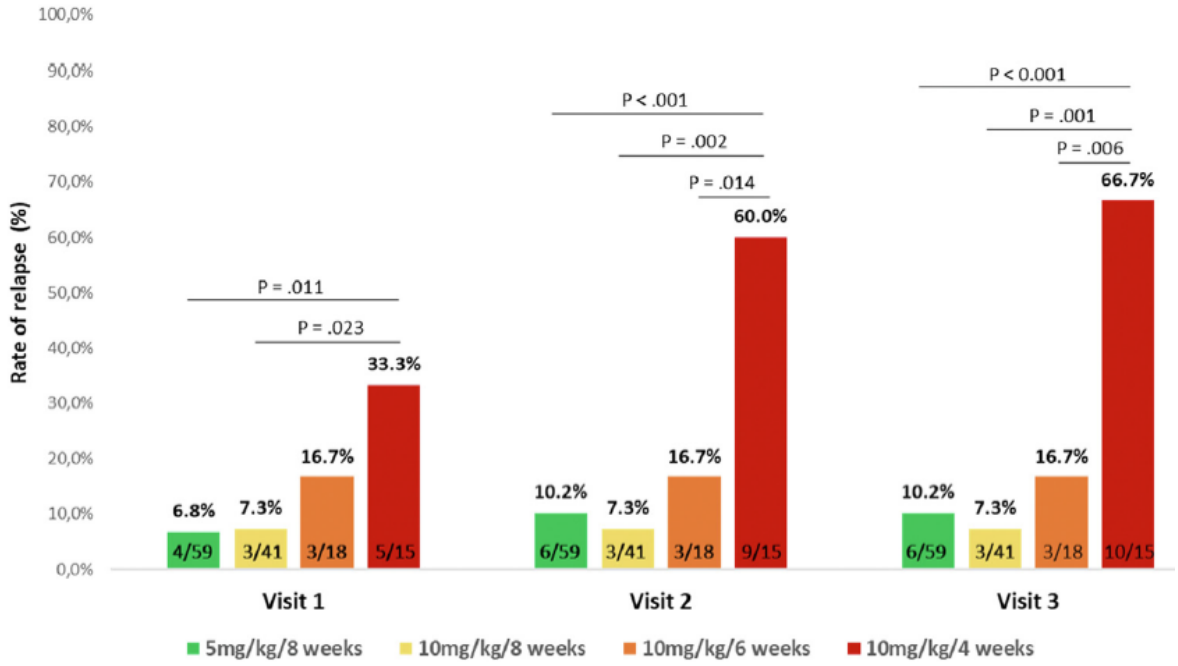
Age at the time of inclusion, y	39.3 ± 15.5
Female	72 (54.1)
Disease duration at baseline, y	13.5 ± 9.4
Body mass index, kg/m^2	22.2 (21.1–25.6)
Type of IBD	
CD	96 (72.2)
UC	37 (27.8)
Montreal classification	
UC extent	
E1	3/37 (8.1)
E2	10/37 (27.0)
E3	24/37 (64.9)
CD behavior	
B1	46/96 (47.9)
B2	23/96 (24.0)
B3	26/96 (27.1)
Perianal lesions	40/96 (41.6)
Prior intestinal resection	32/96 (33.3)
Disease activity at baseline	
Harvey-Bradshaw index	0 (0–1)
Partial Mayo score	0 (0–1)
C-reactive protein level, mg/L	1 (0–3.4)
Fecal calprotectin level, μg/g	39 (16–112)
Medications at baseline	
Infliximab maintenance therapy duration, y	5.4 ± 3.8
Intravenous infliximab maintenance regimen	
5 mg/kg every 8 wk	59 (44.4)
10 mg/kg every 8 wk	41 (30.8)
10 mg/kg every 6 wk	18 (13.5)
10 mg/kg every 4 wk	15 (11.3)
Infliximab trough level at baseline, μg/mL	6.5 (4.0–11.5)
Detectable anti-infliximab antibodies	2 (1.5)
Concomitant immunosuppressive therapy	34 (25.6)

Values are mean ± SD, n (%), median (interquartile range), or n/n (%).
CD, Crohn's disease; IV, intravenous; IBD, inflammatory bowel disease; REMSWITCH, effectiveness of switching from intravenous to subcutaneous infliximab in patients with inflammatory bowel diseases treated with intensified doses; UC, ulcerative colitis.

Rate of Relapse After Switching From IV to SC Infliximab

At visit 3, a relapse occurred in 10.2% (n=6 of 59), 7.3% (n=3 of 38), 16.7% (n=3 of 18), and 66.7% (n=10 of 15) (P < .001) of patients receiving 5 mg/kg Q8W, 10 mg/kg Q8W, 10 mg/kg Q6W, and 10 mg/kg Q4W, respectively. The side-by-side comparisons at V1, V2, and V3 are shown in Figure 31.

Figure 31. Cumulative rate of relapse at V1, V2, and V3 according to the IV infliximab maintenance regimen at baseline.

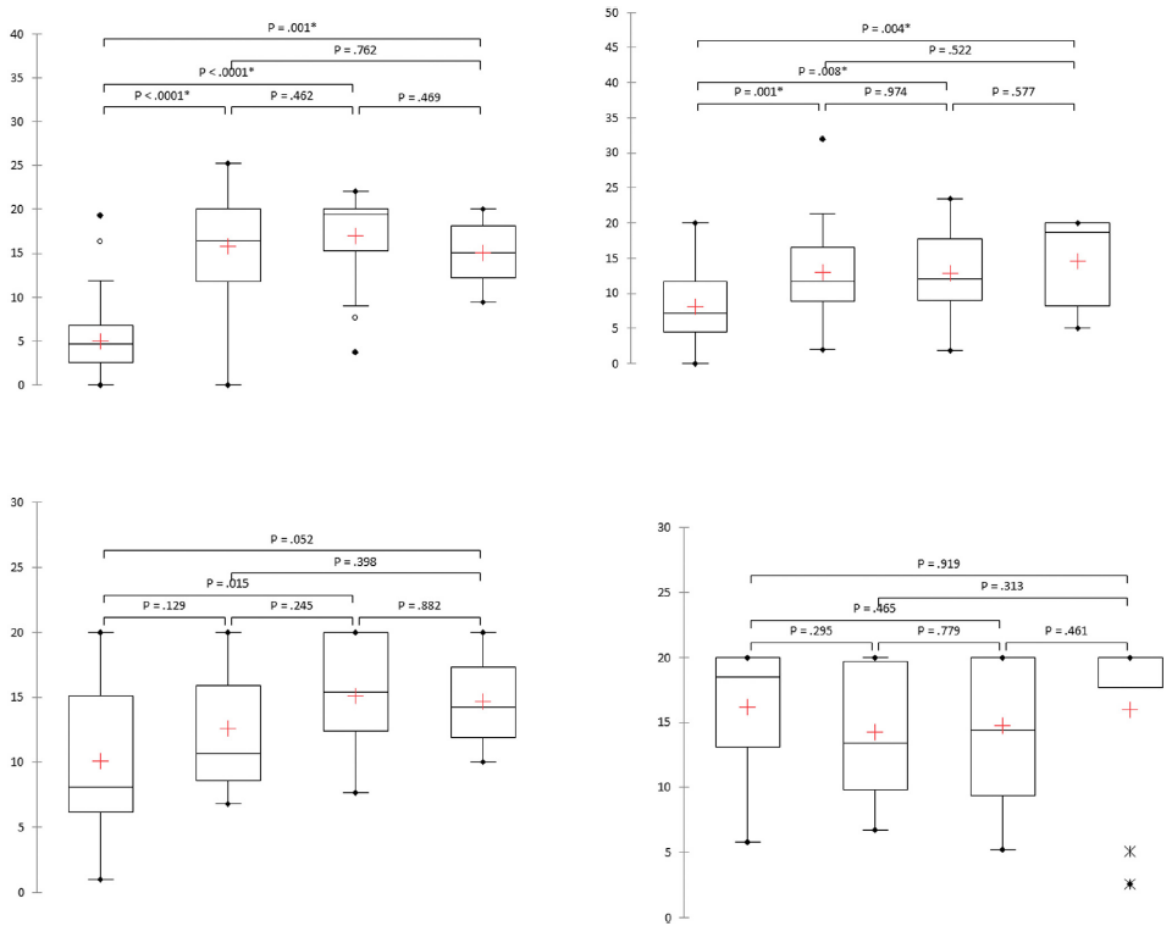


Drug concentrations After Switching From IV to SC Infliximab

The median trough levels according to the IV maintenance regimen at baseline were 4.7 (IQR, 2.4 to 6.8) mg/mL, 7.2 (IQR, 4.4 to 11.9) mg/mL, 8.1 (IQR, 6.2 to 15.1) mg/mL, and 18.5 (IQR, 11.9 to 20.0) mg/mL (P < 0.001) among the patients treated with IV 5 mg/kg Q8W, 10 mg/kg Q8W, 10 mg/kg Q6W, and 10 mg/kg Q4W, respectively.

Serum levels of infliximab significantly increased after the switch from IV to SC infliximab in all the subgroups except for the patients receiving 10 mg/kg every 4 weeks (Figures 32 A–D).

Figure 32. Evolution of infliximab serum levels after switching from intravenous to subcutaneous formulation in patients with IBD treated with (A) 5 mg/kg every 8 weeks (B), 10 mg/kg every 8 weeks (C), 10 mg/kg every 6 weeks (D), and 10 mg/kg every 4 weeks of intravenous infliximab at baseline (only statistically significant P values were depicted).



Prediction of Relapse After Switching From IV to SC Infliximab

None of the following baseline factors were associated with the risk of relapse: sex (*P*= *0*.24), body weight (*P*= *0*.097), body mass index (*P*= *0*.10), Crohn's disease location (*P*= *0*.66), Crohn's disease phenotype (*P*= *0*.34), perianal lesions (*P*= *0*.79), ulcerative colitis extension (*P*= *0*.29), concomitant immunosuppressive therapy (*P*= *0*.42), Harvey-Bradshaw index (*P*= *0*.30), partial Mayo score (*P*= *0*.49), and C-reactive protein level at baseline (*P*= *0*.32).

In univariable analysis including the 133 patients, older age (46.3 ± 16.6 years vs 38.4 ± 16.6 years; *P*= *0*.048) and higher fecal calprotectin level at baseline (272 [IQR, 52 to 899] mg/g vs 30 [IQR, 15 to 100] mg/g; *P* < 0.001) were associated with higher risk of relapse. Regarding pharmacokinetics data, higher infliximab trough level at baseline (11.7 [IQR, 5.8–18.5] mg/mL vs 6.1 [IQR, 3.8 to 9.0] mg/mL; *P* ¼ .035) was associated with higher risk of relapse while the serum level of infliximab at V1 (first visit after the switch) did not (15.2 [IQR, 10.1 to 20.0] mg/mL in non-relapsers vs 12.1 [IQR, 8.9 to 17.6] mg/mL in relapsers; *P*= *0*.21). Using a receiver-operating characteristic curve, we determined that an infliximab trough level >11.0 mg/mL and a level of fecal calprotectin >250 mg/g at baseline were associated with the risk of relapse.

Recapture of Clinical Remission After Therapeutic Escalation Among the Patients Who Relapsed After Switching From IV to SC Infliximab

Among the 22 patients who experienced relapse within the first 6 months after the switch, 15 received therapeutic escalation to 240 mg every other week including 10 patients before V1, 3 patients between V1 and V2, and 2 patients between V2 and V3. Dose escalation led to recapture of clinical remission in 93.3% (n=14 of 15) of the patients and combined clinical and biological remission (fecal calprotectin <150 mg/g) in 80.0% (n = 12 of 15) of them at V3.

CHMP comment:

The REMSWITCH study was submitted to justify the following amendment in section 4.2 of the SPC:

There is insufficient information regarding the switching of patients who received the intravenous infusions of infliximab higher than 3 mg/kg for rheumatoid arthritis ~~or 5 mg/kg for Crohn's disease~~ every 8 weeks to the subcutaneous formulation of Remsima.

The MAH proposes to delete the part of the phrase concerning Crohn's disease since new information about switching of patients who received IV infusions higher than 5 mg/kg Q8W for CD patients to Remsima SC is now available from the REMSWITCH study.

However, it is confusing to imply in the SPC that there is sufficient information on switching in Crohn's (but not in rheumatoid arthritis) but not to include any details regarding this information. Therefore, the REMSWITCH study is assessed here based on what additional information could potentially be added to be useful for the prescriber.
In this context, it is a major problem that the REMSWITCH study was not designed to demonstrate either an absolute benefit risk of a switching regimen or non-inferiority of switching compared to not switching from high-dose (> 5 mg/kg) IV maintenance to SC 120mg.

In the REMSWITCH study, 37 UC and 96 CD patients in remission who were initially on infliximab IV 5 mg/kg Q8W, 10 mg/kg Q8W, 10 mg/kg Q6W or 10 mg/kg Q4W were all switched to Remsima 120mg SC and there was no control group of patients who did not switch.

Rates of relapse and drug concentrations were collected for up to 6 months after the switch. In general, patients with a very high dose at baseline had a higher risk of relapse after the switch to Remsima SC than those with a standard dose. Within 6 months after the switch, patients who were initially treated with IV 5 mg/kg Q8W, 10 mg/kg Q8W or 10 mg/kg Q6W relapsed with a frequency of 10.2% and 7.3% and 16.7%, respectively, while patients initially treated with IV 10 mg/kg Q4W relapsed with a frequency of 66.7%.

It is not known whether the patients differed at baseline in terms of disease duration, duration of remission, concomitant medication or other characteristics relevant for the risk of relapse as no randomisation was performed and there were no true control groups. It can be assumed that patients who were initially on high dose infliximab (10mg/kg Q4W) have a different disease profile than those who responded to lower doses and stayed on the initial dose. Therefore, no causality can be deduced between the switch to SC and risk of relapse in patients with high baseline dose as we do not know how many of the high dose patients would have relapsed within 6 months if they remained on the IV treatment.

The median trough serum levels of infliximab significantly increased after the switch from IV to SC infliximab in all the subgroups except for the patients receiving 10 mg/kg every 4 weeks. In line with this observation, the authors concluded that variation of serum levels of infliximab between

baseline (V0) and the first visit after the switch (V1) was associated with the risk of relapse. Especially an infliximab trough level >11.0 mg/mL and a level of faecal calprotectin >250 mg/g at baseline were associated with a higher risk of relapse. Interestingly, while patients with increased serum infliximab levels experienced some relapses after the switch (12.7%), both reduced (41.7%) and stable (36.8%) serum levels of infliximab were associated with a clearly higher risk of relapse. Hence, maintaining a stable C_{trough} was not sufficient to protect from relapses. Moreover, serum level of infliximab at V1 (first visit after the switch) was not associated with the risk of relapse as relapsers and non-relapsers had similar levels.

Based on these results, it is still unclear whether the high concentrations following IV administration are important in terms of efficacy and the results even imply that the maximum concentrations (C_{max}), which are higher after the IV administration compared to the SC formulation, could be more important for efficacy than previously thought as relapses occurred frequently among patients with a stable C_{trough}. It is not known whether these relapses would have occurred anyway or whether they could have been caused by a difference in PK parameters.

To conclude, the REMSWITCH study offers descriptive data on 74 UC and CD patients who were switched from a higher dose than 5 mg/kg of IV infliximab to Remsima SC 120mg Q2W. 41 patients were initially on IV 10mg/kg Q8W. This is the group of relevance for this variation, as it is the only approved elevated dose (described in section 5.1 of the SPC). However, it is not clear how many of these patients had UC and how many CD.

Some patients relapsed, others did not, but the study design does not enable conclusions on causality of the outcome and information on what dose to use in case of a switch cannot be substantiated. Hence, information is available, as the MAH states, but the data is of limited value for decision making.

The provided data does not justify the proposed amendment to the wording of the SPC
which implies that sufficient information on switching from higher than 5 mg/kg IV doses to SC Remsima is available in Crohn's disease.

Other indications than RA and CD have not been mentioned in the paragraph on switching from high dose IV as a possibility for dose increase of the IV product has only been approved for RA and CD (as described in section 5.1 of the SPC). While it is understood by the regulator that this paragraph only mentions the indications where higher IV doses are approved, it is considered confusing for non-regulators. Therefore, it is proposed to delete any reference to indications from the paragraph, as follows:

There is insufficient information regarding switching to the subcutaneous formulation of Remsima in patients who received the intravenous infusions of infliximab in doses higher than the initial maintenance dose (see section 5.1).

Information on the PK of Remsima after SC dosing is already available in the SPC and can be of some guidance to the clinician in case a switch from high dose IV to SC is warranted.

On an additional note, while the study reports that dose escalation led to recapture of clinical remission in 93.3% (n=14 of 15) of the patients, no information is given on patient characteristics, the time to response or duration of response. Without a proper control group and sufficient follow-up time, this information is not helpful in determining the B/R balance of the 240mg Q2W dosing.

Updated comments (RSI AR)

After the first RSI the Applicant withdrew the proposal of switching from high-dose (>5 mg/kg) IV maintenance to SC treatment. Therefore, questions related to this variation are no longer relevant.

7.4. Discussion

Design and conduct of clinical studies

Two clinical studies were submitted to support the proposed variations in posology.

Study CT-P3.7 was a randomised, placebo-controlled Phase 3 study to evaluate the efficacy, PK, PD and safety of CT P13 SC as maintenance therapy in patients with moderately to severely active UC.

Study CT-P3.8 was a randomised, placebo-controlled Phase 3 study to evaluate the efficacy, PK, PD and safety of CT P13 SC as maintenance therapy in patients with moderately to severely active CD.

Both studies included an open-label induction phase where the patients received a CT-P13 (Remsima) IV infusion (5 mg/kg) during on-site visits at Weeks 0, 2, and 6 as induction treatments. Patients who were classified as a clinical responder at Week 10 after receiving 3 full doses of CT-P13 5 mg/kg IV were randomly assigned to receive either CT-P13 120mg SC or Placebo SC, before treatment on Day 70 (Week 10). The double-blind maintenance phase consisted of CT-P13 120mg SC or Placebo SC every 2 weeks via PFS through Week 54 in both studies. Open-label extension phases up to week 102 were ongoing at the time of initial submission. During the assessment process, safety and efficacy data up to week 102 were submitted for both studies. Usability data for patients who self-injected a study drug via AI were submitted up to Week 62 from study 3.8.

In study 3.7 response and remission was primarily assessed using the modified Mayo score, which includes the endoscopic sub-score. In study 3.8 absolute CDAI score and endoscopic response were the primary efficacy parameters. These endpoints are in line with EMA guidance and are as such acceptable but the results are confounded because patients were allowed to switch to higher dose of Remsima (also in the placebo group) before the analysis timing for the primary endpoint.

In both studies, patients who lost response in both treatment arms were offered a switch to Remsima 240 mg Q2W from week 22 onward. In theory, the studies were double blind and the blinding was adequate up to week 22. However, if the dose was escalated, both the investigator and the patient knew that the patient received active treatment because a double dose was always active. Furthermore, the investigator knew that as a result of dose escalation the patient automatically is a non-responder in the efficacy analyses. Hence, the studies cannot be considered adequately blinded up to week 54, which was the time of assessment of the primary efficacy endpoint in both studies.

Furthermore, as patients who lost response in both treatment arms were offered a switch to Remsima 240 mg Q2W from week 22 onward, comparisons of efficacy between Remsima SC 120mg Q2W and placebo beyond week 22 are compromised due to the intercurrent event, including the primary endpoint measured at Week 54. Basically, patients in the placebo group who received active treatment after loss of response are automatically counted as non-responders which may skew the results in favour of the active arm because placebo patients are more likely to lose their response and hence, be offered a higher dose. After dose increase, these patients are automatically counted as non-responders although we do not know whether a fluctuation back to "responder" would have occurred with equal frequency in each arm due to the natural course of the disease.

In the context of this variation application, studies 3.7 and 3.8 were submitted to support the following amendments to the SPC:

a) addition of a new induction regimen (induction with 3-IV doses instead of 2)

b) addition of the possibility to increase the dose for patients with loss of initial response

c) inclusion of the efficacy and safety results in Section 5.1 and 4.8.

After the first RSI the MAH withdrew the proposal for dose escalation in UC.

While no comparative data is available for the new proposed induction, the benefit-risk of the regimen may be assessed based on totality of data as it does not differ a lot from the already approved induction regimens.

However, the study designs were not adequate to answer the question whether dose adjustment from SC 120 mg to 240 mg for patients with loss of response is more effective (and sufficiently safe) compared to continuing treatment with SC 120 mg.

As there was no randomised treatment arm where patients with a loss of response continued on the previously assigned SC 120mg treatment, it is difficult to know how the disease would have progressed without the dose escalation. As UC and CD are fluctuating refractory diseases with sometimes long symptom free periods, some patients could have achieved remission again by week 54 after loss of response, even without dose escalation. Furthermore, as dose escalation was not mandatory for all patients who fulfilled the criteria, there is a potential for selection bias. Some patients who lost response were dose adjusted and others were not, but these different pathways were neither randomised nor based on any predefined characteristics. Therefore, the intercurrent event of loss of response comprises a flaw in the study design and could skew the results of both the primary outcome and the dose escalation outcome. Lastly, the studies did not include any prospectively defined endpoints to assess dose escalation and the analyses planned and included in the initial submission were minimal and not comprehensive. Despite the mentioned shortcomings of the study design, the BR of a dose escalation was assessed and conclusions were based on the totality of data including PK, efficacy, safety and immunogenicity data.

While the design of the two studies, and the dose escalation in particular, is not optimal for interpretation of the results at Week 54 (primary endpoint), the use of *rescue therapy/ escape procedure* at intermediate time-point is in line with the EMA guideline on development of medicinal products for ulcerative colitis/ Crohn's disease. However, it should be noted that Remsima was already approved as maintenance treatment at the time of study initiation and was used as the protocol-defined rescue therapy in both studies. Hence, the concept of *rescue therapy/ escape procedure* may not be as intended in the EMA guideline. Despite these shortcomings in the setup of the studies, the primary efficacy results could be considered of value for the prescriber and for inclusion in the SPC. However, because the possibility to dose adjust is significantly intertwined in the primary endpoints as only patients who did not dose adjust had a possibility to be a responder at week 54, the W54 results cannot be presented in the SPC without explaining the impact of dose adjustment.

Efficacy data and additional analyses

Results in patients with ulcerative colitis (Study 3.7)

Out 548 UC patients who were enrolled and treated with CT-P13 5 mg/kg IV during induction, 438 patients were randomly assigned to study treatment and initiated the double-blind maintenance phase at Week 10 (294 and 144 patients in the CT-P13 SC 120 mg and Placebo SC groups, respectively). At Week 10 65/548 patients (11.9%) were non-responders.

Among responders at week 10, demographic characteristics at baseline were balanced between treatment groups.

The proportion of patients who achieved a clinical remission by modified Mayo at Week 54 was higher in the CT-P13 SC 120 mg treatment group (127 [43.2%]) than in the Placebo SC treatment group (30 [20.8%]). All sensitivity analyses showed similar results. The difference between placebo and CT-P13 SC 120 mg treatment was notable also for all secondary efficacy endpoints. However, as there were major

protocol violations affecting a high proportion of patients, the results of the primary endpoint do not provide an accurate estimate of the treatment effect and do not provide a clinically meaningful interpretation.

Effect of dose adjustment in UC

81 [27.6%] and 70 [48.6%] UC patients in the CT-P13 SC and Placebo groups, respectively received a dose adjustment prior to Week 54. Among the patients with dose adjustment in the CT-P13 SC 120 mg group 40/81 (49.4%) patients regained clinical response by Week 54. However, upon repeated request, the MAH provided data which showed that 35% of the dose escalation decisions were off protocol. These patients never lost response according to the protocol defined criteria and could therefore not be classified as regainers of response either.

The MAH withdrew the application for a dose adjustment in UC patients but the possibility to adjust the dose and the handling of the intercurrent event of loss of response affect the primary outcome rendering it unintelligible.

Results in patients with Crohn's disease (Study 3.8)

Out of 396 CD patients who were enrolled and treated with CT-P13 5 mg/kg IV during induction, 343 patients were randomly assigned to study treatment and initiated the double-blind maintenance phase at Week 10 (231 and 112 patients in the CT-P13 SC 120 mg and Placebo SC groups, respectively). At Week 10 22/369 patients (6%) were non-responders.

Among responders at week 10, demographic characteristics at baseline were balanced between the two main treatment groups and there was no meaningful difference between the subgroups of patients with and without dose adjustment in terms of baseline characteristics. However, among patients who received a dose escalation, the use of oral corticosteroids was more frequent at baseline compared to those who did not require a dose increase. This could possibly reflect a more severe form of disease among those who lost response.

The co-primary endpoints were clinical remission based on CDAI at Week 54 and endoscopic response based on central SES-CD at Week 54. Patients who received a dose escalation after W22 were automatically classified as non-responders although some of them did not lose response and some of the patients who lost response did not receive a dose escalation.

The proportion of patients who achieved clinical remission by CDAI at Week 54 was higher in the CT-P13 SC 120 mg group than Placebo SC group (144 [62.3%] and 36 [32.1%], respectively).

The proportion of patients who achieved endoscopic response (defined as a 50% decrease in SES-CD score) at Week 54 was 118 [51.1%] and 20 [17.9%] in CT-P13 SC 120 mg and Placebo SC groups, respectively.

All sensitivity analyses and subgroup analyses of the primary endpoints showed similar results. All secondary endpoints supported the finding that CT-P13 SC 120mg is superior to placebo in the maintenance treatment of patients with moderately to severely active CD.

Although the intercurrent event of loss of response was handled differently for different patients and this flaw in the study design could skew the results of the primary outcome, the difference in the proportion of remitters is considered clinically meaningful and the magnitude of the difference sufficiently large to be relevant for the prescriber and to be included in Section 5.1 even if there was some bias involved.

In an open label extension phase 192 patients on CT-P13 and 86 patients on placebo continued the study after week 54. The proportion of patients who achieved clinical remission and the improved mean CDAI scores were more or less maintained at Week 102 compared to Week 54 in both CT-P13 and placebo groups. Of patients originally randomised to placebo 27/112 (24%) were in clinical remission two years after a successful induction treatment with infliximab IV despite no active treatment after week 10.

Effect of dose adjustment in CD

A total of 41 patients in the CT-P13 SC 120 mg group and 48 patients in the placebo group experienced LoR prior to Week 54. Among these patients, 34/41 (82.9%) in CT-P13 SC 120 mg group and 41/48 (85.4%) in placebo group received adjusted dose while 7 patients in each group remained on the initially assigned treatment. A few patients received adjusted dose despite not being eligible for the dose adjustment, 5/182 (2.7%) in CT-P13 SC 120 mg group and 4/57 (7.0%) in placebo group. This protocol violation seems to be driven by the clinicians' desire to improve the treatment for poor responders but exposes poor adherence to GCP. However, the frequency of these protocol violations is small enough not to pursue the issue further. .

Among the 34 patients with dose adjustment in the CT-P13 SC 120 mg group 17 (50%) patients achieved clinical remission by CDAI and 7 (20.6%) patients achieved endoscopic response at Week 54. On the other hand, in the 7 patients who experienced a LoR but did not receive a dose adjustment, regain of clinical remission by CDAI occurred in 1/7 (14.3%) and endoscopic response re-emerged in 3 (42.9%) of these patients on initial active treatment. Regain of response occurred in 21/34 (61.8%) patients with a dose escalation while patients who lost response but remained on active treatment had a renewed response in 2 (28.6%) cases. Spontaneous regain of response and remission was also seen in patients who remained on placebo (3 and 1 patients, respectively).

Although the numbers are small, it can be concluded that spontaneous regain of response is not negligible. However, regain of response according to CDAI is more common and the improvement in absolute CDAI score is more pronounced in patients with a dose adjustment than in those who remained on initial treatment despite a LoR. Although the groups are not comparable, the totality of data is sufficiently compelling in terms of magnitude and consistency to support a dose increase in patients who lost response.

A clear difference between patients who experienced LoR and those who did not is seen in terms of serum drug concentration before LoR. This finding supports the theory of loss of response being associated with suboptimal drug concentrations. It seems that loss of response is often due to a more pronounced development of ADAs (higher titres) and lower drug concentrations as a result. It is still unclear how drug concentrations developed among those with a dose increase and for how long patients with high ADA titres at dose adjustment could maintain a potential benefit from a higher dose. However, as these are not issues which could affect the wording in the SPC, they will not be pursued further. Anyway, the provided spaghetti plots show that a majority of patients in the active treatment arm who received a dose adjustment had a positive outcome 16 weeks after the dose increase.

Data on switching from high dose IV infliximab to 120mg SC Remsima (**REMSWITCH Study)**

To support amendments regarding switching from high dose IV regimens to Remsima SC, the MAH submitted a published peer reviewed article of the REMSWITCH Study. No complete CSR was available.

The REMSWITCH Study was a multicenter observational study performed in 3 IBD referral centers in France. In this study, 37 UC and 96 CD patients in remission who were initially on infliximab IV 5 mg/kg Q8W, 10 mg/kg Q8W, 10 mg/kg Q6W or 10 mg/kg Q4W were all switched to Remsima 120mg SC. There was no control group of patients who did not switch as the REMSWITCH study was not designed to demonstrate either an absolute benefit risk of a switching regimen or non-inferiority of switching compared to not switching from high-dose (> 5 mg/kg) IV maintenance to SC 120mg.

Rates of relapse and drug concentrations were collected for up to 6 months after the switch. Within 6 months after the switch, patients who were initially treated with IV 5 mg/kg Q8W, 10 mg/kg Q8W or 10 mg/kg Q6W relapsed with a frequency of 6/49 (10.2%) and 3/41 (7.3%) and 3/18 (16.7%), respectively, while patients initially treated with IV 10 mg/kg Q4W relapsed with a frequency of 10/15 (66.7%).

It is not known whether the patients differed at baseline in terms of disease duration, duration of remission, concomitant medication or other characteristics relevant for the risk of relapse as no randomisation was performed and there were no true control groups. It can be assumed that patients who were initially on high dose infliximab (10mg/kg Q4W) have a different disease profile than those who responded to lower doses and stayed on the initial dose. Therefore, no causality can be deduced between the switch to SC and risk of relapse in patients with high baseline dose as we do not know how many of the high dose patients would have relapsed within 6 months if they remained on the IV treatment.

Questions related to this variation are no longer relevant as the Applicant withdrew the proposed changes to the PI.

New proposed 3-IV induction regimen

The induction regimen proposed now for UC, CD and fistulising CD and used in studies 3.7 and 3.8 is identical to the induction regimens currently approved for all above indications with IV Remsima. It has already been shown that a switch to SC Remsima from IV Remsima does not attenuate efficacy after an initial induction of 6 weeks and a switch to SC Remsima is approved at any time during maintenance, starting 8 weeks after the last IV dose. Therefore, the switch to SC Remsima at week 10, starting only 4 weeks after the last IV dose, as proposed now, does not introduce any new efficacy issues compared to already approved regimens.

Also PK analyses showed that trough drug concentration levels remained close to the steady state plasma concentration throughout the SC dosing regimen without any concentration falls due to the switch (see PK assessment in section 6).

To conclude, based on pharmacokinetic reasoning and previously established positive benefit-risk for very similar dosing regimens, introduction of the 3-IV induction dosing regimen (5 mg/kg at Weeks 0, 2 and 6) followed by SC maintenance treatment (120 mg Q2W from week 10) is acceptable for both CD and UC patients.

7.4.1. Conclusions

- Addition of a 3-IV induction dosing regimen (5 mg/kg at Weeks 0, 2 and 6) followed by SC maintenance treatment (120 mg Q2W) is acceptable for CD and UC.
- The benefit-risk of a dose adjustment from Remsima SC 120 mg to Remsima SC 240 mg for CD patients with loss of response is positive. It should be noted that the study design was not suitable to conclude on the benefit-risk balance of a dose adjustment and the assessment is based on post-hoc analyses that were not pre-defined in the protocol.
- SmPC-updates pertaining to description of the new phase 3 study in CD patients in sections 5.1 are acceptable.
- Results from Study 3.7 in UC patients do not provide an accurate estimate of the treatment effect nor a clinically meaningful interpretation. Hence, these results will not be included in the SPC section 5.1.

8. Clinical Safety aspects

8.1. Methods – analysis of data submitted

The assessment of the safety of the currently proposed amended posology in CD and UC is based on the results of two clinical studies included in the submission with Week 54 clinical study reports:

- Study CT-P13 3.7: Phase 3, randomised, double-blind, placebo-controlled, parallel group study in which 436 patients with moderately to severely active UC were treated with Placebo SC or CT-P13 SC via pre-filled syringe (PFS)
- Study CT-P13 3.8: Phase 3, randomised, double-blind, placebo-controlled, parallel group study in which 343 patients with moderately to severely active CD were treated with Placebo SC or CT-P13 SC via PFS (from Week 56, CT-P13 SC 120 mg via PFS or auto-injector [AI] through Week 102)

Prior data on CT-P13 SC

The safety results from six controlled, comparative, clinical studies during the development of CT-P13 SC were included in previous submission packages with the final CSRs and are not included in the current analysis. A total of 1,598 subjects have been treated in these six studies for CT-P13 SC:

- Study CT-P13 3.5 Part 1 and Part 2: Phase 1/3, randomised, multi-dose, parallel-group study in which 391 patients with rheumatoid arthritis (RA) (48 patients in Part 1 and 343 patients in Part 2) were treated with CT-P13 SC or CT-P13 IV
- Study CT-P13 1.6 Part 1 and Part 2: Phase 1, open-label, randomised, multi-dose, parallel-group study in which 175 patients with UC or CD (44 CD patients in Part 1 and 78 UC and 53 CD patients in Part 2) were treated with CT-P13 SC or CT-P13 IV
- Study CT-P13 1.5: Phase 1, open-label, dose-escalating, single-dose study in which 38 healthy subjects were treated with CT-P13 SC or CT-P13 IV
- Study CT-P13 1.9: Phase 1, open-label, single-dose pharmacokinetics (PK) and safety study in which 215 healthy subjects were treated with CT-P13 SC via AI or PFS.

See Section 7.1, figures 7.1.1.1, 7.1.1.2 and 7.2.1.1 for details of studies CT-P13 3.7 and CT-P13 3.8.

In both studies, there was an open-label induction phase, for which the patients who met all the inclusion criteria and none of the exclusion criteria were enrolled on Day 0 (Week 0). All enrolled patients received a 2-hour CT-P13 IV infusion (5 mg/kg) during onsite visits at Weeks 0, 2, and 6 as induction treatments. Only subjects that were deemed to be responders at Week 10 after receiving 3 full doses of CT-P13 via IV infusion and for whom there were no safety concerns based on the investigator's discretion were randomly assigned to receive either CT-P13 SC or placebo SC, before treatment on Week 10.

The safety assessments in studies CT-P13 3.7 and Study CT-P13 3.8 included monitoring of adverse events (AEs), serious adverse events (SAEs), treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), adverse events of special interest (AESIs) and death; hypersensitivity monitoring (including delayed hypersensitivity monitoring); vital signs measurements (including blood pressure, heart rate, respiratory rate and body temperature); weight; 12-lead electrocardiogram (ECG); monitoring for signs and symptoms of tuberculosis, chest X-ray and interferon-γ release assay (IGRA); diabetes mellitus assessment; physical examination; clinical laboratory analyses; local site pain using 100 mm Visual Analogue Scale (VAS); recording of prior and concomitant medications; pregnancy tests; monitoring of cardiovascular disease related signs and symptoms and monitoring of drug-induced liver injury.

Adverse events were graded for severity according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 with Grade 1=Mild AE; Grade 2=Moderate AE; Grade 3=Severe and undesirable AE; Grade 4=Life-threatening or disabling AE; and Grade 5=Death related to AE.

The causality or association to study drug in causing or contributing to the AE was classified into the following categories:

- Unrelated: This relationship suggests that there was no association between the study drug and the reported event.
- Possible: This relationship suggests that treatment with the study drug caused or contributed to the AE, i.e., the event followed a reasonable temporal sequence from the time of drug administration or followed a known response pattern to the study drug but could also have been produced by other factors.
- Probable: This relationship suggests that a reasonable temporal sequence of the event with drug administration existed and based upon the known pharmacological action of the drug, known or previously reported adverse drug reactions to the drug or class of drugs, or judgment based on the Investigator's clinical experience, the association of the event with the study drug seemed likely.
- Definite: This relationship suggests that a definite causal relationship existed between drug administration and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) did not appear to explain the event.

The immunogenicity of CT-P13 was assessed by measuring anti-drug antibodies (ADA) and neutralising antibodies (NAb) at Weeks 10, 22, 30 and 54.

An independent data and safety monitoring board (DSMB) assessed the progress of each clinical study, including unblinded safety assessments at specified intervals, and recommended to the Sponsor whether to continue, modify, or stop the study.

Safety analyses were performed on the safety population, defined as all randomised patients who received a complete (full) or partial dose of study drug at Week 10 or thereafter. Non-responders to induction treatment and subjects with safety concerns during the induction phase were not randomised to the maintenance phase and were not included in the safety population. The adverse event data are partly also reported for the "treatment period", which includes the induction phase and maintenance phase of the studies.

For safety and immunogenicity assessment, only data collected before initiation of dose adjustment was used for Placebo SC group and all data collected regardless of dose adjustment was used for CT-P13 120 mg SC group, unless otherwise specified.

CHMP comment

The adverse event data are partly also reported for the "treatment period", which includes the induction phase and maintenance phase of the studies. Comparison of the active and placebo groups is not feasible for such data, since both study arms received active induction treatment during the induction phase in both phase 3 studies.

The MAH had not described in detail the populations for the comparison between placebo and CT-P13 SC and between the 120 mg and 240 mg doses and how exposure time for each dose was accounted in the analyses. Therefore, the submitted safety data was not considered robust.

Furthermore, taking in account the effects from active IV induction treatment in both study arms, the results from the treatment period (which includes the induction and maintenance periods) were not suitable for comparison of safety between placebo and CT-P13 SC.

Several clarifications and reanalyses were requested, and the MAH provided an adequate response to all safety questions, including analyses on TEAEs observed during use of both the 120 mg SC dose and the 240 mg SC dose vs. placebo. The duration of treatment with each dosing regimen (120 mg SC, 240 mg SC and placebo) was accounted for by calculating the incidence of TEAEs per 100 PY. These analyses included final study data per 100 patient years (PY).

It is noteworthy that no comparative data between induction treatment with 2 IV doses vs. the newly proposed induction treatment with 3 IV doses are available. Comparison between the currently submitted phase 3 studies and a former Phase I study (CT-P13 1.6 Part 2) have however been conducted (see Section 8.2.5 of this AR). Nevertheless, such comparison between different trials is not regarded as robust evidence on comparative safety of the two IV induction regimens.

8.2. Results

8.2.1. Patient exposure

In study CT-P13 3.7 (Ulcerative Colitis), all 548 enrolled patients received CT-P13 IV in the induction phase. 110 patients discontinued in the induction phase due to being non-responder at Week 10 (65 patients), withdrawal by patient (15 patients), adverse event (13 patients), progressive disease (6 patients), physician's decision (5 patients), protocol deviation (3 patients), lost to follow-up (2 patients) and other (1 patient). (Figure 7.1.3.1 of this AR). The mean total dose administered during the induction phase was similar between the two treatment arms (1094.01 mg in the active arm and 1145.78 mg in the placebo arm). Of 438 randomised subjects, 436 were treated: 294 received CT-P13 SC 120 mg and 144 received placebo SC.

In study CT-P13 3.8 (Crohn's Disease), all 396 enrolled patients received CT-P13 IV in the induction phase. According to the CSR, 53 patients discontinued in the induction phase due to being non-responder at Week 10 (22 patients), withdrawal by patient (12 patients), adverse event (11 patients), progressive disease (2 patients), protocol deviation (2 patients), lost to follow-up (2 patients), and death and physician decision (1 patient each) (Figure 7.2.3.1 of this AR). The mean total dose administered during the induction phase was similar between the two treatment arms (1047.67 mg in the active arm and 1018.64 mg in the placebo arm). Of 343 randomised subjects, 231 received CT-P13 SC 120 mg and 112 received placebo SC.

The safety population from both studies consists of 779 patients (436 UC patients from Study CT-P13 3.7 and 343 CD patients from Study CT-P13 3.8), who were exposed to at least 1 dose (full or partial) of CT-P13 SC or Placebo SC. The number of patients exposed to CT-P13 SC in the two studies is summarised in Table 48.

Table 49. Number of Patients Exposed to CT-P13 SC in Studies CT-P13 3.7 and CT-P13 3.8: Safety Population

Study	Indication	Dosage (mg)	Study Duration	Number of Patients	
				Receiving at Least 1 Dose of CT-P13 SC	Completing CT-P13 SC Treatment up to Week 54
CT-P13 3.7	UC	120	54 Weeks	296	244
CT-P13 3.8	CD	120	54 Weeks	238	203
Total				**534**	**447**

Sources: CSR CT-P13 3.7 Post-text Table 14.1.10; CSR CT-P13 3.8 Post-text Table 14.1.10
Note: For the number of patients completing the Maintenance Phase with CT-P13 SC treatment up to Week 54, the number of patients who completed treatment is counted regardless of doses skipped in between or dose adjustment from 120 mg to 240 mg of CT-P13 SC.
Abbreviations: CD, Crohn's disease; UC, ulcerative colitis

In Studies CT-P13 3.7 and CT-P13 3.8, dose adjustment was allowed from the Week 22. Patients in both CT-P13 SC 120 mg and Placebo SC groups were allowed dose adjustment if patients initially responded but then lost response according to the loss of response criteria.
In Study CTP-13 3.7 (ulcerative colitis), 92/296 (31.1%) of patients in the active group had a dose escalation from 120 to 240 mg and 75/140 (53.6 % in the placebo group had a dose adjustment from placebo to 240 mg during the maintenance phase. In Study CT-P13 3.8 (Crohn's disease) dose was adjusted at least once for 45 subjects [18.9%] and 48 [45.1%] patients in the CT-P13 SC 120 mg and placebo SC groups, respectively.

CHMP comment

It is noteworthy that randomisation to the active and placebo groups only occurred at end of the open-label induction period at Week 10. During the induction period, study subjects received a 2-hour CT-P13 IV infusion (5 mg/kg) during onsite visits at Weeks 0, 2, and 6 as induction treatment. Any subjects who were non-responders to induction treatment (as assessed at 10 weeks) or had safety concerns during the open-label induction period were excluded from randomisation in the study at Week 10.

Notably, there are now data on 92 patients with UC and 45 patients with CD, who were switched to the higher 240mg dose from the 120 mg dose and 75 UC patients and 48 CD patients who were switched from placebo to the 240 mg dose. In previous studies on UC and CD, the steady state C_{trough} of infliximab has been around 6-8 microg/l with the double IV dose of 10 mg/kg. In studies 3.7 and 3.8, the normal SC dose of 120mg gave median C_{trough} concentrations of 13-16 microg/l. Hence, already the 120mg SC dose gives rise to considerably higher trough concentrations than those achieved with the highest approved IV dosing in CD. With the proposed 240mg SC dosing the C_{trough} levels would be even higher and especially the long term safety of such doses is unknown.

Originally, only subjects from the active study group were included in the comparative analyses between doses. Furthermore, it was unclear if the dose adjustment (escalation to 240 mg) could only occur temporarily or if the escalated dose was continued throughout the study (See Section 8.2.3.4 of this AR). From tables included in the document "Post-hoc Analyses" (Module 5.3.5.3) it is understood that there were 534 subjects in the pooled analysis, of whom 137 with dose adjustment and 397 without dose adjustment. The MAH was requested to further clarify the patient populations used for investigating effects of dose escalation in the pooled data set and in the separate analyses of both phase 3 trials. The MAH informed that for the active arm group with dose adjustment, all data were collected regardless of dose adjustment for CT-P13 SC 120 mg group and for the placebo arm, data collected before initiation of dose adjustment to 240 mg were included. However, it was unclear if data data from subjects who were switched from

placebo to active treatment with 240 dose were omitted; if the data for subjects with dose escalation only from the period when the patient used that dose or from the entire study duration; and how different duration of use of different doses addressed in the analyses.

In their response, the Applicant stated that they are no more applying for dose escalation to subjects with UC. Therefore, re-analyses were performed only on subjects with CD from study CT-P13 3.8. The Applicant compared safety of the 120 SC dose, 240 mg SC dose and placebo according to exposure of all patients to study treatment (Placebo, CT-P13 SC 120 mg or CT-P13 SC 240 mg), regardless of treatment phase and treatment group. Also, to take into account the different duration of use for each treatment (Placebo, CT-P13 SC 120 mg and CT-P13 SC 240 mg), the incidence rates per 100 Person Year (PY) was calculated,(table 8.2.1.2, table 1 from the response document). The safety data were analysed for the maintenance and extension phases of the study.

Table 50. Summary of Safety by the Dosage of Study Drug in Study CT-P13 3.8 (Maintenance Phase + Extension Phase): Safety Population

	Placebo (N=105, PY=60.22)	CT-P13 SC 120 mg (N=275, PY=363.58)	CT-P13 SC 240 mg (N=105, PY=118.54)
	Number (%, 100PY) of Patients with ≥ 1 Event		
TEAE	64 (61.0%, 106.27)	202 (73.5%, 55.56)	67 (63.8%, 56.52)
TESAE	8 (7.6%, 13.28)	28 (10.2%, 7.70)	7 (6.7%, 5.91)
TEAE Leading to Study Drug Discontinuation	5 (4.8%, 8.30)	14 (5.1%, 3.85)	5 (4.8%, 4.22)
SIR	1 (1.0%, 1.66)	3 (1.1%, 0.83)	0
Delayed Hypersensitivity	0	0	0
Localised ISR	1 (1.0%, 1.66)	18 (6.5%, 4.95)	8 (7.6%, 6.75)
Infection	19 (18.1%, 31.55)	105 (38.2%, 28.88)	40 (38.1%, 33.74)
Malignancy	1 (1.0%, 1.66)	0	0

Source: Section 5.3.5.3 Post-hoc Table 3.114
Abbreviations: ISR, injection site reaction; PY, person year; SIR, systemic injection reaction; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event

Based on the submitted data, the 240 mg SC dose is overall associated with a closely similar safety profile as the 120 mg SC dose in subjects with CD. There were somewhat more infections with the 240 mg dose (table 8.2.1.2). However, the number of treatment-emergent serious adverse events (TESAE) was similar: 28/275 (10.2%, PY 7.70) during use of CT-P13 120 mg SC and 7/105 (6.7%, PY 5.91) during use of CT-P13 240 mg SC. Furthermore, injections-site reactions were more frequent with the higher dose, but this was expected since the 240 mg SC regimen included two injections instead of only one.

Table 50 (of CSR CT-P13 37) Summary of Total Number of Doses and Total Amount of Study Drug Received (Extension Phase): Safety Population

	CT-P13 SC 120 mg (N=296)	Placebo (N=140)	Total (N=436)
Extension Phase			
Total number of doses received			
n	241	107	348
Mean (SD)	22.3 (5.06)	22.7 (4.43)	22.4 (4.87)
Median (min, max)	24.0 (1, 24)	24.0 (1, 24)	24.0 (1, 24)
Total administered dose (mg)			
n	241	107	348
Mean (SD)	3363.49 (1351.550)	4175.33 (1586.401)	3613.10 (1474.090)
Median (min, max)	2880.00 (240, 5760)	3480.00 (120, 5760)	2880.00 (120, 5760)

Abbreviations: max, maximum; min, minimum; SC, subcutaneous; SD, standard deviation.
Note: For patients with dose adjustment, all data collected regardless of dose adjustment for both treatment groups were included in this summary.

Table 51 (of CSR CT-P13 38) Summary of Total Number of Doses and Total Amount of Study Drug Received (Extension Phase): Safety Population

	CT-P13 SC 120 mg (N=238)	Placebo SC (N=105)	Total (N=343)
Extension Phase			
Total number of doses received			
n	199	79	278
Mean (SD)	22.64 (4.758)	23.10 (3.041)	22.77 (4.339)
Median (min, max)	24.00 (1, 24)	24.00 (6, 24)	24.00 (1, 24)
Total administered dose (mg)			
n	199	79	278
Mean (SD)	3209.82 (1218.336)	4285.06 (1506.436)	3515.37 (1391.425)
Median (min, max)	2880.00 (120, 5760)	5280.00 (720, 5760)	2880.00 (120, 5760)

Abbreviations: max, maximum; min, minimum; SC, subcutaneous; SD, standard deviation.
Note: For patients with dose adjustment, all data collected regardless of dose adjustment for both treatment groups were included in this summary.

In study CT-P13 3.8 (CD), the mean and median duration of treatment for patients who received CT-P13 SC 240 mg were 58.9 weeks and 68.1 weeks, respectively, and 73 patients received CT-P13 SC 240 mg as maintenance treatment for at least 44 weeks. Therefore, the post-hoc analysis result is considered to sufficiently represent long-term safety profile of CT-P13 SC 240 mg in subjects with CD.

For subjects with UC, the MAH no more applies for dose escalation to 240 mg SC.

8.2.2. Adverse events

The intensity of the AE was graded based on the Common Terminology Criteria for Adverse Events (CTCAE v5.0) or based on the following general guidelines (a semicolon indicates "or" within each description):

Grade 1: Mild AE (minor; no specific medical intervention; asymptomatic laboratory findings only; radiographic findings only; marginal clinical relevance)

Grade 2: Moderate AE (minimal intervention; local intervention; non-invasive intervention [packing, cautery])

Grade 3: Severe and undesirable AE (significant symptoms requiring hospitalization or invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation)

Grade 4: Life-threatening or disabling AE (complicated by acute, life-threatening metabolic or cardiovascular complications such as circulatory failure, haemorrhage, or sepsis; life-threatening physiological consequences; need for intensive care or emergent invasive procedure; emergent interventional radiological procedure, therapeutic endoscopy, or operation)

Grade 5: Death related to AE

8.2.2.1. Treatment-emergent adverse events (TEAE)

Summaries of TEAEs during the treatment period (which includes the induction and maintenance phases of the studies, but not the extension phase, for which results are still pending) are given for both phase 3 studies in tables 50 and 51. In both studies, around ¾ of subjects experienced adverse events, and around ¼ experienced adverse events deemed to be related to study medications. In tables 50 and 51, the proportions of subjects experiencing adverse events is approximately similar in the active and placebo groups. However, the tables include adverse events occurring during the treatment period that includes both the active induction phase with CT-P13 induction treatment given to all subjects and the placebo-controlled maintenance period. Since the adverse events for the induction phase in both studies were not reported separately, as detailed below, assessment of tolerability of CT-P13 based on the numbers in tables 8.2.2.1.1 and 8.2.2.1.2 is not possible.

In the CSR of study CT-P13 3.7 (ulcerative colitis), according to data on patient disposition a total of 110 subjects who discontinued induction phase, 13 subjects discontinued induction phase due to adverse events. Of 54 subjects who discontinued maintenance phase, 11 subjects discontinued due to adverse events. Hence, the number of subjects who discontinued treatment phase due to adverse events should be 24. However, according to table 50, in total only 14 subjects discontinued study due to TEAEs during the treatment phase that includes both induction and maintenance phases of the study.

Table 52. Summary of Treatment-Emergent Adverse Events during the Treatment Period: Safety Population, CT-P13 3.7, Ulcerative colitis

	CT-P13 SC 120 mg (N=296)	Placebo (N=140)	Total (N=436)
Total number of TEAEs	**828**	**337**	**1165**
Number (%) of patients with at least 1 TEAE	227 (76.7)	103 (73.6)	330 (75.7)
Related to the study drug	72 (24.3)	37 (26.4)	109 (25.0)
Unrelated to the study drug	215 (72.6)	94 (67.1)	309 (70.9)
Total number of TESAEs	**31**	**11**	**42**
Number (%) of patients with at least 1 TESAE	25 (8.4)	9 (6.4)	34 (7.8)
Related to the study drug	3 (1.0)	1 (0.7)	4 (0.9)
Unrelated to the study drug	22 (7.4)	8 (5.7)	30 (6.9)
Total number of TEAEs leading to study drug discontinuation	**10**	**4**	**14**
Number (%) of patients with at least 1 TEAE leading to study drug discontinuation	10 (3.4)	4 (2.9)	14 (3.2)
Related to the study drug	5 (1.7)	2 (1.4)	7 (1.6)
Unrelated to the study drug	5 (1.7)	2 (1.4)	7 (1.6)
Total number of TEAEs classified as IRR	**10**	**4**	**14**
Number (%) of patients with at least 1 TEAE classified as IRR	9 (3.0)	3 (2.1)	12 (2.8)
Total number of TEAEs classified as SIR	**19**	**4**	**23**
Number (%) of patients with at least 1 TEAE classified as SIR	12 (4.1)	4 (2.9)	16 (3.7)
Total number of TEAEs classified as delayed hypersensitivity	**0**	**0**	**0**
Number (%) of patients with at least 1 TEAE classified as delayed hypersensitivity	0	0	0
Total number of TEAEs classified as localized ISR	**47**	**4**	**51**
Number (%) of patients with at least 1 TEAE classified as localized ISR	11 (3.7)	3 (2.1%)	14 (3.2)
Total number of TEAEs classified as infection	**169**	**68**	**237**
Number (%) of patients with at least 1 TEAE classified as infection	103 (34.8)	49 (35)	152 (34.9)
Total number of TEAEs classified as malignancy	**1**	**0**	**1**
Number (%) of patients with at least 1 TEAE classified as malignancy	1 (0.3)	0	1 (0.2)
Total number of TEAEs classified as COVID-19	**43**	**13**	**56**
Number (%) of patients with at least 1 TEAE classified as COVID-19	39 (13.2)	12 (8.6)	51 (11.7)
Total number of TEAEs classified as ADE	**0**	**0**	**0**
Number (%) of patients with at least 1 TEAE classified as ADE	0	0	0

Similar to study CT-P13 3.7, the CSR of study CT-P13 3.8 (Crohn's disease) does not report separately for the induction phase the TEAEs leading to discontinuation of the study. However, according to data on patient disposition (figure 7.2.3.1 in Section 7.2.3), of a total of 53 subjects who discontinued induction phase,11 subjects discontinued induction phase due to adverse events. Of 35 subjects who discontinued maintenance phase, 8 subjects discontinued due to adverse events. Hence, the number of subjects who discontinued treatment phase due to adverse events should be 19, but according to table 8.2.2.1.2, in total only 16 subjects discontinued study due to TEAEs during the treatment phase.

Table 53. Summary of Treatment-Emergent Adverse Events During the Treatment Period: Safety Population, CT-P13 38, Crohn's disease

	CT-P13 SC 120 mg (N=238)	Placebo SC (N=105)	Total (N=343)
Total number of TEAEs	**786**	**253**	**1039**
Number (%) of patients with at least 1 TEAE	187 (78.6)	80 (76.2)	267 (77.8)
Related	80 (33.6)	23 (21.9)	103 (30.0)
Unrelated	174 (73.1)	73 (69.5)	247 (72.0)
Total number of TESAEs	**19**	**11**	**30**
Number (%) of patients with at least 1 TESAE	16 (6.7)	9 (8.6)	25 (7.3)
Related	1 (0.4)	1 (1.0)	2 (0.6)
Unrelated	16 (6.7)	8 (7.6)	24 (7.0)
Total number of TEAEs leading to study drug discontinuation	**10**	**6**	**16**
Number (%) of patients with at least 1 TEAE leading to study drug discontinuation	10 (4.2)	6 (5.7)	16 (4.7)
Related	6 (2.5)	2 (1.9)	8 (2.3)
Unrelated	4 (1.7)	4 (3.8)	8 (2.3)
Total number of TEAEs classified as IRR[1]	**9**	**2**	**11**
Number (%) of patients with at least 1 TEAE classified as IRR	7 (2.9)	2 (1.9.)	9 (2.6)
Total number of TEAEs classified as SIR[1]	**5**	**2**	**7**
Number (%) of patients with at least 1 TEAE classified as SIR	3 (1.3)	2 (1.9)	5 (1.5)
Total number of TEAEs classified as delayed hypersensitivity	**0**	**0**	**0**
Number (%) of patients with at least 1 TEAE classified as delayed hypersensitivity	0	0	0
Total number of TEAEs classified as localized ISR	**51**	**7**	**58**
Number (%) of patients with at least 1 TEAE classified as localized ISR	15 (6.3)	1 (1.0)	16 (4.7)
Total number of TEAEs classified as infection	**134**	**39**	**173**
Number (%) of patients with at least 1 TEAE classified as infection	88 (37.0)	29 (27.6)	117 (34.1)
Total number of TEAEs classified as malignancy	**0**	**1**	**1**
Number (%) of patients with at least 1 TEAE classified as malignancy	0	1 (1.0)	1 (0.3)
Total number of TEAEs classified as COVID-19	**35**	**7**	**42**
Number (%) of patients with at least 1 TEAE classified as COVID-19	34 (14.3)	7 (6.7)	41 (12.0)
Total number of TEAEs classified as ADE	**0**	**0**	**0**
Number (%) of patients with at least 1 TEAE classified as ADE	0	0	0

CHMP comment:

During the open-label induction phase subjects were administered three doses of CT-P13 IV 5 mg/kg at Weeks 0, 2 and 6. For both pivotal trials, discrepant numbers are given in the figures and tables on disposition of patients vs. the summary tables on adverse events regarding subjects discontinuing treatment due to adverse events during the induction and maintenance phases of the studies. The Applicant was requested to clarify the root cause of these discrepancies and to confirm numbers of subjects who discontinued treatment due to adverse events during the induction and maintenance phases of studies CTP-13 37 and CTP-13 38. Details of TEAEs leading to discontinuation were reported by the MAH separately for

the induction and maintenance periods of both studies. The received clarifications on this issue are deemed adequate (see assessment of question 43 in Section 13.2 of this AR).

Overall, the number of reported TEAEs and subcategories thereof were similar in subjects with UC and CD Further clarifications and analyses were requested from the MAH. Since the MAH withdrew the application for dose escalation in patients with UC, re-analyses were only received for patients with CD.

Sufficient data were received for subjects with CD, confirming that the higher dose of 240 mg caused per patient year slightly more infections and injection site reactions overall than the 120 mg dose, but there was no difference in treatment-emergent serious adverse events (TESAE). Injection site reactions were probably more frequent also because the 240 mg dose involved two injections and the 120 mg SC dose only one injection. All TEAE were markedly more frequent per patient year in the placebo group vs. both active groups. Potentially a large part of reported TEAEs represented symptoms of the disease, which might be speculated to explain the larger among of TEAEs in the placebo group (see also assessment of Question 42 in Section 13.2 of this AR).

8.2.3. TEAEs during maintenance phase

In the tables reporting adverse events, at each level of summarization, patients were counted once if they reported one or more events. Only the most severe event was counted. The event was considered to be related if the relationship was defined as 'Possible', 'Probable', or 'Definite'.

TEAEs reported from the maintenance phase of Studies CT-P13 3.7 and CT-P13, from randomization at Week 10 to Week 54 are presented in table 8.2.3.1.

A majority of subjects experienced TEAEs in Study CT-P13 3.7 (ulcerative colitis): 200/296 (67.6%) in the active group and 83/140 (59.3 %) in the placebo group. The proportions of subjects experiencing TEAEs in the active and placebo arms of study CT-P13 3.8 (Crohn's disease) were similar: 172/238 (72.3 %) and 65/105 (61.9 %), respectively. The proportion of subjects experiencing TEAEs considered to be related to study drug were in the active arms of studies CT-P13 3.7 and CT-P13 3.8 the following: 19.3 % and 26.1 %, respectively.

CHMP comment:

It is noteworthy that even in the placebo arms of the study, 15.0 % and 14.3 % of subjects in studies CT-P13 3.7 and CT-P13 3.8, respectively, experienced TEAEs that were considered to be related to study drug. The MAH was requested to clarify if the TEAEs related to study drug occurred in the placebo group during placebo treatment or during active treatment with CT-P13 after dose adjustment. The MAH confirmed that for both Study CT-P13 3.7 and Study CT-P13 3.8, only data collected before initiation of dose adjustment for Placebo SC group were included in Treatment-Emergent Adverse Event (TEAE) summary tables. Hence, these AEs that were reported for the Placebo group in the blind state were in retrospect not drug-related.

Table 54. Overview of Treatment-Emergent Adverse Events in Patients with Ulcerative Colitis or Crohn's Disease (Maintenance Phase): Safety

	Ulcerative Colitis (Study CT-P13 3.7)		Crohn's Disease (Study CT-P13 3.8)	
	CT-P13 SC 120 mg (N=296)	Placebo SC (N=140)	CT-P13 SC 120 mg (N=238)	Placebo SC (N=105)
Total number of TEAEs	595	207	569	170
Number (%) of patients with ≥ 1 TEAE	200 (67.6)	83 (59.3)	172 (72.3)	65 (61.9)
Related	57 (19.3)	21 (15.0)	62 (26.1)	15 (14.3)
Unrelated	184 (62.2)	76 (54.3)	156 (65.5)	59 (56.2)
Number (%) of patients with ≥ 1 TEAE leading to death	0	0	1 (0.4)	0
Related	0	0	0	0
Unrelated	0	0	1 (0.4)	0
Number (%) of patients with ≥ 1 TESAE	19 (6.4)	4 (2.9)	16 (6.7)	8 (7.6)
Related	2 (0.7)	1 (0.7)	1 (0.4)	1 (1.0)
Unrelated	17 (5.7)	3 (2.1)	16 (6.7)	7 (6.7)
Number (%) of patients with ≥ 1 TEAE leading to study drug discontinuation	10 (3.4)	4 (2.9)	9 (3.8)	5 (4.8)
Related	5 (1.7)	2 (1.4)	6 (2.5)	2 (1.9)
Unrelated	5 (1.7)	2 (1.4)	3 (1.3)	3 (2.9)
Number (%) of patients with ≥ 1 TEAE of SIR[1]	12 (4.1)	4 (2.9)	3 (1.3)	1 (1.0)
Related	12 (4.1)	4 (2.9)	3 (1.3)	1 (1.0)
Unrelated	0	0	0	0
Number (%) of patients with ≥ 1 TEAE of delayed hypersensitivity[1]	0	0	0	0
Number (%) of patients with ≥ 1 TEAE of localised ISR[2]	10 (3.4)	3 (2.1)	14 (5.9)	1 (1.0)
Related	10 (3.4)	3 (2.1)	14 (5.9)	1 (1.0)
Unrelated	0	0	0	0
Number (%) of patients with ≥ 1 TEAE of infection	83 (28.0)	36 (25.7)	74 (31.1)	19 (18.1)
Related	11 (3.7)	10 (7.1)	15 (6.3)	6 (5.7)
Unrelated	80 (27.0)	29 (20.7)	65 (27.3)	16 (15.2)
Number (%) of patients with ≥ 1 TEAE of malignancy	1 (0.3)	0	0	1 (1.0)
Related	0	0	0	0
Unrelated	1 (0.3)	0	0	1 (1.0)

Sources: CSR CT-P13 3.7 Post-text Tables 14.3.1.1A, 14.3.1.2A, 14.3.1.4A, 14.3.1.5A, 14.3.1.7A, 14.3.1.9A and 14.3.1.10A; CSR CT-P13 3.8 Post-text Tables 14.3.1.1A, 14.3.1.2A, 14.3.1.4A, 14.3.1.5A, 14.3.1.7A, 14.3.1.9A and 14.3.1.10A

[1] SIR/delayed hypersensitivity was reported as injection related reaction in the eCRF.

[2] Localised ISR was reported as injection site reaction in the eCRF.

Abbreviations: eCRF, electronic case report form; ISR, injection site reaction; SIR, systemic injection reaction; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event

8.2.3.1. Most Commonly Reported Treatment-Emergent Adverse Events

The TEAEs reported for at least 2 % of subjects in the active arms of the study and more frequently than in the placebo arms are presented for study CT-P13 3.7 (ulcerative colitis) in table 53 and for study CT-P13 3.8 (Crohn's disease) in table 54.

Of the events that occurred in at least 2 % of patients in the CT-P13 SC 120 mg arm of study CT-P13 3.7 (ulcerative colitis), TEAEs of (aggravation of) colitis ulcerative, nasopharyngitis and blood creatine phosphokinase increased were according to the MAH reported at a higher rate in the Placebo SC arm compared to the CT-P13 SC 120 mg arm. In study CT-P13 3.8 (Crohn's disease), adverse events occurring in at least 2% of subjects in the active arm but with a higher rate in the placebo arm, according to the

MAH, were anaemia, (aggravation of) Crohn's disease and nausea. Contrary to study CT-P13 3.8, CPK elevations were more frequent in the placebo than active arm in study CT-P13 3.7.

Table 55. TEAEs Reported for at Least 2 % of Patients in the CT-P13 SC Treatment Arm and Higher than the Placebo SC Arm by SOC and PT in Study CT-P13 3.7 (Maintenance Phase): Safety Population

System Organ Class Preferred Term	**CT-P13 SC 120 mg (N=296)**	**Placebo SC (N=140)**
Number (%) of patients with ≥ 1 TEAE	**200 (67.6)**	**83 (59.3)**
Blood and lymphatic system disorders	**27 (9.1)**	**11 (7.9)**
Anaemia	14 (4.7)	5 (3.6)
Thrombocytosis	6 (2.0)	2 (1.4)
General disorders and administration site conditions	**31 (10.5)**	**10 (7.1)**
Injection site reaction[1]	10 (3.4)	3 (2.1)
Pyrexia	8 (2.7)	3 (2.1)
Infections and infestations	**83 (28.0)**	**36 (25.7)**
COVID-19	30 (10.1)	9 (6.4)
Pharyngitis	6 (2.0)	0
Upper respiratory tract infection	9 (3.0)	3 (2.1)
Urinary tract infection	6 (2.0)	2 (1.4)
Injury, poisoning and procedural complications	**19 (6.4)**	**4 (2.9)**
Injection related reaction[2]	12 (4.1)	4 (2.9)
Investigations	**33 (11.1)**	**17 (12.1)**
Alanine aminotransferase increased	10 (3.4)	2 (1.4)
Musculoskeletal and connective tissue disorders	**28 (9.5)**	**7 (5.0)**
Arthralgia	13 (4.4)	2 (1.4)
Nervous system disorders	**24 (8.1)**	**9 (6.4)**
Headache	17 (5.7)	7 (5.0)
Vascular disorders	**13 (4.4)**	**3 (2.1)**
Hypertension	9 (3.0)	1 (0.7)

Table 56. TEAEs Reported for at Least 2 % of Patients in the CT-P13 SC Treatment Arm and Higher than the Placebo SC Arm by SOC and PT in Study CT-P13 3.8 (Maintenance Phase): Safety Population

System Organ Class Preferred Term	CT-P13 SC 120 mg (N=238)	Placebo SC (N=105)
Number (%) of patients with ≥ 1 TEAE	**172 (72.3)**	**65 (61.9)**
Blood and lymphatic system disorders	**27 (11.3)**	**8 (7.6)**
Leukopenia	6 (2.5)	0
Neutropenia	8 (3.4)	0
Gastrointestinal disorders	**55 (23.1)**	**34 (32.4)**
Abdominal pain	11 (4.6)	4 (3.8)
Diarrhoea	11 (4.6)	2 (1.9)
General disorders and administration site conditions	**32 (13.4)**	**7 (6.7)**
Injection site reaction[1]	14 (5.9)	1 (1.0)
Infections and infestations	**74 (31.1)**	**19 (18.1)**
COVID-19	27 (11.3)	5 (4.8)
Nasopharyngitis	5 (2.1)	2 (1.9)
Oral herpes	6 (2.5)	1 (1.0)
Urinary tract infection	7 (2.9)	2 (1.9)
Investigations	**32 (13.4)**	**10 (9.5)**
Alanine aminotransferase increased	9 (3.8)	1 (1.0)
Blood creatine phosphokinase increased	9 (3.8)	2 (1.9)
Metabolism and nutrition disorders	**10 (4.2)**	**2 (1.9)**
Hypertriglyceridemia	5 (2.1)	1 (1.0)
Musculoskeletal and connective tissue disorders	**22 (9.2)**	**6 (5.7)**
Arthralgia	9 (3.8)	3 (2.9)
Nervous system disorders	**26 (10.9)**	**5 (4.8)**
Dizziness	6 (2.5)	0
Headache	18 (7.6)	5 (4.8)
Vascular disorders	**10 (4.2)**	**2 (1.9)**
Hypertension	8 (3.4)	1 (1.0)

TEAEs by relationship to treatment

Study CT-P13 3.7 (Ulcerative Colitis)

During the Maintenance Phase, TEAEs considered to be related to study drug were reported for 57 (19.3%) and 21 (15.0%) patients in the CT-P13 SC 120 mg and Placebo SC arms, respectively. The most commonly reported related TEAEs in the CT-P13 SC 120 mg arm (≥ 2% patients in the CT-P13 SC 120 mg arm and reported at a higher rate than the Placebo SC arm) were SIR (PT injection related reaction) (12 [4.1%] and 4 [2.9%] patients, respectively) and localised ISR (PT injection site reaction) (10 [3.4%] and 3 [2.1%] patients, respectively).

Study CT-P13 3.8 (Crohn's Disease)

During the Maintenance Phase, TEAEs considered to be related to study drug were reported for 62 (26.1%) and 15 (14.3%) patients in the CT-P13 SC 120 mg and Placebo SC arms, respectively. The most commonly reported drug-related TEAEs in the CT-P13 SC 120 mg arm (≥ 2% patients in the CT-P13 SC 120 mg arm and reported at a higher rate than the Placebo SC arm) were localised ISR (14 [5.9%] and 1 [1.0%]

patients, respectively), alanine aminotransferase increased (7 [2.9%] patients in the CT-P13 SC 120 mg arm) and neutropenia (5 [2.1%] patients in the CT-P13 SC 120 mg arm).

CHMP comment

Of the adverse reactions occurring more frequently in the active than placebo arm of study CT-P13 3.7 (table 8.2.3.1.1), thrombocytosis is not currently included in Section 4.8 of the SmPC of Remsima. Furthermore, the adverse reactions hypertriglyceridaemia, and increase in creatine phosphokinase (CPK) were more frequent in the active than placebo arm of study CT-P13 3.8 (table 8.2.3.1.2) and are not mentioned in Section 4.8 of the SmPC. The MAH was requested to clarify for both pivotal studies the numbers of the adverse reactions which occurred more frequently in active than placebo arms but are nevertheless not proposed to be included in the SmPC and to discuss the potential relatedness of these ADRs with the medication and justify for each adverse reaction why they are not proposed to be included in the SmPC or alternatively, add them in the proposed SmPC. The MAH submitted information from pooled placebo-controlled studies on TEAEs reported for at least 1% of patients in the CT-P13 SC 120 mg group and at a higher rate than the Placebo SC group and adequately justified for each observed TEAE the inclusion or omission of that AE from the table in Section 4.8 of the SmPC (see assessment of Question 45 in Section 13.2 of this AR). Based on these data, no change is warranted on the table except for Covid-19, which was added in the updated tabulated list in Section 4.8 of SmPC as Very Common adverse event of Viral infection.

8.2.3.2. Serious adverse events and deaths

Study CT-P13 3.7 (Ulcerative Colitis)

All treatment-emergent serious adverse events (TESAE) experienced during the maintenance phase are summarized by SOC and PT for the safety population in Table 55.

Treatment-emergent SAEs considered by the investigator to be related to study drug during the maintenance phase were similar between CT-P13 SC 120 mg group and Placebo SC group (2 [0.7%] patients in the CT-P13 SC 120 mg group and 1 [0.7%] patient in the Placebo SC group). All TESAEs considered by the investigator to be related to study drug during maintenance phase were grade 3 in intensity (urinary tract infection and pneumonia were reported in CT-P13 SC 120 mg group and cellulitis was reported in Placebo SC group).

Table 57. Treatment-Emergent Serious Adverse Events During the Maintenance Phase by System Organ Class and Preferred Term: Safety Population, study CT-P13 3.7 (Ulcerative Colitis)

System Organ Class[1] Preferred Term[1]	CT-P13 SC 120 mg (N=296)	Placebo (N=140)	Total (N=436)
	Number (%) of patients		
Total number of TESAEs	**25**	**5**	**30**
Number (%) of patients with at least 1 TESAE	**19 (6.4)**	**4 (2.9)**	**23 (5.3)**
Related	2 (0.7)	1 (0.7)	3 (0.7)
Unrelated	17 (5.7)	3 (2.1)	20 (4.6)
Blood and lymphatic system disorders	**2 (0.7)**	**0**	**2 (0.5)**
Anaemia	2 (0.7)	0	2 (0.5)
Iron deficiency anaemia	1 (0.3)	0	1 (0.2)
Cardiac disorders	**1 (0.3)**	**0**	**1 (0.2)**
Aortic valve incompetence	1 (0.3)	0	1 (0.2)
Cardiac failure	1 (0.3)	0	1 (0.2)
Gastrointestinal disorders	**4 (1.4)**	**2 (1.4)**	**6 (1.4)**
Colitis ulcerative	3 (1.0)	1 (0.7)	4 (0.9)
Duodenal ulcer perforation	1 (0.3)	0	1 (0.2)
Rectal haemorrhage	0	1 (0.7)	1 (0.2)
Infections and infestations	**7 (2.4)**	**1 (0.7)**	**8 (1.8)**
COVID-19	1 (0.3)	0	1 (0.2)
COVID-19 pneumonia	2 (0.7)	0	2 (0.5)
Cellulitis	0	1 (0.7)	1 (0.2)
Cystitis	1 (0.3)	0	1 (0.2)
Pneumonia	1 (0.3)	0	1 (0.2)
Salpingitis	1 (0.3)	0	1 (0.2)
Urinary tract infection	1 (0.3)	0	1 (0.2)
Injury, poisoning and procedural complications	**1 (0.3)**	**0**	**1 (0.2)**
Clavicle fracture	1 (0.3)	0	1 (0.2)
Metabolism and nutrition disorders	**1 (0.3)**	**0**	**1 (0.2)**
Hypokalaemia	1 (0.3)	0	1 (0.2)
Musculoskeletal and connective tissue disorders	**3 (1.0)**	**0**	**3 (0.7)**
Arthritis	1 (0.3)	0	1 (0.2)
Scleroderma	1 (0.3)	0	1 (0.2)
Spondyloarthropathy	1 (0.3)	0	1 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (0.3)**	**0**	**1 (0.2)**
Colorectal adenoma	1 (0.3)	0	1 (0.2)
Nervous system disorders	**0**	**1 (0.7)**	**1 (0.2)**
Neuromyopathy	0	1 (0.7)	1 (0.2)
Vascular disorders	**0**	**1 (0.7)**	**1 (0.2)**
Deep vein thrombosis	0	1 (0.7)	1 (0.2)

CHMP comment

Even though only 2 subjects in the active arm and one subject in the placebo arm experienced TESAEs considered by the investigator to be related to study drug, it is noteworthy that more than twice as great percentage of subjects experienced at least one TESAE in the active arm (n=19/296, 6.4%) vs. placebo arm (n=4/140, 2.9%) of the study. The total number of TESAEs was 25/296 in the active vs. 5/140 in the

placebo arm (table 8.2.3.2.1). Regardless of investigator-assessed non-relation to study drug, it is likely that the higher incidence of TESAE's in the active group is caused by the active treatment.

Study CT-P13 3.8 (Crohn's Disease)

All TESAEs experienced during the maintenance phase are summarized by SOC and PT for the safety population in Table 56.

The TESAEs considered by the investigator to be related to study drug during the maintenance phase were reported for 1 (0.4%) patient in the CT-P13 SC 120 mg and 1 (1.0%) patient in the placebo SC group.

Table 58. Treatment-Emergent Serious Adverse Events During the Maintenance phase by System Organ Class and Preferred Term: Safety Population, Study CT P13 3.8 (Crohn's Disease)

System Organ Class[1] Preferred Term[1]	CT-P13 SC 120 mg (N=238)	Placebo SC (N=105)	Total (N=343)
	Number (%) of patients		
Total number of TESAEs	**19**	**9**	**28**
Number (%) of patients with at least 1 TESAE	**16 (6.7)**	**8 (7.6)**	**24 (7.0)**
Related	1 (0.4)	1 (1.0)	2 (0.6)
Unrelated	16 (6.7)	7 (6.7)	23 (6.7)
Blood and lymphatic system disorders	**0**	**1 (1.0)**	**1 (0.3)**
Anaemia	0	1 (1.0)	1 (0.3)
Gastrointestinal disorders	**5 (2.1)**	**2 (1.9)**	**7 (2.0)**
Crohn's disease	3 (1.3)	1 (1.0)	4 (1.2)
Haemorrhoids	1 (0.4)	0	1 (0.3)
Intestinal perforation	0	1 (1.0)	1 (0.3)
Subileus	1 (0.4)	0	1 (0.3)
General disorders and administration site conditions	**1 (0.4)**	**0**	**1 (0.3)**
Accidental death	1 (0.4)	0	1 (0.3)
Infections and infestations	**6 (2.5)**	**1 (1.0)**	**7 (2.0)**
Abscess intestinal	1 (0.4)	0	1 (0.3)
Anal abscess	1 (0.4)	0	1 (0.3)
Appendicitis	1 (0.4)	0	1 (0.3)
Arthritis bacterial	1 (0.4)	0	1 (0.3)
Bartholinitis	1 (0.4)	0	1 (0.3)
Bronchiolitis	1 (0.4)	0	1 (0.3)
Peritonitis	0	1 (1.0)	1 (0.3)
Urinary tract infection	1 (0.4)	0	1 (0.3)
Injury, poisoning and procedural complications	**1 (0.4)**	**1 (1.0)**	**2 (0.6)**
Humerus fracture	0	1 (1.0)	1 (0.3)
Skin laceration	1 (0.4)	0	1 (0.3)
Investigations	**0**	**1 (1.0)**	**1 (0.3)**
Blood creatine phosphokinase increased	0	1 (1.0)	1 (0.3)
Musculoskeletal and connective tissue disorders	**1 (0.4)**	**0**	**1 (0.3)**
Intervertebral disc degeneration	1 (0.4)	0	1 (0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**1 (1.0)**	**1 (0.3)**
Colon cancer stage III	0	1 (1.0)	1 (0.3)
Nervous system disorders	**2 (0.8)**	**0**	**2 (0.6)**
Altered state of consciousness	1 (0.4)	0	1 (0.3)
Neurovascular conflict	1 (0.4)	0	1 (0.3)
Psychiatric disorders	**1 (0.4)**	**1 (1.0)**	**2 (0.6)**
Mixed anxiety and depressive disorder	1 (0.4)	0	1 (0.3)
Psychotic disorder	0	1 (1.0)	1 (0.3)
Skin and subcutaneous tissue disorders	**1 (0.4)**	**0**	**1 (0.3)**
Acne fulminans	1 (0.4)	0	1 (0.3)

CHMP comment

Contrary to Study CT-P13 3.7, in this study, the percentage of patients with Crohn's disease who experienced at least 1 TESAE during the maintenance phase was similar between 2 groups (16 [6.7%] and 8 [7.6%] patients in the CT-P13 SC 120 mg and placebo SC groups, respectively).

Deaths

There were no deaths reported in patients from study CT-P13 3.7 (ulcerative colitis). One death was reported in study CT-P13 3.8 (Crohn's disease): a patient (CT-P13 SC 120 mg arm) experienced a Grade 5 treatment-emergent serious adverse event (TESAE) of accidental death which was fatal, and the patient died on the same day. The patient's wife reported that there was an explosion in a garage where the patient was working. The patient subsequently had a cardiac arrest which was fatal. The event of accidental death was considered by the investigator to be unrelated to the study drug.

8.2.3.3. TEAEs of special interest

The following events were evaluated as protocol-defined adverse events of special interest (AESI): SIR (hypersensitivity/anaphylactic reaction), delayed hypersensitivity, localised ISR, infection, and malignancy.

Study CT-P13 3.7 (Ulcerative Colitis)

Systemic Injection Reaction (SIR)
During the Maintenance Phase, SIRs were reported for 12 (4.1%) and 4 (2.9%) patients in the CT-P13 SC 120 mg and placebo SC arms, respectively. Grade 3 SIR was reported for 3 (1.0%) patients in the CT-P13 SC 120 mg arm and 1 (0.7%) patient in the placebo SC arm. One patient in each treatment arm experienced SIR that led to study drug discontinuation. The patient in the CT-P13 SC 120 mg arm who discontinued study medication first experienced grade 3 TEAE of SIR with signs and symptoms of pruritus, rash, throat irritation and urticaria 1 day after Week 18 SC administration. The patient recovered by receiving treatment of desloratadine and prednisone. The symptoms recurred on the day of Week 20 SC administration, after which the patient was withdrawn from the study.

Delayed Hypersensitivity
During the Maintenance Phase, no delayed hypersensitivity was reported in either treatment arm.

Localised Injection Site Reaction (ISR)
During the Maintenance Phase, localised ISRs were reported for 10 (3.4%) and 3 (2.1%) patients in the CT-P13 SC 120 mg and placebo SC arms, respectively. All events were grade 1 or 2 in severity, non-serious, and did not lead to study drug discontinuation.

CHMP comments

The MAH proposes to update the data on injection site and systemic injection reactions in adults administered Remsima SC in Section 4.8 of the SmPC based on a Phase 1 study conducted in patients with active Crohn's disease and active ulcerative colitis and the phase 3 studies assessed in this variation. The proposed updated text is the following:
"In the integrated analysis including a Phase I study conducted in patients with active Crohn's disease and active ulcerative colitis, a Phase III study conducted in patients with active Crohn's disease and a Phase III study conducted in patients with active ulcerative colitis, the safety population consisted of 631 patients in the Remsima subcutaneous group (297 patients with active Crohn's disease and 334 patients with active ulcerative colitis) and 245 patients in the Placebo group (105 patients with active Crohn's disease and 140 patients with active ulcerative colitis). For study details, see Section 5.1.

The incidence rate of systemic injection reactions (e.g. nausea and dizziness) was 3.56 patients per 100 patient-years in the Remsima subcutaneous group.

The incidence rate of localised injection site reactions (e.g. injection site erythema, pain, pruritus, bruising) was 8.68 patients per 100 patient-years in the Remsima subcutaneous group. Most of these reactions were mild to moderate and mostly resolved spontaneously without any treatment within a few days."
However, the accuracy of the proposed update could not be assessed since the assessor could not locate in the submission the integrated safety data compiled from the Phase 1 study in UC/CD and the two Phase 3 studies. Some integrated post-hoc analyses were presented in Module 5.3.5.3 of the submission, but the data presented there were pooled from the two Phase 3 studies and do not include the Phase 1 study.

It was not clear why the new data were only included in the SmPC for SIR and ISR and not for any other adverse reactions. Furthermore, it was not understood why the integrated analyses did not include all studies conducted with SC administered Remsima but only the one Phase 1 study in CD/UC in addition to the two Phase 3 studies included in the current variation. After all, according to the MAH, there have been two controlled, comparative, clinical studies in patients during the development of CT-P13 SC prior to the two Phase 3 studies that are currently under assessment.

The current safety database in the SPC includes 168 patients with RA and 97 patients with CD or UC. In the current variation, additional >600 patients have been exposed to Remsima SC (297 CD and 334 UC). This is a significant amount of new safety data. Thus, a new integrated safety analysis was requested, including all exposed patients in clinical trials on SC administered Remsima in the approved indications: studies CT-P13 3.7 (UC), CT-P13 3.8 (CD), CT-P13 3.5 Part 1 and Part 2 (rheumatoid arthritis, RA) and CT-P13 1.6 Part 1 and Part 2 (UC and CD) for subjects administered 120 mg or 240 mg SC doses (90 mg and 180 mg SC doses should be omitted as not relevant for the current update and not feasible to be administered by the approved formulations). These data were also requested to include patients from the placebo group who received the 240 mg SC Remsima as "rescue medication" in the currently assessed studies.

In conclusion, the MAH was requested to submit analyses for the integrated data for SC administered Remsima in all approved indications separately 1) for subjects who were administered the 120 mg SC dose and 2) for subjects who were administered the 240 mg SC dose in studies CT-P13 3.7 (UC), CT-P13 3.8 (CD), CT-P13 3.5 Part 1 and Part 2 (rheumatoid arthritis, RA) and CT-P13 1.6 Part 1 and Part 2 (UC and CD); and 3) pooled together for both SC doses. Adverse events occurring prior to dose escalation from 120 mg SC to 240 mg SC vs. after dose escalation should be compared, with adjustment for duration of exposure to each dose. The same analysis was requested to be conducted for the patients who originally were administered placebo and were switched to the 240 mg SC dose. The MAH provided in their response the requested analyses. The pooled analysis included final data from each study:

- Study 1.6 Part 1 (CD): CT-P13 SC 120 mg group and CT-P13 SC 240 mg group from Week 6
- Study 1.6 Part 2 (CD/UC): CT-P13 SC 120/240 mg group from Week 6 and CT-P13 IV 5 mg/kg group from Week 30
- Study 3.5 Part 1 (RA): CT-P13 SC 120 mg group from Week 6
- Study 3.5 Part 2 (RA): CT-P13 SC 120 mg group from Week 6 and CT-P13 IV 3 mg/kg group from Week 30
- Study CT-P13 3.7 (UC): CT-P13 SC 120 mg group from Week 10 and Placebo group from Week 56 or after dose adjustment
- Study CT-P13 3.8 (CD): CT-P13 SC 120 mg group from Week 10 and Placebo group from Week 56 or after dose adjustment.

For the Phase 3 studies, the analysis on dose adjustment was performed only for Study CT-P13 3.8, since the MAH withdrew the proposed dose adjustment from CT-P13 SC 120 mg to 240 mg for patients with ulcerative colitis (UC),

In the pooled analysis of all CT-P13 SC studies, there were slightly more TEAE, TESAE, TEAE leading to study drug discontinuation, SIR, delayed hypersensitivity and infections with the 240 mg SC dose than the 120 mg SC dose (Table 7 of the response; see Section 13.2, assessment of question 46). Regarding malignancy, there were only 2/1056 cases (0.2%, 0.18 100 PY) in the 120 mg SC group and 3/342 cases (0.9%, 0.87 100PY) in the 240 mg SC group, so interpretation of the difference in malignancy is futile.

In study CT-P13 3.8, interestingly, there were markedly more TEAE with placebo (54%, 151.42/100 PY)) and CT-P13 120 mg SC (61.1%, 107.07/100 PY) than in subjects with dose escalation from 120 mg to 240 mg SC (63.0%, 64.66/100 PY) or subjects with dose escalation from placebo to 240 mg SC (64%, 49.14/100 PY) (Table 8 of the response). Hence, these TEAE may have actually been symptoms of CD?

Only studies CT-P13 3.7, CT-P13 3.8 and CT-P13 1.6 Part 2 were included in the pooled analysis on safety of dose escalation, as these are the only studies that allowed dose adjustment to CT-P13 SC 240 mg. In this analysis (table 9 of the response) that includes subjects with both CD and UC (from studies CT-P13 3.7, CT-P13 3.8 and CT-P13 1.6), there were also markedly more TEAE in the CT-P13 120 mg SC group than in the CT-P13 240 mg SC groups (escalation from 120 mg SC of from placebo) or placebo. However, the occurrence of TESAE was slightly larger in the 240 mg SC group, regardless of if the escalation occurred from placebo or from CT-P13 120 mg SC. Notably, also infections occurred less often during treatment with CT-P13 240 mg SC than CT-P13 120 mg SC or placebo.

Overall, the results do not indicate that the safety profile of the 240 mg SC dose would relevantly differ from the safety profile of 120 mg SC of CT-P 13. The MAH did not propose changes in the submitted Product Information based on these data and none are deemed to be warranted.

Infection

During the Maintenance Phase, infections were reported for 83 (28.0%) and 36 (25.7%) patients in the CT-P13 SC 120 mg and Placebo SC arms, respectively. A majority of the infections were Grade 1 or 2 (Table 57).

Table 59. Summary of Infection in Study CT-P13 3.7 (UC, Maintenance Phase): Safety Population

	CT-P13 SC 120 mg (N=296)	Placebo SC (N=140)
Total number of infection	**127**	**46**
Number (%) of patients with ≥ 1 infection	**83 (28.0)**	**36 (25.7)**
Related	11 (3.7)	10 (7.1)
Grade 1	2 (0.7)	5 (3.6)
Grade 2	6 (2.0)	3 (2.1)
Grade 3	3 (1.0)	2 (1.4)
Unrelated	80 (27.0)	29 (20.7)
Grade 1	34 (11.5)	18 (12.9)
Grade 2	39 (13.2)	10 (7.1)
Grade 3	6 (2.0)	1 (0.7)
Grade 4	1 (0.3)	0

The most commonly reported infection in the CT-P13 SC 120 mg arm (≥2% patients in the CT-P13 SC 120 mg arm and reported at a higher rate than the placebo SC arm) was COVID-19 reported in 30 (10.1%) patients for the CT-P13 SC 120 mg group and 9 (6.4%) patients for the placebo SC group. (Table 58)

Table 60. Treatment-Emergent Adverse Events Classified as Infection During the Maintenance Phase: Safety Population Study CT-P13 3.7 (UC)

System Organ Class[1] Preferred Term[1]	CT-P13 SC 120 mg (N=296)	Placebo (N=140)	Total (N=436)
	Number (%) of patients		
Total number of TEAEs classified as infection	**127**	**46**	**173**
Number (%) of patients with at least 1 TEAE classified as infection	**83 (28.0)**	**36 (25.7)**	**119 (27.3)**
Related	11 (3.7)	10 (7.1)	21 (4.8)
Unrelated	80 (27.0)	29 (20.7)	109 (25)
Infections and infestations	**83 (28.0)**	**36 (25.7)**	**119 (27.3)**
Abscess limb	1 (0.3)	0	1 (0.2)
Anal abscess	1 (0.3)	0	1 (0.2)
Ascariasis	1 (0.3)	0	1 (0.2)
Asymptomatic bacteruria	0	1 (0.7)	1 (0.2)
Bronchitis	3 (1.0)	0	3 (0.7)
COVID-19	30 (10.1)	9 (6.4)	39 (8.9)
COVID-19 pneumonia	3 (1.0)	0	3 (0.7)
Candida infection	1 (0.3)	0	1 (0.2)
Cellulitis	0	1 (0.7)	1 (0.2)

Table 61. Treatment-Emergent Adverse Events Classified as Infection During the Maintenance Phase: Safety Population Study CT-P13 3.7 (UC) - continued

System Organ Class[1] Preferred Term[1]	CT-P13 SC 120 mg (N=296)	Placebo (N=140)	Total (N=436)
	Number (%) of patients		
Chronic sinusitis	2 (0.7)	0	2 (0.5)
Conjunctivitis	2 (0.7)	0	2 (0.5)
Cystitis	4 (1.4)	0	4 (0.9)
Erythema migrans	0	1 (0.7)	1 (0.2)
Escherichia urinary tract infection	0	1 (0.7)	1 (0.2)
Furuncle	1 (0.3)	0	1 (0.2)
Gastroenteritis	2 (0.7)	0	2 (0.5)
Gastrointestinal viral infection	1 (0.3)	0	1 (0.2)
Herpes simplex	2 (0.7)	2 (1.4)	4 (0.9)
Herpes zoster	3 (1.0)	2 (1.4)	5 (1.1)
Influenza	1 (0.3)	0	1 (0.2)
Latent tuberculosis	2 (0.7)	3 (2.1)	5 (1.1)
Nasopharyngitis	7 (2.4)	7 (5)	14 (3.2)
Oral candidiasis	1 (0.3)	0	1 (0.2)
Oral herpes	5 (1.7)	0	5 (1.1)
Otitis externa	2 (0.7)	0	2 (0.5)
Otitis media acute	0	1 (0.7)	1 (0.2)
Peritonitis	1 (0.3)	0	1 (0.2)
Pharyngitis	6 (2.0)	0	6 (1.4)
Pneumonia	1 (0.3)	0	1 (0.2)
Pulpitis dental	0	1 (0.7)	1 (0.2)
Pyelonephritis	1 (0.3)	0	1 (0.2)
Respiratory tract infection	3 (1.0)	1 (0.7)	4 (0.9)
Respiratory tract infection viral	2 (0.7)	0	2 (0.5)
Rhinitis	2 (0.7)	2 (1.4)	4 (0.9)
Salpingitis	1 (0.3)	0	1 (0.2)
Salpingo-oophoritis	1 (0.3)	0	1 (0.2)
Sinusitis	2 (0.7)	0	2 (0.5)
Streptococcal impetigo	1 (0.3)	0	1 (0.2)
Tinea cruris	0	1 (0.7)	1 (0.2)
Tinea pedis	0	1 (0.7)	1 (0.2)
Tonsillitis	1 (0.3)	2 (1.4)	3 (0.7)
Tooth abscess	0	1 (0.7)	1 (0.2)
Upper respiratory tract infection	9 (3.0)	3 (2.1)	12 (2.8)
Urinary tract infection	6 (2.0)	2 (1.4)	8 (1.8)
Vaginal infection	1 (0.3)	0	1 (0.2)
Varicella	1 (0.3)	0	1 (0.2)
Viral upper respiratory tract infection	1 (0.3)	1 (0.7)	2 (0.5)

The TEAEs classified as infection considered by the investigator to be related to study drug during the maintenance phase were reported in 21 (4.8%) patients (11 [3.7%] and 10 [7.1%] patients in the CT-P13 SC 120 mg and Placebo SC groups, respectively).

Treatment-emergent serious adverse events (TESAE) of infection were reported for 7/296 subjects in the CT_P13 SC group and 1/140 subjects in the placebo group. These included in the active group, COVID-19 (n=1), COVID-19 pneumonia (n=2), cystitis (n=1), pneumonia (n=1), salpingitis (n=1) and urinary trat infection (n=1), and in the placebo group, cellulitis (n=1).

During the Maintenance Phase, TEAE of latent tuberculosis was reported for 2 (0.7%) patients in the CT-P13 SC 120 mg arm and 3 (2.1%) patients in the placebo SC arm.

CHMP comment

The overall incidence of infections reported as TEAE was closely similar between the study arms: 28.0% vs. 25.7.% of study subjects suffered an infection in the CT-P13 and placebo arms, respectively. However, treatment-emergent serious adverse events (TESAE) occurred in 7 subjects in the active and only 1 subject in the placebo arm.

Of the 39 COVID-19 cases, 30 occurred in the active arm. Additionally, there were three cases of COVID-19 pneumonia in the active group and none in the placebo group. Hence, it is obvious that infliximab predisposes to symptomatic COVID-19 infection. The SmPC of Remsima already includes the information on susceptibility to infections caused by infliximab and that viral infections (e.g., influenza, herpes virus infection) are a very common adverse reactions of infliximab. COVID-19 was requested to be added in these examples of infections mentioned in parentheses, with an asterisk referring to a footnote describing that these ADRs were seen with the SC administered Remsima; and the MAH performed this change.

Section 4.8 of the SmPC is proposed to be updated regarding description of the adverse drug reactions 'systemic injection reaction' and 'localised injection site reaction'. As described earlier, the update of Section 4.8 is based on data pooled from the two phase 3 studies currently under assessment and one phase 1 study. However, the update should be based on the comprehensive data package obtained so far for approved SC doses used for approved indications. With their response, the MAH provided pooled analyses that did not change the safety profile (see assessment of Question 46 in Section 13.2 of this AR). Also, the injection site reactions in the pooled analyses corresponded to the frequency of "common", in line with the currently proposed Product Information.

Malignancy

In Study CT-P13 3.7, during the Maintenance Phase, grade 3 TEAE of prostate cancer was reported for 1 patient in the CT-P13 SC 120 mg arm. The AE was deemed unrelated to study drug by the investigator.

Study CT-P13 3.8 (Crohn's Disease)

Systemic Injection Reaction

During the maintenance phase, SIRs were reported for 3 (1.3%) and 1 (1.0%) patients in the CT-P13 SC 120 mg and placebo SC arms, respectively. All events were grade 1 in severity and non-serious. No action was taken with the study drug and all patients recovered without receiving treatment for the SIR.

Delayed Hypersensitivity

No cases of delayed hypersensitivity were reported.

Localised Injection Site Reaction

During the Maintenance Phase, localised ISRs were reported for 14 (5.9%) and 1 (1.0%) patients in the CT-P13 SC 120 mg and placebo SC groups, respectively. All TEAEs classified as localized ISRs were grade 1 or 2 in intensity and most patients' localized ISR recovered in both treatment groups. No serious localized ISRs were reported.

Infection

The TEAEs classified as infection are presented in table 8.2.3.3.3. Overall, at least one TEAE of infection was reported for 31.1% of subjects in the CT-P13 group and 18.1% of subjects in the placebo group. Of these, investigators assessed the TEAEs to be related to study drug in 15 subjects (6.3%) in the active group and 6 subjects (5.7%) in the placebo group.

The most frequently reported TEAEs classified as infection during the maintenance phase were COVID-19 reported in 32 (9.3%) patients (27 [11.3%] and 5 [4.8%]) and patients for the CT-P13 SC 120 mg and placebo SC groups, respectively), followed by urinary tract infection in 7 (2.9%) patients for the CT-P13 SC 120 mg group and latent tuberculosis, nasopharyngitis, respiratory tract infection viral, and urinary tract infection each reported in 2 (1.9%) patients for the placebo SC group.

Treatment-emergent serious adverse events (TESAE) of infection were reported according to Table 1 (under subtitle 8.2.3.2 Serious adverse events and deaths) for 6/238 (2.5%) subjects in the CT-P13 SC group and 1 (1.0%) subjects in the placebo group. The seven TESAE reported for the six subjects in the active group included one of each of the following: abscess intestinal, anal abscess, appendicitis, arthritis bacterial, bartholinitis, bronchiolitis, and urinary tract infection. In the placebo group there was one TESAE of peritonitis.

Two cases of latent tuberculosis were reported in the placebo group and none in the active group.

Table 62. Preferred Term: Safety Population Study CT-P13 3.8 (Crohn's disease)

System Organ Class[1] Preferred Term[1]	CT-P13 SC 120 mg (N=238)	Placebo SC (N=105)	Total (N=343)
	Number (%) of patients		
Total number of TEAEs classified as infection	108	25	133
Number (%) of patients with at least 1 TEAE classified as infection	74 (31.1)	19 (18.1)	93 (27.1)
Related	15 (6.3)	6 (5.7)	21 (6.1)
Grade 1	4 (1.7)	5 (4.8)	9 (2.6)
Grade 2	10 (4.2)	1 (1.0)	11 (3.2)
Grade 3	1 (0.4)	0	1 (0.3)
Unrelated	65 (27.3)	16 (15.2)	81 (23.6)
Grade 1	27 (11.3)	6 (5.7)	33 (9.6)
Grade 2	34 (14.3)	7 (6.7)	41 (12.0)
Grade 3	4 (1.7)	2 (1.9)	6 (1.7)
Grade 4	0	1 (1.0)	1 (0.3)
Infections and infestations	74 (31.1)	19 (18.1)	93 (27.1)
Abdominal abscess	0	1 (1.0)	1 (0.3)
Abscess intestinal	1 (0.4)	0	1 (0.3)
Abscess limb	0	1 (1.0)	1 (0.3)
Abscess rupture	1 (0.4)	0	1 (0.3)

System Organ Class[1] Preferred Term[1]	CT-P13 SC 120 mg (N=238)	Placebo SC (N=105)	Total (N=343)
	Number (%) of patients		
Acute sinusitis	1 (0.4)	0	1 (0.3)
Anal abscess	1 (0.4)	0	1 (0.3)
Appendicitis	1 (0.4)	0	1 (0.3)
Arthritis bacterial	1 (0.4)	0	1 (0.3)
Bartholinitis	1 (0.4)	0	1 (0.3)
Bronchiolitis	1 (0.4)	0	1 (0.3)
COVID-19	27 (11.3)	5 (4.8)	32 (9.3)
Cellulitis	1 (0.4)	0	1 (0.3)
Chronic sinusitis	1 (0.4)	0	1 (0.3)
Conjunctivitis	2 (0.8)	0	2 (0.6)
Cystitis	0	1 (1.0)	1 (0.3)
Ear infection	1 (0.4)	0	1 (0.3)
Folliculitis	2 (0.8)	0	2 (0.6)
Gastroenteritis	3 (1.3)	1 (1.0)	4 (1.2)
Gastroenteritis viral	1 (0.4)	0	1 (0.3)
Gingivitis	1 (0.4)	0	1 (0.3)
Herpes dermatitis	1 (0.4)	0	1 (0.3)
Herpes zoster	4 (1.7)	0	4 (1.2)
Infected fistula	1 (0.4)	0	1 (0.3)
Latent tuberculosis	0	2 (1.9)	2 (0.6)
Nasal herpes	1 (0.4)	0	1 (0.3)
Nasopharyngitis	5 (2.1)	2 (1.9)	7 (2.0)
Onychomycosis	1 (0.4)	0	1 (0.3)
Oral herpes	6 (2.5)	1 (1.0)	7 (2.0)
Orchitis	1 (0.4)	0	1 (0.3)
Otitis media	1 (0.4)	0	1 (0.3)
Periodontitis	1 (0.4)	0	1 (0.3)
Peritonitis	0	1 (1.0)	1 (0.3)
Pharyngitis	4 (1.7)	0	4 (1.2)
Pharyngitis streptococcal	1 (0.4)	0	1 (0.3)
Pilonidal disease	1 (0.4)	0	1 (0.3)
Pneumonia	1 (0.4)	0	1 (0.3)
Pulpitis dental	1 (0.4)	0	1 (0.3)
Pustule	1 (0.4)	0	1 (0.3)
Pyoderma	2 (0.8)	1 (1.0)	3 (0.9)
Respiratory tract infection	1 (0.4)	0	1 (0.3)
Respiratory tract infection viral	3 (1.3)	2 (1.9)	5 (1.5)
Rhinitis	2 (0.8)	0	2 (0.6)

System Organ Class[1] Preferred Term[1]	CT-P13 SC 120 mg (N=238)	Placebo SC (N=105)	Total (N=343)
	Number (%) of patients		
Rhinovirus infection	1 (0.4)	0	1 (0.3)
Sinusitis	2 (0.8)	0	2 (0.6)
Skin bacterial infection	1 (0.4)	0	1 (0.3)
Tinea versicolour	1 (0.4)	0	1 (0.3)
Tonsillitis	0	1 (1.0)	1 (0.3)
Tooth infection	2 (0.8)	0	2 (0.6)
Upper respiratory tract infection	1 (0.4)	1 (1.0)	2 (0.6)
Urinary tract infection	7 (2.9)	2 (1.9)	9 (2.6)

Abbreviations: MedDRA, medical dictionary for regulatory activities; 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. For patients with dose adjustment, all data collected regardless of dose adjustment for CT-P13 SC 120 mg group and data collected before initiation of dose adjustment for placebo SC group were included in this summary.

CHMP comment

Overall, TEAEs reported as infection were markedly more frequent in the active group (31.1% of subjects) than the placebo group (18.1% of subjects). Of these, investigators assessed the TEAEs to be related to study drug in 15 subjects (6.3%) in the active group and 6 subjects (5.7%) in the placebo group. It is obvious that the assessment of relatedness has not been accurate.

Subjects in the active group were more susceptible to clinical COVID-19 infection, which was reported for 11.3% of subjects in the active group and only 4.8% in the placebo group. Five cases of herpes infections were reported in the active group: 4 herpes zoster and 1 herpes dermatitis, whereas no cases of herpes were reported in the placebo group. The Section 4.4 (Warnings and precautions for use) of the SmPC of Remsima already includes the information that patients taking TNF-blockers are more susceptible to serious infections. Tuberculosis, bacterial infections, including sepsis and pneumonia, invasive fungal, viral, and other opportunistic infections have been observed in patients treated with infliximab. Advice is included that patients should be advised of and avoid exposure to potential risk factors for infection as appropriate; and that patients who develop a new infection should be monitored closely and undergo a complete diagnostic evaluation and that administration of infliximab should be discontinued if a patient develops a new serious infection or sepsis. As described earlier in this AR, Table 1 of Section 4.8. of the SmPC includes the information that viral infection (e.g., influenza, herpes virus infection) is a very common AE, in line with the SmPC of the originator product. Upon request, the MAH added COVID-19 to the list of examples together with influenza and herpes virus infection.

Malignancy

In Study CT-P13 3.8, during the Maintenance Phase, only one case of malignancy (stage III colon cancer) was reported in the placebo group and none in the active group. The AE was deemed unrelated to study drug by the investigator.

8.2.3.4. Dose adjustment vs. no dose adjustment

Dose adjustment from CT-P13 SC 120 mg to 240 mg every 2 weeks was allowed for patients with loss of response starting from Week 22 in both pivotal trials. The data on subgroups treated with CT-P13 SC and with and without dose escalation have been provided by the MAH 1) separately for both trials and 2) pooled across the two trials. The MAH explains that pooling of safety data provides a larger number of patients within each subgroup for the evaluation of rare events and other targeted events in a controlled setting such as serious infection. The patients from these studies are considered to be sufficiently similar that pooling of the data is appropriate.

CHMP comment

It is agreed that pooling of data of patients with ulcerative colitis and Crohn's disease according to dose adjustment is acceptable, as far as data from both studies are also provided for each individual study. From tables included in the document "Post-hoc Analyses" (Module 5.3.5.3) it is understood that there were 534 subjects in the pooled analysis, of whom 137 with dose adjustment and 397 without dose adjustment. The MAH was however requested to further clarify the patient populations used for investigating effects of dose escalation in the pooled data set and in the separate analyses of both phase 3 trials. The re-analyses were requested to be also performed separately for subjects with UC and CD for confirmation of safety in each indication. The MAH provided the requested pooled analyses from all studies where CT-P13 was administered SC and also separately for study CTP-13 3.8 (CS) for subjects administered the 120 mg SC dose, 240 mg SC dose, or placebo, where incidence of TEAEs was calculated per 100 patient-years (PY). Similar analyses were not performed in subjects with UC in study CT-P 13 3.7, since the MAH withdraws the escalation in UC patients due to insufficient data. Please see assessments of questions 42 and 46 in Section 13.2 of this AR.

In **Study CTP-13 3.7 (ulcerative colitis),** 92/296 (31.1%) of patients in the active group needed dose escalation from 120 to 240 mg and 75/140 (53.6 % in the placebo group and needed dose escalation from placebo to 240 mg during the maintenance phase.

Amongst these patients, TEAEs were reported for 67 (72.8%) and 133 (65.2%) patients in the subgroups with dose adjustment and without dose adjustment, respectively, apparently only from the active study group. More subjects suffered (aggravation of) colitis ulcerative in the active vs. placebo group (15 [16.3%] and 5 [2.5%] patients, respectively) and anaemia (6 [6.5%] and 8 [3.9%] patients, respectively). Discontinuation of study drug or numbers of treatment-emergent adverse events of special interest were not affected by dose adjustment, including systemic and injection site reactions (data for the individual study not shown for brevity).

In **Study CT-P13 3.8 (Crohn's disease)**, in the maintenance phase, dose was adjusted at least once for 45 subjects [18.9%] and 48 [45.1%] patients in the CT-P13 SC 120 mg and placebo SC groups, respectively. Apparently, only subjects from the active study group were included in the comparison between doses (see earlier). Amongst these patients, TEAEs were reported for 32 (71.1%) and 140 (72.5%) patients in the subgroups with dose adjustment and without dose adjustment, respectively. Similar to the study CT-P13 3.7, aggravation of the disease to be treated - in this study, Crohn's disease - was more common in the group with dose escalation. By SOC, the largest difference was seen in musculoskeletal and connective tissue disorders including arthralgia, which AEs were however mostly considered unrelated to study drug (data not shown for brevity).

The MAH concludes that dose escalation did not increase TEAEs leading to drug discontinuation rate or frequency of AESI.

CHMP comment

As described earlier, the subjects switched from placebo to 240 mg dose of CT-P13 SC constituted a great part of subjects using the 240 mg dose, since dose escalation was more frequent in the placebo groups than in the active study groups of both phase 3 trials, as expectable. Therefore, these subjects should be included in the analyses on safety of the 240 mg dose. Nevertheless, for comparison of safety between the 120 mg and 240 mg doses it is of utmost importance that the ADRs for each dose are only included for the time when the dose was used. The MAH provided analyses on TEAE per exposure time to each dose (per 100 PY), as requested..

The currently submitted data on safety of the 240 mg dose are now available for the entire treatment time (induction, maintenance and long-term extension periods) and are considered sufficient for confirmation of safety of this proposed higher dose (please see assessment of Questions 42 and 46 in Section 13.2 of this AR and the assessment of the final CSR later in this section).

Pooled data

The subgroup analysis of TEAEs by dose adjustment in the pooled analysis of Studies CT-P13 3.7 and CT-P13 3.8 is provided in Table 8.2.3.4.1. In the pooled data, the number of CT-P13 SC treated patients with dose adjustment from CT-P13 SC 120 mg to 240 mg was 137/534 (25.7%) patients and without dose adjustment was 397/534 (74.3%) patients during the Maintenance Phase.

TEAEs were reported for 99 (72.3%) and 273 (68.8%) patients in the subgroups with dose adjustment and without dose adjustment, respectively. The most commonly reported TEAEs in the subgroup with dose escalation (≥ 5% patients in the subgroup with dose adjustment and reported at a higher rate than the subgroup without dose adjustment) were (aggravation of) colitis ulcerative (15 [10.9%] and 5 [1.3%] patients, respectively), (aggravation of) Crohn's disease (8 [5.8%] and 7 [1.8%] patients, respectively), anaemia (9 [6.6%] and 18 [4.5%] patients, respectively), localised ISR (7 [5.1%] and 17 [4.3%] patients, respectively) and arthralgia (7 [5.1%] and 15 [3.8%] patients, respectively). By SOC, the largest difference was seen in gastrointestinal disorders; however, this was due to (aggravation of) colitis ulcerative and (aggravation of) Crohn's disease, which were TEAEs by PT with the largest difference between the subgroups.

Table 63. TEAEs by Dose Adjustment Reported for at Least 2% of Patients in the Subgroup with Dose Adjustment by SOC and PT in the Pooled Analysis (Maintenance Phase): Safety Population

System Organ Class Preferred Term	Pooled CT-P13 SC (N=534)	
	Patients with Dose Adjustment (N'=137)	Patients without Dose Adjustment (N'=397)
Total number of TEAEs	**301**	**863**
Number (%) of patients with ≥ 1 TEAE	**99 (72.3)**	**273 (68.8)**
Blood and lymphatic system disorders	**15 (10.9)**	**39 (9.8)**
Anaemia	9 (6.6)	18 (4.5)
Iron deficiency anaemia	3 (2.2)	2 (0.5)
Neutropenia	3 (2.2)	8 (2.0)
Gastrointestinal disorders	**38 (27.7)**	**63 (15.9)**
Abdominal pain	4 (2.9)	10 (2.5)
(Aggravation of) colitis ulcerative	15 (10.9)	5 (1.3)
(Aggravation of) Crohn's disease	8 (5.8)	7 (1.8)
Diarrhoea	3 (2.2)	11 (2.8)
Haemorrhoids	3 (2.2)	2 (0.5)
Large intestine polyp	3 (2.2)	3 (0.8)
General disorders and administration site conditions	**20 (14.6)**	**43 (10.8)**
Injection site reaction[1]	7 (5.1)	17 (4.3)
Peripheral swelling	3 (2.2)	2 (0.5)
Pyrexia	4 (2.9)	6 (1.5)
Infections and infestations	**41 (29.9)**	**116 (29.2)**
COVID-19	13 (9.5)	44 (11.1)
Oral herpes	4 (2.9)	7 (1.8)
Upper respiratory tract infection	4 (2.9)	6 (1.5)
Injury, poisoning and procedural complications	**8 (5.8)**	**22 (5.5)**
Injection related reaction[2]	5 (3.6)	10 (2.5)
Investigations	**17 (12.4)**	**48 (12.1)**
Alanine aminotransferase increased	3 (2.2)	16 (4.0)
Musculoskeletal and connective tissue disorders	**18 (13.1)**	**32 (8.1)**
Arthralgia	7 (5.1)	15 (3.8)
Arthritis	3 (2.2)	4 (1.0)
Nervous system disorders	**11 (8.0)**	**39 (9.8)**
Headache	7 (5.1)	28 (7.1)
Skin and subcutaneous tissue disorders	**17 (12.4)**	**34 (8.6)**
Pruritus	3 (2.2)	3 (0.8)
Rash	3 (2.2)	5 (1.3)
Vascular disorders	**8 (5.8)**	**15 (3.8)**
Hypertension	5 (3.6)	12 (3.0)

Dose adjustment did not affect the incidence rates of TESAE, TEAE leading to study drug discontinuation or TEAESIs. The incidence rates of SIR (3.6% vs 2.5%), localised ISR (5.1% vs 4.3%) and infection (29.9% vs 29.2%) were similar between the subgroups with and without dose escalation, respectively. (Table 61)

Table 64. Summary of TESAE, TEAE Leading to Study Drug Discontinuation and TEAESIs by Dose Adjustment for Patients from the CT-P13 SC Treatment Groups in the Pooled Analysis (Maintenance Phase): Safety Population

	CT-P13 SC 120 mg (N=534)	
	Patients with Dose Adjustment (N'=137)	Patients without Dose Adjustment (N'=397)
Number (%) of patients with ≥ 1 TESAE	8 (5.8)	27 (6.8)
Number (%) of patients with ≥ 1 TEAE leading to study drug discontinuation	3 (2.2)	16 (4.0)
Number (%) of patients with ≥ 1 SIR	5 (3.6)	10 (2.5)
Number (%) of patients with ≥ 1 localised ISR	7 (5.1)	17 (4.3)
Number (%) of patients with ≥ 1 infection	41 (29.9)	116 (29.2)
Number (%) of patients with ≥ 1 malignancy	0	1 (0.3)

Assessor's conclusions on comparison between doses of 120 mg and 240 mg

The reported results on subgroups administered the 120 mg and 240 mg dose showed no dose-dependently increased risk for infection or serious adverse reactions with the higher vs. lower dose. Systemic and localised injection reaction rates were similar between the two doses.
It is an expected finding that aggravation of the disease was more frequent in patients with loss of response who needed dose escalation from 120 mg to 240 mg of CT-P13 SC. However, the submitted data are not deemed confirmatory.

From tables included in the document "Post-hoc Analyses" (Module 5.3.5.3) it is understood that there were 534 subjects in the pooled analysis, of whom 137 with dose adjustment and 397 without dose adjustment. The MAH was however requested to further clarify the patient populations used for investigating effects of dose escalation in the pooled data set and in the separate analyses of both phase 3 trials.

For further assessment of the effects of dose escalation, the MAH was requested to conduct an additional analysis of the patients in the active arm who received dose escalation from 120 mg to 240 mg, where adverse events occurring prior to dose escalation vs. after dose escalation are compared, with adjustment for duration of exposure to each dose. The same analysis was requested to be conducted for the patients who originally were administered placebo and were switched to the 240mg dose. The requested pooled analyses were received, as were data on the 240 mg SC dose in subjects with CD in study CT-P13 38. The data on 240 mg SC dose form study CT-P13 37 were not included separately in the MAH's response, since the MAH no more applies for dose escalation in subjects with UC. (please see assessment of Questions 42 and 46 in Section 13.2 and assessment of the final CSR in Section 8.2.3.7 of this AR).

8.2.3.5. Clinical laboratory evaluation and vital signs

The majority of laboratory parameters had no CTCAE grade (e.g., the post-baseline laboratory result did not satisfy any CTCAE grade criteria) or were CTCAE Grade 1 (mild) or Grade 2 (moderate) with transient changes over time. Grade 3 (severe) or higher clinical laboratory findings from Studies CT-P13 3.7 and CT-P13 3.8 are summarised below. Laboratory parameters evaluated as PD parameters (C-reactive protein [CRP] and faecal calprotectin [FC] concentrations) are not included in this section of the AR.

In **Study CT-P13 3.7** (ulcerative colitis), there were no notable differences of the mean change from baseline for all clinical chemistry, haematology, and urinalysis laboratory parameters in both treatment groups (except for CRP, erythrocyte sedimentation rate [ESR], and FC, the levels of which changed in line with treatment effect).

However, individual patients had clinically relevant changes in laboratory values. CTCAE Grade 3 or higher laboratory results are summarized in Table 63. Apart from anaemia and neutropenia, both of which occurred more frequently in the active group, there appear to be no relevant differences between the active and placebo arms of the study in ≥Grade 3 laboratory results.

Table 65. Post-baseline CTCAE Grade 3 or Higher Laboratory Results in Study CT-P13

3.7 (Maintenance Phase): Safety Population (ulcerative colitis)

Parameter CTCAE Grade	CT-P13 SC 120 mg (N=296)	Placebo SC (N=140)
Clinical Chemistry		
ALT increased		
Grade 3	1 (0.3)	0
AST increased		
Grade 3	2 (0.7)	0
CPK increased		
Grade 3	5 (1.7)	4 (2.9)
Grade 4	4 (1.4)	2 (1.4)
Cholesterol high		
Grade 3	0	1 (0.7)
GGT increased		
Grade 3	0	1 (0.7)
Hyperkalemia		
Grade 3	1 (0.3)	0
Hypertriglyceridemia		
Grade 3	4 (1.4)	1 (0.7)
Grade 4	0	1 (0.7)
Hyponatremia		
Grade 4	1 (0.3)	0
Haematology		
Anemia		
Grade 3	6 (2.0)	1 (0.7)
Lymphocyte count decreased		
Grade 3	1 (0.3)	1 (0.7)
Neutrophil count decreased		
Grade 3	11 (3.7)	1 (0.7)
Grade 4	0	1 (0.7)
White blood cell decreased		
Grade 3	0	1 (0.7)

Note: At each level of summarisation, only the most severe case is counted.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; CTCAE, common terminology criteria for adverse events; GGT, gamma-glutamyl transferase

Study CT-P13 3.8 (Crohn's Disease)

Post-baseline CTCAE grade 3 or higher laboratory results are summarised for the safety population in Table 8.2.3.5.1.

Grade 3 neutropenia was reported for 11 subjects (3.7%) in the active group, whereas 2 subjects had Grade 3 or 4 neutropenia in the placebo group.

In this study, unlike study CT-P13 3.7, CPK increase was more frequent in the active arm than the placebo arm. Grade 4 CPK increased was reported for 8 (3.4%) and 2 (1.9%) patients in the CT-P13 SC 120 mg and placebo SC arms, respectively. Except for one subject in the CT-P13 SC 120 mg arm, these findings were either reported as a study drug-unrelated TEAE or not reported as a TEAE. The CPK levels for all patients immediately returned to normal by the next assessment except for CPK increased reported at Week 54.

Grade 3 and grade 4 hypertriglyceridemia were reported for 5 (2.1%) and 1 (0.4) patients, respectively, in the CT-P13 SC 120 mg arm. For the 5 patients with grade 3 hypertriglyceridemia, two patients had medical history of hypertriglyceridemia or obesity and other three patients had grade 2 or 3 hypertriglyceridemia during the Induction Phase. One patient had grade 4 hypertriglyceridemia at Week 46, which was reported as study drug-unrelated TEAE of hypertriglyceridemia. The patient received medication treatment for the event and was recovering as triglyceride level decreased at Week 54.

Table 66. Post-baseline CTCAE Grade 3 or Higher Laboratory Results in Study CT-P13 3.8 (Maintenance Phase): Safety Population (Crohn's disease)

Parameter CTCAE Grade	CT-P13 SC 120 mg (N=238)	Placebo SC (N=105)
Clinical Chemistry		
ALT increased		
Grade 3	2 (0.8)	0
AST increased		
Grade 3	1 (0.4)	0
Blood bilirubin increased		
Grade 3	5 (2.1)	1 (1.0)
CPK increased		
Grade 3	6 (2.5)	1 (1.0)
Grade 4	8 (3.4)	2 (1.9)
GGT increased		
Grade 3	1 (0.4)	1 (1.0)
Hypertriglyceridemia		
Grade 3	5 (2.1)	0
Grade 4	1 (0.4)	0
Hypocalcemia		
Grade 3	1 (0.4)	0
Hypokalemia		
Grade 3	1 (0.4)	0
Haematology		
Anemia		
Grade 3	5 (2.1)	4 (3.8)
Lymphocyte count decreased		
Grade 3	2 (0.8)	5 (4.8)
Neutrophil count decreased		
Grade 3	11 (4.6)	0
Grade 4	2 (0.8)	0

CHMP comment

Laboratory findings showed increased frequency of Grade 3 to 4 neutropenia in active arms of both studies and anaemia in study CT-P13 3.7. Neutropenia and anaemia are known common side effects of infliximab; hence, this is an expected finding. Neutropenia was in most cases transient, and neutrophil levels returned to normal immediately. Dyslipidaemia is mentioned in Table 1 of Section 4.8 of the SmPC with the frequency of uncommon. The patients with hypertriglyceridaemia had also other risk factors for hypertriglyceridaemia.

Vital signs, physical examination and other observations related to safety

Vital signs

In studies CT-P13 3.7 and CT-P13 3.8, mean changes from baseline in vital sign values were small, and there were no notable differences between the treatment arms at any time point (data not shown for brevity).

Hypersensitivity monitoring (including delayed hypersensitivity) was assessed in both studies by vital signs (including BP, heart and respiratory rates, and body temperature) measured prior to the beginning of study drug administration, within 15 minutes and 1 hour (+ 10 minutes) after the drug administration. If patients

had signs and symptoms of hypersensitivity at home, patients or caregivers were advised to call the study centre or get immediate help.

In both treatment groups in both trials, the most commonly reported clinically notable vital sign results during hypersensitivity monitoring were high diastolic blood pressure (DBP). Generally, there were no clinically notable differences between the treatment groups for vital sign results after the start of the study drug administration during hypersensitivity monitoring (data not shown for brevity).

ECG

Three patients in study CT-P13 3.7 had electrocardiogram findings, all of which were considered unrelated to study drug. One case of atrioventricular (AV) block was reported at screening (I degree AV block with sequalae of II degree AV block, recovered without treatment) and again during maintenance phase (II degree AV block, recovered without treatment) in the CT-P13 SC 120 mg group. One case was reported of abnormal, clinically significant single ventricular ectopic beats at Weeks 6 and 14 in the CT-P13 SC 120 mg group; considered unrelated to study drug and recovered without medication. One case of supraventricular extrasystoles at week 6., 10. and 14 in the CT-P13 SC 120 mg group was reported as TEAE related to the study drug; dose of study drug was not changed, and the events recovered without medication.

In study CT-P13 3.8, 3 patients in the CT-P13 SC 120 mg group and one patient in the placebo SC group had ECG findings: all four reports concerned a grade 1 TEAE of right bundle branch block during the maintenance phase (while the ECG had been normal at screening). All of these grade 1 TEAEs recovered without treatment medication and were considered as unrelated to the study drug, and the dose of the study medication was not changed.

Physical examination

The majority of patients in both studies had normal baseline physical examination findings, which remained normal at each post-baseline visit. There were no notable differences between active and placebo groups (data not shown for brevity).

Tuberculosis assessment

Tuberculosis (TB) was assessed using interferon-γ release assay (IGRA), chest X-ray, and clinically monitored throughout the study.

In study CT-P13 3.7, at baseline, the IGRA results were negative and positive for 429 (98.4%) and 7 (1.6%) patients respectively during the treatment period (post-baseline). All 7 patients who reported positive IGRA results at baseline reported latent TB or IGRA assay positive as medical history or adverse event and received prophylaxis for latent TB. In total, 12 (2.8%) patients (6 patients each [2.0% and 4.3%] in the CT-P13 SC 120 mg and placebo SC group) were reported as IGRA positive conversion (positive result from the post-baseline IGRA test following a negative result at baseline). None of the 12 patients who had IGRA conversion during treatment period developed an active TB. None of the patients had signs or symptoms present indicative of TB during the treatment period.

In study CT-P13 3.8, at baseline, IGRA results were negative for 332 (96.8%) and positive for 9 (2.6%) patients. All 9 patients with positive IGRA results at baseline reported latent TB or IGRA assay positive as medical history or adverse event and received prophylaxis for latent TB. During the treatment period (except for the extension phase), 9 (2.6%) patients (7 [2.9%] and 2 [1.9%] patients in the CT-P13 SC 120 mg and placebo SC groups, respectively) were reported as IGRA positive conversion. All IGRA conversions were reported as TEAE of latent TB or interferon-γ release assay positive. During treatment period (except for the extension phase), 4 (1.2%) patients (3 [1.3%] patient and 1 [1.0%] patients in the CT-P13 SC 120 mg and placebo SC groups, respectively) were reported indeterminate IGRA result without positive result, following negative result at baseline. None of the patients had the progression to active TB during the treatment period.

In Studies CT-P13 3.7 and CT-P13 3.8, all patients had normal or abnormal, not clinically significant results for chest X-ray at screening and no abnormal, clinically significant chest X-ray results related to tuberculosis were reported.

CHMP comment

There were no notable effects on vital signs or physical examination. A few ECG findings were reported in both phase 3 studies (including right bundle branch block, AV block, ventricular and supraventricular extrasystoles) in both active and placebo arms of the studies. These abnormalities were considered unrelated to study drug except for one (a patient with recurring supraventricular extrasystoles) and all of them resolved without medicinal treatment.

At baseline, 1.6% patients in study CT-P13 3.7 and 2.6% patients in study CT-P13 3.8 were IGRA positive at baseline, all reported latent TB or IGRA assay positive as medical history or adverse event and received prophylaxis for latent TB. In study CT-P13 3.7, IGRA positive conversion occurred in 2.0% and 4.3% in the CT-P13 SC 120 mg and placebo SC groups. In study CT-P13 3.8, IGRA conversion occurred in 2.9% and 1.9% patients in the CT-P13 SC 120 mg and placebo SC groups, respectively. Furthermore, in study CT-P13 3.8, during the treatment period, 1.3% and 1.0% patients in the CT-P13 SC 120 mg and placebo SC groups, respectively, were reported indeterminate IGRA result without positive result, following negative result at baseline. None of the patients with positive conversion progressed to active TB during the treatment period in either study.

Local site pain assessment: Visual Analogue Scale (VAS)

The scale of VAS value is from 0 to 100 mm. In study CT-P13 3.7, during the maintenance phase, the mean VAS of local site pain for the CT-P13 SC 120 mg arm ranged from 8.88 to 10.44 mm, and for the placebo arm from 3.90 to 6.68 mm. In study CT-P13 3.8, the mean VAS of local stie pain was in the range of 10.77 to 14.68 in the CT-P13 SC 120 arm and in the range of 6.10 to 8.34 mm in the placebo arm.

CHMP comment

The VAS of local site pain was generally higher in the active than placebo arms of both phase 3 studies. However, considering the maximum VAS value of 100 mm, the VAS values were relatively low (up to 10.44 for UC patients and 14.68 for CD patients in the active arms of the studies).

8.2.3.6. Subgroup analyses

The MAH pooled data from studies CT-P13 3.7 and CT-P13 3.8 for subgroup analyses conducted for incidence rates of TEAE, TESAE, TEAE leading to study drug discontinuation and TEAESIs by the following categories:

- Age: < 65 years old and ≥ 65 years old
- Gender: Male and Female
- Race: Asian/Oriental, Caucasian/White, American Indian/Alaska Native and Other
- Baseline disease activity: Moderate and Severe

For patients with dose adjustment to 240 mg of CT-P13 SC, data collected before initiation of dose adjustment for the CT-P13 SC and Placebo SC arms are included in the subgroup analyses.

CHMP comment

It is noteworthy that in studies CT-P13 3.7 and CT-P13 3.8, the age-based subgroup analysis on efficacy was conducted with a markedly lower cut-point (<35 years, ≥35 years). No subgroup analysis on safety were predefined in the protocols of studies CT-P13 3.7 and CT-P13 3.8.

Age

Safety data for the subgroups aged < 65 years and ≥ 65 years are presented below in table 65. Two subjects in the age group ≥ 65 years were reported to have experienced TESAE. One patient from the CT-P13 SC 120 mg arm of study CT-P13 3.7 had Grade 2 TESAEs of aortic valve incompetence and cardiac failure and grade 4 TESAE of duodenal ulcer perforation. Another subject from the CT-P13 SC 120 mg arm of Study CT-P13 3.8 was reported to have had Grade 2 TESAE of bronchiolitis. All of these TESAEs were considered unrelated to study medication.

Table 67. Summary of Safety by Age for Patients in the Pooled Analysis (Maintenance Phase): Safety Population

	Pooled CT-P13 SC[1]		Pooled Placebo SC[2]	
	< 65 Years (N=520)	≥ 65 Years (N=14)	< 65 Years (N=238)	≥ 65 Years (N=7)
	Number (%) of Patients with at Least 1 Event			
TEAE	343 (66.0)	7 (50.0)	144 (60.5)	4 (57.1)
TESAE	28 (5.4)	2 (14.3)	12 (5.0)	0
TEAE leading to study drug discontinuation	15 (2.9)	1 (7.1)	8 (3.4)	1 (14.3)
TEAE of SIR	11 (2.1)	1 (7.1)	5 (2.1)	0
TEAE of delayed hypersensitivity	0	0	0	0
TEAE of localised ISR	21 (4.0)	0	4 (1.7)	0
TEAE of infection	138 (26.5)	2 (14.3)	52 (21.8)	3 (42.9)
TEAE of malignancy	0	1 (7.1)	1 (0.4)	0

Sources: Section 5.3.5.3 Post-hoc Tables 3.065, 3.066, 3.067, 3.068, 3.069, 3.070 and 3.071
[1] Pooled data from patients treated with CT-P13 SC in Studies CT-P13 3.7 and CT-P13 3.8
[2] Pooled data from patients treated with Placebo SC in Studies CT-P13 3.7 and CT-P13 3.8

CHMP comment

The number of subjects aged ≥ 65 years was only 14 in the pooled safety data set from studies CT-P13 3.7 and CT-P13 3.8, and TEAEs were reported for 7 subjects of this subgroup. Due to low number of subjects and reported TEAEs in patients aged ≥65 years, no firm conclusions are possible. Since the elderly more often suffer from multiple background diseases and are more prone to infections (e.g., herpes zoster and severe influenza or COVID-19), the MAH was requested to submit data on exposure to the 240 mg dose in subjects aged 65 years and above, and if such subjects exist, safety data in these subjects. Upon request, the MAH informed that two subjects aged above 65 years received the adjusted dose of CT-P13 SC 240 mg during Treatment Period in study CT-P13 3.8 (Crohn's disease). One subject was not reported to have experienced any TEAEs. The other subject was reported with 2 TEAEs of infection and 1 TEAE of blood creatine phosphokinase increased after dose adjustment from placebo to 240 mg S.C.

Hence, one of the two subjects aged >65 years experienced infections (respiratory tract infection and latent tuberculosis) and one did not. For comparison, in the entire study population, the incidence of infections during treatment with the 240 mg SC dose was 21/54 (38.9%, 39.94/100 PY) in subjects who escalated from 120 mg SC, and 19/50 (38%, 29.18/100 PY) in subjects who escalated from placebo (table 8 of the response document, see assessment of Question 46). It is known from previous scientific data that the elderly are more at risk of serious infections during infliximab treatment; but there exists no definitive information if the risk is associated with the level of infliximab. Since the increased risk of infections is already covered in the SmPC Sections 4.4 and 4.8, it is agreed that no amendment is warranted in Section 4.2, which refers to Sections 4.4 and 4.8 regarding this risk in the elderly.

Gender

There were 303 male and 231 female subjects in the pooled safety analysis set. The MAH states that the incidence rates of TEAEs were similar between male and female patients for both CT-P13 SC-treated and Placebo SC-treated groups in the pooled analysis and that gender did not have a significant impact on the safety profile of CT-P13 SC.

CHMP comment
No integrated tables with safety results in both male and female subjects are provided by the MAH. Instead, tables on TEAE analyses have been provided separately for the male subgroup and the female subgroup of the pooled safety analysis set for each ADR (Post-hoc Analysis, Module 5.3.5.3). Therefore, comparison of safety between male and female subjects is cumbersome from the submitted data. The MAH however claims that similar safety results were obtained for both sexes.

Race

The MAH states that the incidence rates of TEAEs were similar regardless of race.

CHMP comment
Similar to gender, the results for each ethnic group have been reported separately and not in an integrated table. The numbers of subjects in different ethnic groups in the pooled analyses are tabulated below by the assessor from multiple submitted tables:

	CT-P13 SC	Placebo
Asian/Oriental	10	3
Caucasian/White	505	233
American Indian/Alaska Native	16	7
Other	3	2

Hence, the numbers of other than Caucasian subjects was very low, therefore, any comparison between ethnic subgroups is futile.

Baseline Disease Activity

To determine the effect of baseline disease activity on the safety profile of CT-P13 SC, the TEAEs were assessed by moderate and severe disease activity based on the following categories:

Category	UC Patients	CD Patients
Moderate	≤ median of modified mayo score	≤ 300 CDAI score
Severe	> median of modified mayo score	> 300 CDAI score

Note: Modified Mayo score is sum of Mayo Scoring System, ranges from 0 to 9, excluding PGA. The baseline value is the last non-missing value before the first administration at Week 0.
Abbreviations: CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; PGA, physician global assessment; UC, ulcerative colitis

In the group with moderate disease activity, 66.1% of subjects in the active group and 61.8% in the placebo group experienced TEAEs. Of subjects with severe disease activity, 64.9% and 57.6 % in the active and placebo groups experienced TEAEs, respectively (tables 66 and 67).

Table 68. TEAEs by Baseline Disease Activity – Pooled Safety Population – Subgroup: Moderate

System Organ Class [1] Preferred Term [1]	Studies 3.7+3.8 CT-P13 SC (N'=330)	 Placebo (N'=152)
Total Number of Treatment-Emergent Adverse Events	677	265
Number of Patients With at Least One Treatment-Emergent Adverse Events	218 (66.1%)	94 (61.8%)
Related	64 (19.4%)	25 (16.4%)
Grade 1	29 (8.8%)	15 (9.9%)
Grade 2	24 (7.3%)	6 (3.9%)
Grade 3	10 (3.0%)	4 (2.6%)
Grade 4	1 (0.3%)	0
Unrelated	197 (59.7%)	88 (57.9%)
Grade 1	73 (22.1%)	35 (23.0%)
Grade 2	82 (24.8%)	39 (25.7%)
Grade 3	34 (10.3%)	11 (7.2%)
Grade 4	7 (2.1%)	3 (2.0%)
Grade 5	1 (0.3%)	0

Table 69. TEAEs by Baseline Disease Activity – Pooled Safety Population – Subgroup: Severe

System Organ Class [1] Preferred Term [1]	Studies 3.7+3.8 CT-P13 SC (N'=202)	 Placebo (N'=92)
Total Number of Treatment-Emergent Adverse Events	356	106
Number of Patients With at Least One Treatment-Emergent Adverse Events	131 (64.9%)	53 (57.6%)
Related	45 (22.3%)	11 (12.0%)
Grade 1	25 (12.4%)	4 (4.3%)
Grade 2	17 (8.4%)	3 (3.3%)
Grade 3	3 (1.5%)	3 (3.3%)
Grade 4	0	1 (1.1%)
Unrelated	119 (58.9%)	46 (50%)
Grade 1	48 (23.8%)	13 (14.1%)
Grade 2	53 (26.2%)	21 (22.8%)
Grade 3	17 (8.4%)	10 (10.9%)
Grade 4	1 (0.5%)	2 (2.2%)
Grade 5	0	0

CHMP comment

Similar to gender and ethnicity, the results for subgroups with moderate and severe baseline disease activity have not been reported in an integrated table but separately. Comparison of subgroups is therefore difficult for, e.g., adverse events of special interest or for TESAEs. The MAH however claims that baseline disease activity did not have a significant impact on the safety profile of CT-P13 SC.

8.2.3.7. Safety data in final study reports for the extension phases of the phase 3 studies

In their response, the MAH submitted data on the entire treatment phase and separately for the extension phase in the final study reports.

Since the interim data for the placebo-controlled double-blind induction and maintenance phases were already assessed during the previous round, only the safety data for the open-label placebo-controlled extension phase of the two phase 3 studies are included below. Relatedness of observed TEAEs is not copied in this AR, since from the reported TEAEs it is obvious that differentiation of TEAEs from symptoms of background diseases has been difficult.

In study CT-P13 3.7, 519 TEAEs were reported during extension phase in 189 (43.3%) patients (127 [42.9%] patients in the CT-P13 SC 120 mg group and 62 [44.3%] patients in the Placebo SC group). The TESAEs during extension phase were reported for 12 (4.1%) patients in the CT-P13 SC 120 mg group and 5 (3.6%) patients in the Placebo SC group.

The TEAEs leading to permanent discontinuation of study drug during the extension phase were reported for 5 (1.7%) patients in CT-P13 SC 120 mg group and 2 (1.4%) patients in the Placebo SC group.

The TEAEs classified as SIR during the extension phase were reported for 4 (1.4%) patients in the CT-P13 SC 120 mg group and 1 (0.7%) patient in the Placebo SC group. All TEAEs classified as SIR during the

extension phase were Grade 1 or 2 in intensity and were considered by the investigator as related to the study drug but were non-serious. No SIR events were reported as TESAE in both CT-P13 SC 120 mg and Placebo SC groups during the extension phase. One delayed hypersensitivity event was reported in the CTP13 SC 120 mg group during the extension phase. There were no delayed hypersensitivity events reported in the Placebo SC group during the extension phase.

The TEAEs classified as localized ISR during the extension phase were reported for 7 (2.4%) patients in CT-P13 SC 120 mg group and 5 (3.6%) patients in the Placebo SC group. All TEAEs classified as localized ISR during the extension phase were Grade 1 or 2 in intensity.

The TEAEs classified as infection during the extension phase were reported for 61 (20.6%) patients in CT-P13 SC 120 mg group and 28 (20%) patients in the Placebo SC group.

No TEAEs classified as malignancy during the extension phase were reported for either treatment group.

In study CT-P13 3.8, 448 TEAEs during extension phase were reported in 152 (44.3%) patients (106 [44.5%] and 46 [43.8%] patients in the CT-P13 SC 120 mg and the placebo SC groups, respectively). The majority of TEAEs were grade 1 or 2 in intensity.

The TESAEs during the extension phase were reported for 16 (6.7%) patients and 4 (3.8%) patients in the CT-P13 SC 120 mg and placebo SC groups, respectively.

The TEAEs leading to discontinuation of study drug during the extension phase were reported for 5 (2.1%) patients and 4 (3.8%) patients in the CT-P13 SC 120 mg and placebo SC groups, respectively.

No TEAEs classified as SIR during the extension phase were reported for either treatment group. No TEAEs classified as delayed hypersensitivity during the extension phase were reported for either treatment group. The TEAEs classified as localized ISR during the extension phase were reported for 4 (1.7%) patients and 5 (4.8%) patients in the CT-P13 SC 120 mg and the placebo SC groups, respectively.

TEAEs classified as infection during the extension phase were reported for 61 (25.6%) patients and 27 (25.7%) patients in the CT-P13 SC 120 mg and the placebo SC groups, respectively.

No TEAEs classified as malignancy during the extension phase were reported for either treatment group.

No death was reported during the extension phase for both treatment groups.

For both phase 3 trials, there were no notable differences of the mean change from baseline for all clinical chemistry, haematology, and urinalysis laboratory parameters in either treatment group during the extension phase.

CHMP comment

There were no notable differences in safety between CT-P13 SC 120 mg and placebo SC groups during the extension phase. No new safety findings occurred during the extension phases of studies CT-P13 3.7 and CT-P13 3.8.

Comparative data on the 120 mg SC and 240 mg SC vs. placebo were received for study CT-P13 3.8 and are assessed in Section 13.2 of this AR.

8.2.4. Immunogenicity

The submission contains immunogenicity data from 779 patients (436 UC and 343 CD patients) from Studies CT-P13 3.7 and CT-P13 3.8. Among the 779 patients, 534 patients (296 UC and 238 CD patients) received at least 1 proposed dose of 120 mg of CT-P13 SC and 447 IBD patients (244 UC and 203 CD patients) provide 1-year immunogenicity data at CT-P13 SC 120 mg.

Methodology for determination of anti-drug antibodies (ADA) and neutralising antibodies (Nab) is assessed in Section 6.1 and discussed in Section 6.3 of this AR. Samples that were positive in the ADA assay were analysed further to conduct a NAb assessment.

ADA testing was conducted in both studies before study drug administration at baseline and at weeks 10, 14, 22, 30, 38, 46, 54 and end-of-study (4 weeks after the last dose of CT-P13. On the day of initiation of dose adjustment, serum samples for immunogenicity analysis were collected before study drug administration. Additional serum samples for immunogenicity testing could be collected if a patient had experienced any delayed hypersensitivity to determine serum sickness. Analysis was performed at the central laboratory.
The rule of ADA and NAb conversion was following

- ADA conversion was defined as patients who reported at least 1 ADA positive result after Week 0 administration in patients who
    1. Had at least 1 immunogenicity result after Week 0 administration, and
    2. Did not have any ADA positive result before Week 0 administration.
- NAb conversion was defined as patients who reported at least 1 NAb positive result after Week 0 administration in patients who
    1. Had at least 1 immunogenicity result after Week 0 administration, and
    2. Did not have any NAb positive result before Week 0 administration.

A listing showing immunogenicity test results for each patient was provided by treatment group and visit for the ITT population.
Immunogenicity test findings for study CT-P13 3.7 (Ulcerative colitis) are summarised for the safety population in Table 8.2.4.1. A total of 12 (2.8%) patients (6 [2.0% and 4.3%] patients each in CT-P13 SC 120 mg group and Placebo SC group, respectively) reported positive ADA already at Week 0, before study drug administration. None of the 12 patients had received biologics for treatment of IBD and/or TNFα inhibitors for treatment of other disease before first study drug administration. None of patients received infliximab before study drug administration.

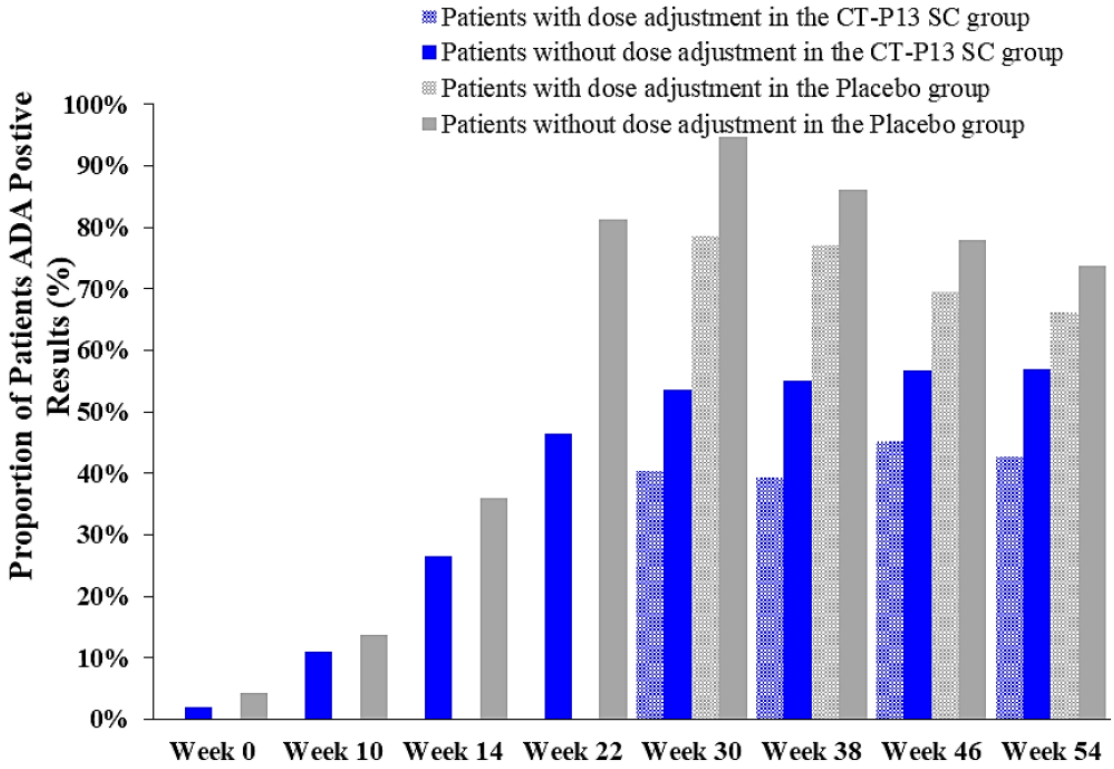
All subjects in both study groups received treatment with CT-P13 during the open-label induction phase (dosing at Weeks 0, 2, and 6). At 10 weeks (baseline of maintenance period), 10.9 % and 13.7% of subjects were ADA positive in the CT-P13 and placebo groups, respectively. Thereafter, a majority of study subjects conversed to ADA-positivity, with a higher proportion of ADA-positive subjects in the placebo group. Of ADA positive subjects, a great majority were also NAb positive in both active and placebo groups.

The proportion of ADA-positive subjects was lower in subjects with dose adjustment from 120 mg to 240 mg dose (in the active study arm) than in subjects without dose escalation. The proportion of subjects conversing to ADA positivity increased in the active study arm up to week 30, whereafter the proportion slowly reached a plateau. In the placebo arm, the proportion conversing to ADA positivity increased up to week 30, after which a slow decline in the proportion of ADA positive subjects is seen. Similar to the active study arm, in the placebo study the proportion of ADA positive subjects was smaller in patients with dose escalation from placebo to 240 mg of CT-P13 than in subjects continuing with placebo treatment.

Table 70. Frequency of ADA and NAb, study CT-P13-3.7

Visit Result	CT-P13 SC 120 mg (N=296)			Placebo SC (N=140)		
	With Dose Adjustment	Without Dose Adjustment	Total	With Dose Adjustment	Without Dose Adjustment	Total
Week 0 (Pre-dose), n (%)						
ADA Positive	N/A	6/294 (2.0)	6/294 (2.0)	N/A	6/140 (4.3)	6/140 (4.3)
NAb Positive (as % of ADA positive)	N/A	1/6 (16.7)	1/6 (16.7)	N/A	1/6 (16.7)	1/6 (16.7)
Week 10, n (%)						
ADA Positive	N/A	32/294 (10.9)	32/294 (10.9)	N/A	19/139 (13.7)	19/139 (13.7)
NAb Positive (as % of ADA positive)	N/A	28/32 (87.5)	28/32 (87.5)	N/A	14/19 (73.7)	14/19 (73.7)
Week 14, n (%)						
ADA Positive	N/A	76/287 (26.5)	76/287 (26.5)	N/A	50/139 (36.0)	50/139 (36.0)
NAb Positive (as % of ADA positive)	N/A	63/76 (82.9)	63/76 (82.9)	N/A	48/50 (96)	48/50 (96)
Week 22, n (%)						
ADA Positive	N/A	128/275 (46.5)	128/275 (46.5)	N/A	108/133 (81.2)	108/133 (81.2)
NAb Positive (as % of ADA positive)	N/A	108/128 (84.4)	108/128 (84.4)	N/A	105/108 (97.2)	105/108 (97.2)
Week 30, n (%)						
ADA Positive	23/57 (40.4)	111/207 (53.6)	134/264 (50.8)	44/56 (78.6)	72/76 (94.7)	116/132 (87.9)
NAb Positive (as % of ADA positive)	18/23 (78.3)	95/111 (85.6)	113/134 (84.3)	37/44 (84.1)	70/72 (97.2)	107/116 (92.2)
Week 38, n (%)						
ADA Positive	22/56 (39.3)	105/191 (55.0)	127/247 (51.4)	44/57 (77.2)	56/65 (86.2)	100/122 (82.0)
NAb Positive (as % of ADA positive)	17/22 (77.3)	87/105 (82.9)	104/127 (81.9)	32/44 (72.7)	51/56 (91.1)	83/100 (83)
Week 46, n (%)						
ADA Positive	28/62 (45.2)	106/187 (56.7)	134/249 (53.8)	39/56 (69.6)	46/59 (78.0)	85/115 (73.9)
NAb Positive (as % of ADA positive)	22/28 (78.6)	87/106 (82.1)	109/134 (81.3)	34/39 (87.2)	41/46 (89.1)	75/85 (88.2)
Week 54, n (%)						
ADA Positive	26/61 (42.6)	106/186 (57.0)	132/247 (53.4)	37/56 (66.1)	42/57 (73.7)	79/113 (69.9)
NAb Positive (as % of ADA positive)	21/26 (80.8)	97/106 (91.5)	118/132 (89.4)	33/37 (89.2)	39/42 (92.9)	72/79 (91.1)
Treatment Period (including EOS and unscheduled visits), n (%)						
Positive Conversion in ADA[1]	49/88 (55.7)	134/199 (67.3)	183/287 (63.8)	68/72 (94.4)	57/62 (91.9)	125/134 (93.3)
Positive Conversion in NAb[1] (as % of ADA positive)	43/49 (87.8)	118/134 (88.1)	161/183 (88.0)	66/68 (97.1)	56/57 (98.2)	122/125 (97.6)

Figure 33. Frequency of ADA in Study CT-P13 3.7: Safety Population

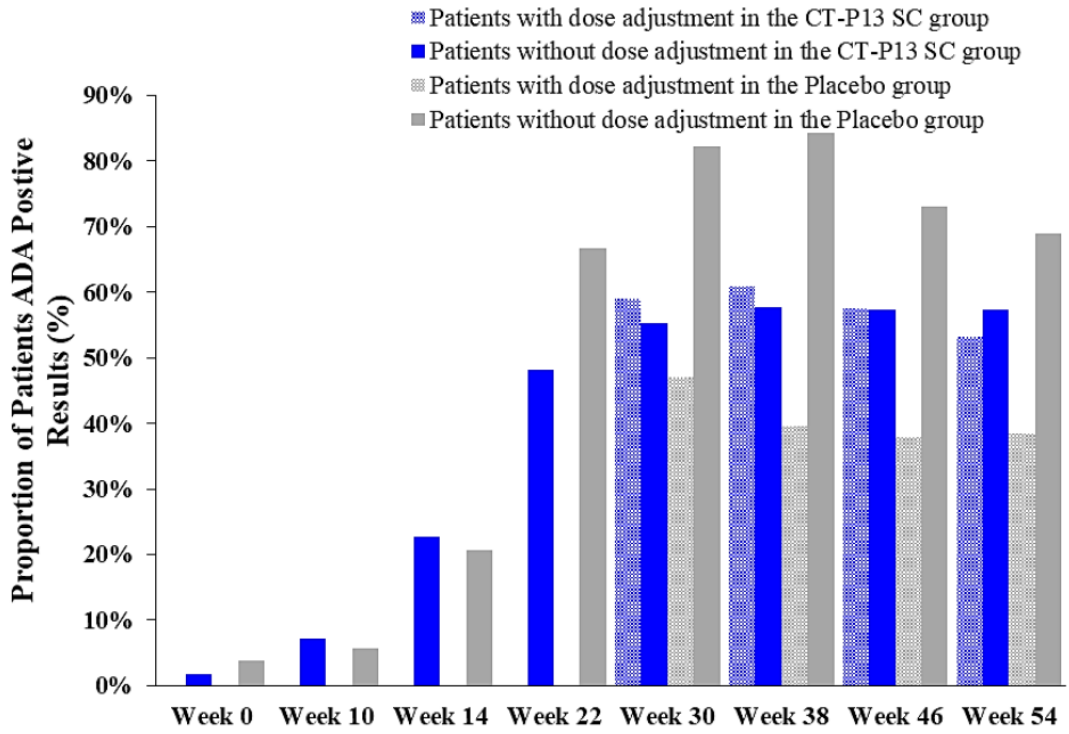


Immunogenicity test findings for study CT-P13 3.8 (Crohn's disease) are presented in Table 69 and Figure 34. Similar to findings in study CT-P13 3.7, conversion to ADA positivity was frequent across the study. Overall, also in this study, a great majority of ADA positive subjects were also NAb positive. In the active study group, the proportion of ADA positive subjects increased up to Week 30 and reached a plateau between 50 % to 60 % of subjects during weeks 30 to 54. The incidence of ADA positivity was highest in the placebo group without dose escalation and reached a peak at Week 38 (84.3% of subjects). Dose escalation from placebo to treatment with CT-P13 (240 mg) was associated with a lower incidence of ADA positivity than continuation with placebo. In subjects originally on placebo and switched to CT-P13 (240 mg), the proportion of ADA positive patients decreases clearly from 30 to 54 weeks. (Figure 34).

Table 71. Frequency of ADA and NAb, study CT-P13-3.8

Visit Result	CT-P13 SC 120 mg (N=238)			Placebo SC (N=105)		
	With Dose Adjustment	Without Dose Adjustment	Total	With Dose Adjustment	Without Dose Adjustment	Total
Week 0 (Pre-dose), n (%)						
ADA Positive	N/A	4/236 (1.7)	4/236 (1.7)	N/A	4/105 (3.8)	4/105 (3.8)
NAb Positive (as % of ADA positive)	N/A	2/4 (50)	2/4 (50)	N/A	2/4 (50)	2/4 (50)
Week 10, n (%)						
ADA Positive	N/A	17/238 (7.1)	17/238 (7.1)	N/A	6/105 (5.7)	6/105 (5.7)
NAb Positive (as % of ADA positive)	N/A	14/17 (82.4)	14/17 (82.4)	N/A	4/6 (66.7)	4/6 (66.7)
Week 14, n (%)						
ADA Positive	N/A	53/232 (22.8)	53/232 (22.8)	N/A	21/102 (20.6)	21/102 (20.6)
NAb Positive (as % of ADA positive)	N/A	50/53 (94.3)	50/53 (94.3)	N/A	20/21 (95.2)	20/21 (95.2)
Week 22, n (%)						
ADA Positive	N/A	110/228 (48.2)	110/228 (48.2)	N/A	66/99 (66.7)	66/99 (66.7)
NAb Positive (as % of ADA positive)	N/A	101/110 (91.8)	101/110 (91.8)	N/A	66/66 (100)	66/66 (100)
Week 30, n (%)						
ADA Positive	13/22 (59.1)	111/201 (55.2)	124/223 (55.6)	16/34 (47.1)	51/62 (82.3)	67/96 (69.8)
NAb Positive (as % of ADA positive)	12/13 (92.3)	101/111 (91.0)	113/124 (91.1)	15/16 (93.8)	51/51 (100)	66/67 (98.5)
Week 38, n (%)						
ADA Positive	14/23 (60.9)	107/185 (57.8)	121/208 (58.2)	15/38 (39.5)	43/51 (84.3)	58/89 (65.2)
NAb Positive (as % of ADA positive)	14/14 (100)	103/107 (96.3)	117/121 (96.7)	15/15 (100)	41/43 (95.3)	56/58 (96.6)
Week 46, n (%)						
ADA Positive	19/33 (57.6)	101/176 (57.4)	120/209 (57.4)	14/37 (37.8)	38/52 (73.1)	52/89 (58.4)
NAb Positive (as % of ADA positive)	16/19 (84.2)	95/101 (94.1)	111/120 (92.5)	13/14 (92.9)	36/38 (94.7)	49/52 (94.2)
Week 54, n (%)						
ADA Positive	16/30 (53.3)	98/171 (57.3)	114/201 (56.7)	15/39 (38.5)	31/45 (68.9)	46/84 (54.8)
NAb Positive (as % of ADA positive)	14/16 (87.5)	91/98 (92.9)	105/114 (92.1)	12/15 (80)	27/31 (87.1)	39/46 (84.8)
Treatment Period (including EOS and unscheduled visits) [1], n (%)						
Positive Conversion in ADA	30/44 (68.2)	121/188 (64.4)	151/232 (65.1)	34/46 (73.9)	44/55 (80)	78/101 (77.2)
Positive Conversion in NAb (as % of ADA positive)	29/30 (96.7)	118/121 (97.5)	147/151 (97.4)	34/34 (100)	44/44 (100)	78/78 (100)

Figure 34. Frequency of ADA in Study CT-P13 3.8 (Safety Population)



ADA titre results are summarised in Tables 70 (study CT-P13 3.7) and Table 71 (study CT-P13 3.8) and Figures 35 (study CT-P13 3.7) and 36 (study CT-P13 3.8). To estimate the magnitude of ADA positive response, a titration assay was performed with a series of at least five, 1:3 dilutions, starting at a 1:3 dilution.

Table 72. Summary of Non-transformed ADA Titre Results in Study CT-P13 3.7, Safety Population

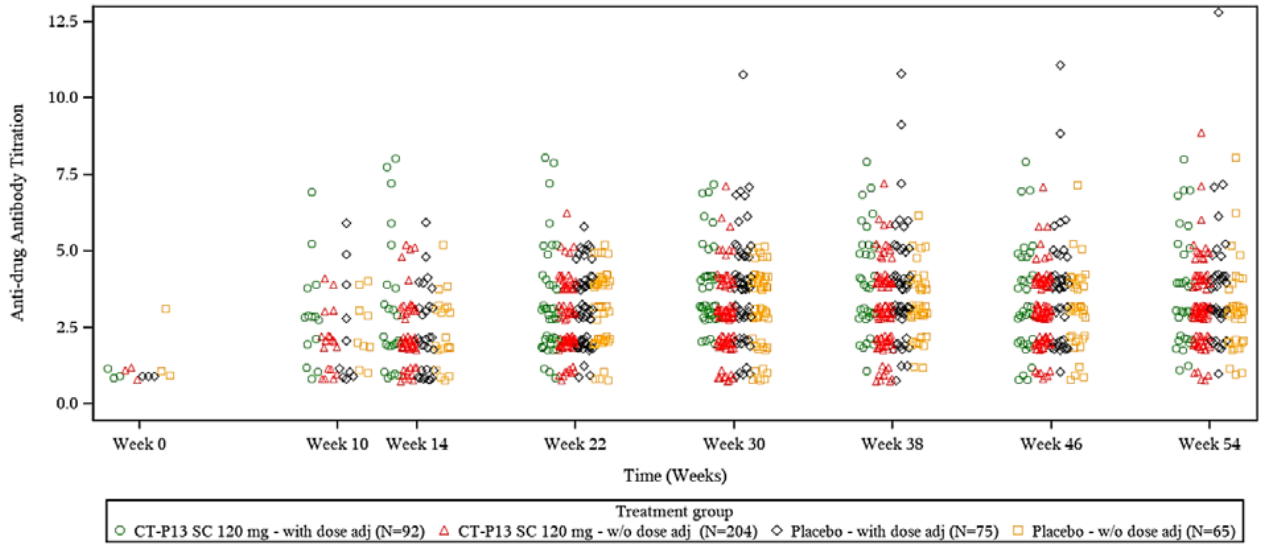
Visit	Statistic	CT-P13 SC 120 mg (N=296)			Placebo SC (N=140)		
		With Dose Adjustment	Without Dose Adjustment	Total	With Dose Adjustment	Without Dose Adjustment	Total
Week 0	n	N/A	6	6	N/A	6	6
	Mean (± SD)	N/A	21.0 (±0.00)	21.0 (±0.00)	N/A	49.0 (±68.59)	49.0 (±68.59)
	Median (Min, Max)	N/A	21 (21, 21)	21 (21, 21)	N/A	21 (21, 189)	21 (21, 189)
Week 10	n	N/A	32	32	N/A	19	19
	Mean (± SD)	N/A	669.4 (±2691.09)	669.4 (±2691.09)	N/A	498.5 (±1185.64)	498.5 (±1185.64)
	Median (Min, Max)	N/A	63 (21, 15309)	63 (21, 15309)	N/A	63 (21, 5103)	63 (21, 5103)
Week 14	n	N/A	76	76	N/A	50	50
	Mean (± SD)	N/A	1682.2 (±7554.30)	1682.2 (±7554.30)	N/A	305.8 (±776.50)	305.8 (±776.50)
	Median (Min, Max)	N/A	63 (21, 45927)	63 (21, 45927)	N/A	63 (21, 5103)	63 (21, 5103)
Week 22	n	N/A	128	128	N/A	108	108
	Mean (± SD)	N/A	1207.8 (±5853.23)	1207.8 (±5853.23)	N/A	494.3 (±692.86)	494.3 (±692.86)
	Median (Min, Max)	N/A	189 (21, 45927)	189 (21, 45927)	N/A	189 (21, 5103)	189 (21, 5103)
Week 30	n	23	111	134	44	72	116
	Mean (± SD)	1273.7 (±3241.62)	838.3 (±2574.18)	913.0 (±2691.81)	30179.9 (±186683.66)	558.3 (±761.69)	11794.0 (±115064.76)
	Median (Min, Max)	189 (63, 15309)	189 (21, 15309)	189 (21, 15309)	567 (21, 1240029)	378 (21, 5103)	567 (21, 1240029)
Week 38	n	22	105	127	44	56	100
	Mean (± SD)	4432.9 (±10261.25)	720.2 (±1767.27)	1363.3 (±4702.83)	32387.7 (±187444.85)	606.0 (±997.95)	14590.0 (±124550.61)
	Median (Min, Max)	567 (63, 45927)	189 (21, 15309)	189 (21, 45927)	378 (21,1240029)	189 (21, 5103)	189 (21,1240029)
Week 46	n	28	106	134	39	46	85
	Mean (± SD)	3141.0 (±9260.09)	566.2 (±1633.53)	1104.2 (±4540.76)	36020.4 (±199084.94)	779.7 (±2335.97)	16949.0 (±135074.05)
	Median (Min, Max)	189 (21, 45927)	189 (21, 15309)	189 (21, 45927)	567 (21,1240029)	189 (21, 15309)	189 (21,1240029)
Week 54	n	26	106	132	37	42	79
	Mean (± SD)	4282.4 (±9794.18)	1852.0 (±13422.60)	2330.7 (±12792.81)	302587.9 (±1834575.34)	1863.0 (±7383.01)	142708.8 (±1255476.11)
	Median (Min, Max)	567 (21, 45927)	189 (21,137781)	189 (21,137781)	567 (21,11160261)	189 (21, 45927)	189 (21,11160261)

Table 73. Summary of Non-transformed ADA Titre Results in Study CT-P13 3.8, Safety Population

Visit	Statistic	CT-P13 SC 120 mg (N=238)			Placebo SC (N=105)		
		With Dose Adjustment	Without Dose Adjustment	Total	With Dose Adjustment	Without Dose Adjustment	Total
Week 0	n	N/A	4	4	N/A	4	4
	Mean (± SD)	N/A	199.5 (±257.48)	199.5 (±257.48)	N/A	168.0 (±266.74)	168.0 (±266.74)
	Median (Min, Max)	N/A	105 (21, 567)	105 (21, 567)	N/A	42 (21, 567)	42 (21, 567)
Week 10	n	N/A	17	17	N/A	6	6
	Mean (± SD)	N/A	2963.5 (±11079.82)	2963.5 (±11079.82)	N/A	5152.0 (±7867.82)	5152.0 (±7867.82)
	Median (Min, Max)	N/A	63 (21, 45927)	63 (21, 45927)	N/A	126 (21, 15309)	126 (21, 15309)
Week 14	n	N/A	53	53	N/A	21	21
	Mean (± SD)	N/A	500.4 (±1351.94)	500.4 (±1351.94)	N/A	615.0 (±1499.95)	615.0 (±1499.95)
	Median (Min, Max)	N/A	63 (21, 5103)	63 (21, 5103)	N/A	63 (21, 5103)	63 (21, 5103)
Week 22	n	N/A	110	110	N/A	66	66
	Mean (± SD)	N/A	586.5 (±2183.84)	586.5 (±2183.84)	N/A	310.5 (±703.92)	310.5 (±703.92)
	Median (Min, Max)	N/A	63 (21, 15309)	63 (21, 15309)	N/A	63 (21, 5103)	63 (21, 5103)
Week 30	n	13	111	124	16	51	67
	Mean (± SD)	903.0 (±1431.70)	588.6 (±1724.05)	621.5 (±1693.37)	9069.4 (±34328.65)	407.2 (±516.72)	2475.8 (±16789.26)
	Median (Min, Max)	189 (21, 5103)	189 (21, 15309)	189 (21, 15309)	189 (21, 137781)	189 (21, 1701)	189 (21, 137781)
Week 38	n	14	107	121	15	43	58
	Mean (± SD)	510.0 (±668.48)	1607.6 (±6546.57)	1480.6 (±6166.86)	3330.6 (±11785.88)	220.3 (±214.57)	1024.7 (±6003.24)
	Median (Min, Max)	189 (21, 1701)	189 (21, 45927)	189 (21, 45927)	189 (63, 45927)	189 (21, 567)	189 (21, 45927)
Week 46	n	19	101	120	14	38	52
	Mean (± SD)	8120.4 (±31437.56)	1543.0 (±5436.73)	2584.4 (±13421.86)	10035.0 (±36768.19)	155.8 (±159.61)	2815.6 (±19083.99)
	Median (Min, Max)	189 (21, 137781)	189 (21, 45927)	189 (21, 37781)	189 (63, 37781)	126 (21, 567)	189 (21,137781)
Week 54	n	16	98	114	15	31	46
	Mean (± SD)	9045.8 (±34333.54)	1660.7 (±4214.08)	2697.2 (±13355.12)	3515.4 (±11802.64)	216.1 (±410.88)	1292.0 (±6774.68)
	Median (Min, Max)	378 (21, 137781)	189 (21, 15309)	189 (21,137781)	189 (63, 45927)	63 (21, 1701)	63 (21, 45927)

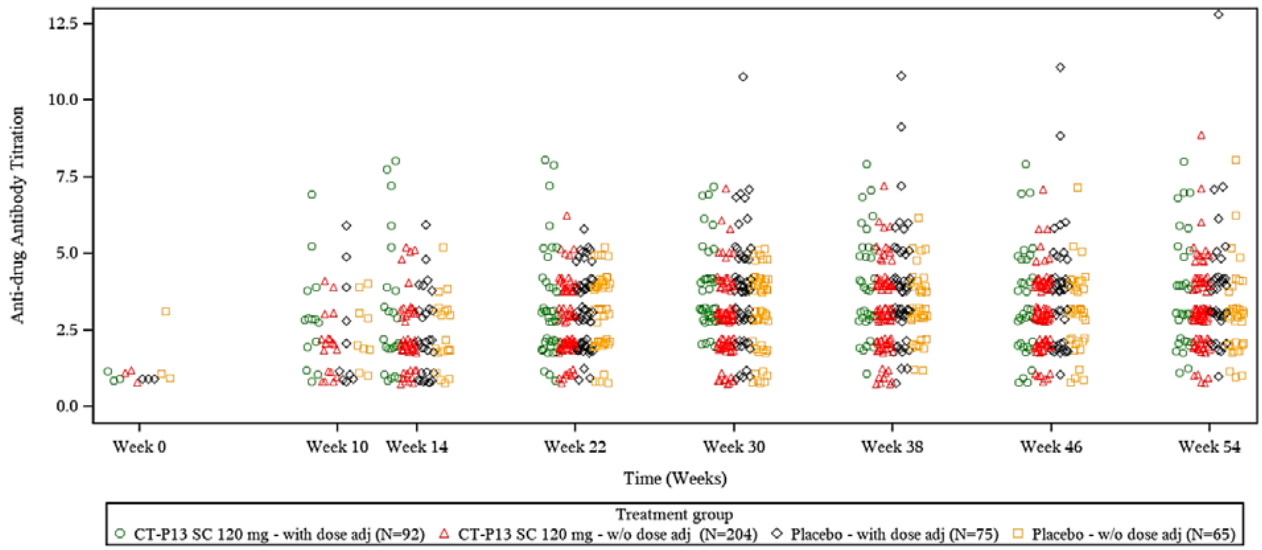
In both Phase 3 studies, the medians of ADA titres were generally comparable between the active and placebo treatment groups up to Week 54 at all sampling timepoints. A few outliers with a high titre were seen in both studies in the placebo group with dose adjustment to active drug and also (but not as high outliers as in the placebo group) for subjects with dose escalation in the active groups.

Figure 35. Scatter Plot of Transformed ADA Titre by Treatment Arm in UC Patients in Study CT-P13 3.7 (MSD ECL ACE ADA Method): Safety Population



Note: The ADA titre values are transformed using a log3(x/21) +1 transformation.
Abbreviations: ACE, affinity capture elution; ADA, anti-drug antibody; ECL, electrochemiluminescence; MSD, Meso Scale Discovery; N, number of patients in each treatment group in Safety Population; SC, subcutaneous

Figure 36. Scatter Plot of Transformed ADA Titre by Treatment Arm in UC Patients in Study CT-P13 3.8 (MSD ECL ACE ADA Method): Safety Population



The MAH has evaluated immunogenicity in all randomised subjects who received a full or partial single dose of study treatment in the previous studies CT-P13 1.5 and CT-P13 1.9 (both on healthy volunteers), CT-P13 3.5 Part 1 and Part 2 (rheumatoid arthritis patients), and CT-P13 1.6 Part 1 (Crohn's Disease Patients). These results are not included in this AR for brevity. The MAH concludes that in the above-mentioned studies, the post-treatment ADA status shows correlation with PK parameters based on post-hoc analyses, but ADA presence did not have evident impact on efficacy and safety.

CHMP comments

In the placebo group with dose escalation to active treatment, occasional high titres of ADA are observed. Some outliers with high ADA titres are also seen in the active study group with dose escalation, however, the highest titres are seen in subjects switched from placebo to the 240 mg dose (Figures 8.2.4.2 and 8.2.4.3).

Upon request, the MAH provided more details on ADA titres, exposure and drug response in CD patients from study 3.8. While it seems clear that loss of response is associated with higher ADA titres and lower drug concentrations, it is still unclear whether subjects who **regained** response had higher drug concentrations compared to those who did not (i.e., whether the regained response can be attributable to higher exposure) and whether patients with high ADA titres at dose adjustment could maintain a potential benefit from a higher dose. While higher drug concentrations might counteract the development of ADAs it is not known whether this is true for patients who have already developed high titres of ADA. Increasing the dose may be beneficial in the short term, but it is not known whether or how fast the development of new ADAs will neutralise the potential benefit of such a dose adjustment. However, as these are not an issues which could affect the wording in SPC, they will not be pursued further. (Please see section 13.2 for more detailed assessment.)The Applicant has conducted post-hoc analyses on impact of ADA on safety in study CT-P13 3.5 Part 2 up to Week 30 (reported in CTD Module 2, Section 2.7.2.4 Integrated Summary of Immunogenicity, section 2.7.2.4.5.2.3). According to the analyses, no apparent correlation was seen between rate of infection and post-treatment ADA status (positive/negative) or titre (data not shown for brevity). No similar analyses were conducted on the phase 3 trials CT-P13 3.7 and Study CT-P13 3.8.

CHMP comments

No information is submitted regarding potential relation of ADA positivity and ADA titres on injection site reactions and other allergic/hypersensitivity events. Since the product is old and it is known that patients who developed antibodies to infliximab were approximately 2–3 fold more likely to develop infusion related reactions, this issue is not pursued further.

Final study report data on ADA conversion during extension phases of phase 3 trials

In study CT-P13 37, in the extension phase, the proportion of patients with the positive ADA conversion after the first study drug administration date in the extension phase was lower in CT-P13 SC 120 mg group compared to Placebo SC group (160/287 [55.7%] and 81/134 [60.4%] patients in the CT-P13 SC 120 mg and Placebo SC groups, respectively). In the extension phase, the proportion of patients with the positive NAb conversion after the first study drug administration date in the extension phase was 140/292 (47.9%) and 79/139 (56.8%) patients in the CT-P13 SC 120 mg and Placebo SC groups, respectively. The ADA titre result was maintained in CT-P13 SC 120 mg group and decreased in Placebo SC group.

In study CT-P13 38, in the extension phase, the proportion of patients with the positive ADA conversion after the first study drug administration date in the extension phase was similar in both CT-P13 SC 120 mg and Placebo SC groups (134/232 [57.8%] and 55/101 [54.5%] patients in the CT-P13 SC 120 mg and placebo SC groups, respectively). The proportion of patients with the positive NAb conversion after the first study drug administration date in the extension phase was also similar in both CT-P13 SC 120 mg and

placebo SC groups (126/234 [53.8%] and 50/103 [48.5%] patients in the CT-P13 SC 120 mg and placebo SC groups, respectively). The ADA titre result was generally decreased in both treatment groups.

8.2.5. Comparison of Safety Results Across Studies

The MAH conducted analyses comparing the safety results from patients who received CT-P13 SC maintenance after three IV doses for induction (Studies CT-P13 3.7 and CT-P13 3.8) to patients who received CT-P13 SC maintenance after two IV induction doses (Study CT-P13 1.6 Part 2 - a Phase 1, open-label, randomised, multi-dose, parallel-group study with 53 CD patients in Part 2). Regardless of number of doses received for the IV induction, comparable incidence rates of TEAEs, TESAEs, TEAEs leading to study drug discontinuation and TEAESIs were observed during the maintenance phase for UC patients and CD patients who received CT-P13 SC maintenance treatment (table 72).

Table 74. Overview of Treatment-Emergent Adverse Events in Patients with Ulcerative Colitis and Crohn's Disease (Maintenance Phase): Safety Population

	Ulcerative Colitis		Crohn's Disease	
	Study CT-P13 3.7	Study CT-P13 1.6 Part 2	Study CT-P13 3.8	Study CT-P13 1.6 Part 2
	CT-P13 SC 120 mg (N=296)	CT-P13 SC 120/240 mg (N=38)	CT-P13 SC 120 mg (N=238)	CT-P13 SC 120/240 mg (N=28)
Total number of TEAEs	595	92	569	140
Number (%) of patients with ≥ 1 TEAE	200 (67.6)	26 (68.4)	172 (72.3)	23 (82.1)
Related	57 (19.3)	14 (36.8)	62 (26.1)	14 (50.0)
Unrelated	184 (62.2)	23 (60.5)	156 (65.5)	19 (67.9)
Number (%) of patients with ≥ 1 TEAE leading to death	0	0	1 (0.4)	0
Related	0	0	0	0
Unrelated	0	0	1 (0.4)	0
Number (%) of patients with ≥ 1 TESAE	19 (6.4)	2 (5.3)	16 (6.7)	3 (10.7)
Related	2 (0.7)	0	1 (0.4)	1 (3.6)
Unrelated	17 (5.7)	2 (5.3)	16 (6.7)	2 (7.1)
Number (%) of patients with ≥ 1 TEAE leading to study drug discontinuation	10 (3.4)	0	9 (3.8)	1 (3.6)
Related	5 (1.7)	0	6 (2.5)	1 (3.6)
Unrelated	5 (1.7)	0	3 (1.3)	0
Number (%) of patients with ≥ 1 TEAE of IRR[1]	0	0	0	0
Related	0	0	0	0
Unrelated	0	0	0	0
Number (%) of patients with ≥ 1 TEAE of SIR[1]	12 (4.1)	0	3 (1.3)	2 (7.1)
Related	12 (4.1)	0	3 (1.3)	2 (7.1)
Unrelated	0	0	0	0
Number (%) of patients with ≥ 1 TEAE of delayed hypersensitivity[1]	0	1 (2.6)	0	1 (3.6)
Related	0	1 (2.6)	0	1 (3.6)
Unrelated	0	0	0	0
Number (%) of patients with ≥ 1 TEAE of localised ISR[2]	10 (3.4)	7 (18.4)	14 (5.9)	8 (28.6)
Related	10 (3.4)	6 (15.8)	14 (5.9)	8 (28.6)
Unrelated	0	1 (2.6)	0	0
Number (%) of patients with ≥ 1 TEAE of infection	83 (28.0)	10 (26.3)	74 (31.1)	11 (39.3)
Related	11 (3.7)	4 (10.5)	15 (6.3)	5 (17.9)
Unrelated	80 (27.0)	7 (18.4)	65 (27.3)	7 (25.0)
Number (%) of patients with ≥ 1 TEAE of malignancy	1 (0.3)	0	0	1 (3.6)
Related	0	0	0	1 (3.6)
Unrelated	1 (0.3)	0	0	0

[1] IRR/SIR/delayed hypersensitivity was reported as injection related reaction in the eCRF for Studies CT-P13 3.7 and CT-P13 3.8 and administration-related reaction in the eCRF for Study CT-P13 1.6 Part 2.
[2] Localised ISR was reported as injection site reaction in the eCRF for Studies CT-P13 3.7, CT-P13 3.8 and CT-P131.6 Part 2.

CHMP comment

Numerically, incidence rates of TEAEs, TESAEs, TEAEs leading to study drug discontinuation and TEAESIs were similar during the maintenance period after induction treatment with three doses of CT-P13 IV (studies CT-P13 3.7 and CT-P13 3.8) than after induction treatment with two IV doses (study CT-P13 1.6 Part 2). However, no firm conclusions can be made by comparisons between different trials.

8.2.6. REMSWITCH study/safety

To support the possibility to switch from high-dose (>5 mg/kg) IV maintenance to SC maintenance treatment, the MAH has submitted a published article by Buisson et al *(Effectiveness of Switching From Intravenous to Subcutaneous Infliximab in Patients With Inflammatory Bowel Diseases: the REMSWITCH Study. Clinical Gastroenterology and Hepatology, Volume 21, Issue 9, August 2023, Pages 2338-2346.e3*). (Please see Section 7.3.1 of this AR).

As described in Section 7.3.1 of this AR, no full CSR is available for assessment. The authors inform that the mean level of acceptability scale (10-point scale) was improved after switching form IV to SC infliximab. Sixteen (12.0%) of 133 patients reported an adverse event. Two subjects wanted to switch back to IV infliximab due to intolerance: one due to myalgia and one due to mild abdominal pain. There were no SAEs. Other observed adverse events included mild and transient erythema (n = 5) or mild pain (n = 2) at the site of injection, fatigue (n = 1), bronchitis (n = 1), and IBD-related symptoms (rectal bleeding = 1, increased stools frequency = 1, or mild abdominal pain = 2). No patient required hospitalisation or surgery.

8.3. Discussion

To support safety of the currently proposed amended posology in CD and UC the MAH submitted results of two ongoing placebo-controlled, randomised phase 3 trials included in the submission with Week 54 interim clinical study reports: Study CT-P13 3.7 in subjects with ulcerative colitis (UC, N= 436) and Study CT-P13 3.8 in moderately to severely active Crohn's disease (CD, N = 343). Details of study designs are given in Section 7 of this AR. This discussion includes first an overall evaluation of safety of CT-P13 as observed in these studies. Thereafter, data are discussed according to each proposed variation.

Overall evaluation of safety in studies CT-P13 3.7 and CT-P13 3.8

In total, 534 subjects received at least 1 dose of CT-P13 SC in both studies (296 UC patients in study ST-P13 3.7 and 238 CD subjects in study CT-P13 3.8). Of these, 447 (244 UC patients and 203 CD patients) completed CT-P13 SC treatment up to Week 54. This is a marked amount of new data on subjects with these indications. The overall findings in the currently submitted data do not raise great concern; however, there are several methodological issues rendering the data inconclusive (see below).

Discrepant numbers of subjects who discontinued treatment due to adverse events were reported in the disposition figures and summary tables of adverse events for both phase 3 trials (CT-P13 3.7 and CT-P13 3.8). The received clarifications on this issue in the MAH's response are deemed adequate (see assessment of question 43 in Section 13.2 of this AR). The root cause for the discrepancy was different source of data and analysis method in the SAP of the studies. In study CT-P13 3.7 (ulcerative colitis), more than twice as great percentage of subjects experienced at least one TESAE in the active arm (6.4%) vs. placebo arm (2.9%), though only one subject in each group had a TESAE considered to be related to study drug. The total number of TESAEs was 25/296 in the active vs. 5/140 in the placebo arm (table 8.2.3.2.1). It is likely that the higher incidence of TESAE's in the active group is caused by the active treatment regardless of investigator's assessment of relatedness. In Study CT-P13 3.8, the percentage of patients with Crohn's disease who experienced at least 1 TESAE during the maintenance phase was similar between active (16

[6.7%]) and placebo groups (8 [7.6%] patients); one TESAE in each group was considered by investigator to be related to study drug.

Even in the placebo arms of the study, 15.0 % and 14.3 % of subjects in studies CT-P13 3.7 and CT-P13 3.8, respectively, experienced TEAEs that were considered to be related to study drug, raising the question if the TEAEs occurred after switch from placebo to active treatment. The MAH clarified in their response that the TEAEs related to study drug occurred in the placebo group during placebo treatment, prior to dose adjustment, since for both Study CT-P13 3.7 and Study CT-P13 3.8, only data collected before initiation of dose adjustment for Placebo SC group were included in TEAE summary tables. Therefore, these AEs were not related to escalated dose of CT-P13. In retrospect, the TEAEs in the placebo arms of the studies were not drug-related.

In UC patients, the total proportion of patients with positive ADA conversion result was 63.8% (183/287) in the CT-P13 SC 120 mg group and 93.3% (97.6%) in the placebo group. Among ADA positive patients, 161 out of the 183 (88.0%) patients developed NAb. In subjects without dose adjustment, positive conversion in ADA (NAb conversion, % of ADA positive) was 67.3% (88.1%) in the active group and 91.9% (98.2%) in the placebo group. In CD patients, the proportion of patients with positive ADA conversion result was 65.1% (151/232) in the CT-P13 SC 120 mg group. Among ADA positive patients, 147 out of the 151 (97.4%) patients developed NAb. In subjects without dose adjustment, positive conversion in ADA (NAb conversion, % of ADA positive) was 64.4% (97.5%) in the active group and 80% (100%) in the placebo group. Hence, the proportion of patients with positive ADA conversion was higher in the placebo SC groups. The median values of ADA titres were roughly similar between active and placebo arms in both studies; but outliers with high ADA titres were found among subjects with dose escalation from 120 mg to 240 mg (in the active arm) and even higher titres were seen in some subjects who switched from placebo to 240 mg (placebo arm). Mean ADA titres were substantially higher among patients who lost response compared to those who did not. No information is submitted regarding potential relation of ADA positivity and titres on injection site reactions and other allergic/hypersensitivity events. Since the product is old and it is known that patients who developed antibodies to infliximab were approximately 2–3 fold more likely to develop infusion related reactions, this issue is not pursued further.

There were no deaths reported in study CT-P13 3.7 (UC). One accidental death was reported in study CT-P13 3.8 (CD) due to an explosion in a garage. Infections occurred in 28.0% and 25.7% of subjects in the CT-P13 120 mg and placebo arms of study CT-P13 3.7 (UC), respectively. In study CT-P13 3.8 (CD), 31.1% and 18.1% of subjects experienced infections in the CT-P13 SC 120 mg and placebo arms, respectively. In both studies, the occurrence of COVID-19 was markedly higher in the active arms of the studies. In study CT-P 3.7 (UC), there were 30/296 patients (10.1%) in the active arm and 9/140 (6.4%) in the placebo arm with COVID-19. In study CT-P13 3.8 (CD), the cases (percentage) of COVID-19 were 27/238 (11.3%) and 5/105 (4.8%) in the active and placebo arms, respectively.

The final reports for both phase 3 studies, CT-P13 3.7 and CT-13 3.8, were received with the MAH's response to the RSI. The safety data from the open-label extension phases include no new safety findings in either patients with UC or with CD. Additional analyses on safety of the 120 mg and 240 mg SC doses vs. placebo were received as responses to the RSI.

Discussion on data submitted for support of each change proposed by the MAH

The grouped variation application includes the following proposed amendments to the Product Information:

1. Addition of a 3-IV induction dosing regimen (5 mg/kg at Weeks 0, 2 and 6) followed by SC maintenance treatment (120 mg Q2W);

2. The possibility for dose adjustment from CT-P13 SC 120 mg to 240 mg for patients with loss of response;
3. Addition of a subcutaneous induction dosing regimen (240 mg at Week 0 followed by 120 mg at Weeks 1, 2, 3 and 4) followed by SC maintenance treatment (120 mg Q2W);
4. The possibility to switch from high-dose (> 5 mg/kg) IV maintenance to subcutaneous maintenance treatment
5. Major SmPC-updates on all of the above, including description of the two new phase 3 studies (CD and UC) in sections 5.1 and 4.8.

The discussion below is numbered according to the above-listed amendments.

1. In both phase 3 studies, CT-P13 3.7 in ulcerative colitis and CT-P13 3.8 in Crohn's disease, both active and comparator arms received the newly proposed induction treatment regimen with 3 IV doses (5 mg/kg at Weeks 0, 2 and 6). Hence, safety of the proposed new induction treatment regimen has not been studied in a comparative randomised setting. Instead, the MAH has conducted analyses comparing the safety results from patients who received CT-P13 SC maintenance after three IV doses for induction in Studies CT-P13 3.7 and CT-P13 3.8 to patients who received CT-P13 SC maintenance after two IV induction doses in Study CT-P13 1.6 Part 2 (a Phase 1, open-label, randomised, multi-dose, parallel-group study with 53 CD patients in Part 2). Comparable incidence rates of TEAEs, TESAEs, TEAEs leading to study drug discontinuation and TEAESIs were observed during maintenance treatment after the old and new induction treatment regimens in these studies. Nevertheless, no firm conclusions can be made by comparisons between very different trials. Consequently, since no comparative trial data have been submitted regarding the proposed addition of a 3-IV induction dosing regimen and the currently approved 2-IV induction dosing regimen, the comparative safety of the regimens cannot be assessed based on clinical data. However, although the drug exposure is expected to be somewhat higher during weeks 10-14 with the currently proposed dosing compared to any of the previously approved regimens, the higher exposure only lasts for a few weeks and peak concentrations are much lower than those seen with a continuous IV regimen. As no specific safety concerns arose during assessment, the 3-IV induction regimen can be considered sufficiently safe.

2. Safety of the proposed escalation of maintenance dose to 240 mg SC in those who lost response has been studied by comparing maintenance treatment with Remsima (CT-P13, infliximab) 120 mg SC Q2W with maintenance treatment with placebo in pooled data from CT-P13 3.7 and CT-P13 3.8. In both active and comparator groups, dose was escalated in those who lost response to 240 mg SC Q2W (from 120 mg Q2W or placebo in the active and placebo arms of both phase 3 studies, respectively). Assessment of safety of the proposed possibility for dose adjustment from CT-P13 SC 120 mg to 240 mg for patients with loss of response needs, however, further clarifications as described below.

   The submitted results on subgroups administered the 120 mg and 240 mg dose show no dose-dependently increased risk for infection, serious adverse reactions, or systemic and localised injection reaction rates. However, the MAH did not describe in detail the populations for the comparison between placebo and CT-P13 SC and between the 120 mg and 240 mg doses and how exposure time for each dose was accounted for in the analyses. Further clarifications and analyses were requested regarding populations used for analyses of safety, duration of use of the different doses and how this was addressed in the analyses; additionally, the analyses are requested to be submitted also separately for both UC and CD subjects. Per the comment from CHMP, the safety data were re-analysed by the MAH to include the data of all patients exposed to study treatment (Placebo, CT-P13 SC 120 mg or CT-P13 SC 240 mg), regardless of treatment phase and treatment group. The re-analysis included the Extension Phase and data collected after dose adjustment from patients in the Placebo arm. All reported

TEAEs had been categorised into subgroups based on the actual treatment the patients received. To take into account the different duration of use for each treatment (Placebo, CT-P13 SC 120 mg and CT-P13 SC 240 mg). The incidence rates were reported per 100 Person Year (PY). The MAH withdrew the application for dose escalation in patients with UC. Re-analyses on safety were received for patients with CD in study CT-P13 3.8. In addition, the MAH conducted upon request an integrated analysis on safety across all studies with SC administration of 120 mg and/or 240 mg of CT-P13: Study 1.6 Part 1 (CD), Study 1.6 Part 2 (CD/UC), Study 3.5 Part 1 (RA), Study 3.5 Part 2 (RA), Study CT-P13 3.7 (UC), and Study CT-P13 3.8 (CD)(Table 7 of the MAH's response). Sufficient data were received, confirming that the higher dose of 240 mg caused slightly more injection site reactions (8.95/100 PY) than the 120 mg dose (5.81/100py); at least partly due to the higher dose requiring two injections instead of one. The overall incidence of TEAE was 60.94 vs. 67.39 with the 120 mg SC vs. 240 mg SC dose. The incidence of TESAE and of TEAE leading to drug discontinuation were also slightly higher with the 240 mg dose. (See assessment of Question 48 in Section 13.2 of this AR).

The rate of TEAE classified as infection was in the integrated analysis 29.56 per 100 PY in the 120 mg SC group and 33.99 per 100 PY in the 240 mg SC group (table 7 of the MAH's response). Analysis on events prior to vs. after dose escalation was conducted for studies that allowed for dose escalation from 120 to 240 mg SC: CT-P13 3.7, CT-P13 3.8 and CT-P13 1.6 Part 2. In this analysis, the incidence of infection as number of subjects/entire group (%, per 100PY) was 34/159 (21.4%, 45.52) with CT-P13 120 mg SC before dose escalation and 51/159 (32.1%, 33.12) after escalation from 120 mg to 240 mg SC. In the placebo group, the incidence was 21/126 (16.7%, 48.25) before dose escalation, and 50/126 (39.7%, 32.65) after escalation to 240 mg SC from placebo (table 9 of the MAH's response). Hence, in the integrated analysis, the rate of infection per 100 PY was higher before escalation to 240 mg SC than after escalation, whether escalating from the 120 mg SC dose or from placebo.

In study CT-P13 3.8 (CD), the incidence of infections/100PY was slightly higher during treatment with 240 mg SC (33.74) than 120 mg SC (28.88) or placebo (31.55) (table 1 of the MAH's response). When excluding TEAEs reported from patients in the placebo group who switched from placebo to CT-P13 SC 120 mg at Week 56 then underwent dose adjustment from CT-P13 SC 120 mg to 240 mg during the extension phase, the number (%, per 100PY) of patients with ≥1 infection was 15/54 (27.8%, 48.67) during treatment with 120 mg SC before escalation and 21/54 (38.9%, 39.94) after escalation from 120 mg to 240 mg SC. In the placebo group the incidence of infections (% of patients, per 100PY) was 5/50 (10%, 28.04) in the placebo group prior to escalation and 19/50 (38%, 29.18) after escalation to 240 mg SC (table 8 of the MAH's response). Hence, a larger proportion of subjects experienced adverse reactions after escalation, during treatment with 240 mg SC, than before escalation, during treatment with 120 mg SC. However, due to longer exposure time on the higher dose, the incidence of infections per 100 PY was lower after escalation. The rate of infection was high also during treatment with placebo, hence, a marked part of infections may be related to the background disease, which could explain the decline in incidence of infection after escalation. These requested analyses indicate that dose escalation would not increase risk for infection; even though from a methodological point of view such non-randomised post-hoc data cannot be considered robust. The somewhat higher overall incidence of infections during treatment with the 240 mg SC dose vs. the 120 mg dose in study CT-P13 3.8 may seem to be in contradiction with the results showing a decreased rate of infections after dose escalation. This discrepancy could however be speculated to be due to selection, since the most severely ill patients that were in need for dose escalation have probably been also most prone to infections. Hence, the lower incidence of infections among subjects treated with the 120 mg SC dose could be speculated to have been driven by the healthier part of study subjects.

There was no difference in treatment-emergent serious adverse events (TESAE) between the doses of 120 mg and 240 mg SC in study CT-P13 3.8; though in the integrated safety analysis there were slightly

more TESAE (8.42 per 100 PY) in subjects administered 240 mg SC vs. subjects administered 120 mg SC (6.42 per 100PY). (see assessment of Questions 42 and 48 in Section 13.2 of this AR).

In tables with numbers of subjects with dose adjustment, the number of such subjects were at some time points reported to be lower than at the previous visit. The MAH confirmed in their response that among patients with dose adjustment in Study CT-P13 3.8 (both CT-P13 SC 120 mg and Placebo SC groups), no patients returned to their previous dose by the decision of the investigator to decrease the dose. The number of patients with dose adjustment appeared to be lower at some visits than the previous visit due to dropouts, dose skip and dosing error (e.g., human error) (CSR CT-P13 3.8 (Week 54) Section 12.1 [SN0264]). The dosing errors were corrected in the subsequent study visit. In all, a total of 93 patients received at least one adjusted dose for the safety population during the Maintenance Phase on or after Week 22 and until Week 54. Among them, 9 patients started the adjusted dose at Week 54, 67 patients maintained the adjusted dose at Week 54 and 17 patients were early terminated before the Week 54 administration.

3. The variation of CT-P13 SC induction posology in patients with CD and UC is supported only by population PK and PK-PD modelling and simulation analyses. There are no observed data with the proposed dosing regimen. In absence of safety data on the proposed SC induction posology the safety of the proposed SC induction posology cannot be assessed based on clinical data. This issue is not pursued further, since the C_{max} concentrations of CT-P13 are expected to be lower with the currently proposed SC induction regimen compared to the approved IV regimen (see Sections 6.2 and 6.3 of this AR). After the first RSI the MAH withdrew the proposal of SC induction. Therefore, the questions related to this variation are no longer relevant.

4. To support the possibility to switch from high-dose (> 5 mg/kg) IV maintenance to subcutaneous maintenance treatment, the MAH had submitted a published article on the REMSWITCH study (see Sections 7.3.1 and 8.2.6 of this AR). There were no deaths or other serious adverse events. Sixteen of 133 (12 %) subjects experienced mild and transient adverse events. In lack of a full protocol and taking in account also the relatively small number of study participants, the data are not regarded to be confirmative, albeit no new signals regarding safety of such switch were seen. After the first RSI the MAH withdrew the proposal of switching from high-dose (>5 mg/kg) IV maintenance to SC treatment. Therefore, the corresponding changes to the PI are no longer proposed and questions related to this variation are no longer relevant.

5. The update of the SmPC proposed by the MAH included new data only for systemic injection reactions (SIR) and injection site reactions (ISR) and not for any other adverse reactions. Furthermore, the MAH had updated Section 4.8 of the SmPC with integrated analyses from one Phase 1 study in UC/CD patients in addition to the two Phase 3 studies that are the basis of the current variation, instead of including all studies conducted with SC administered Remsima. In their response, the MAH justifies not including other studies with SC administered Remsima by the EMA Guideline on SmPC that emphasizes that the frequency of adverse reactions should be derived from pooled placebo-controlled studies. The MAH was also asked to clarify for both pivotal studies the numbers of the adverse reactions which occurred more frequently in active than placebo arms but were nevertheless not proposed to be included in the SmPC. In their response, the MAH listed the TEAEs reported for at least 1% of patients in the CT-P13 SC 120 mg group and at a higher rate than the Placebo SC group. Data after switch to 240 mg SC was not included as it did not represent placebo controlled situation. The MAH identified five TEAEs by preferred term (PT) (thrombocytosis, large intestine polyp, blood creatine phosphokinase increased, arthritis and haematuria) as not being listed in Section 4.8 of the SmPC. The MAH has adequately justified for each observed TEAE the inclusion or omission of that AE from the table in Section 4.8 of the SmPC. Based on these data, no change is warranted on the table except for Covid-19, which was

added in the updated tabulated list in Section 4.8 of SmPC as Very Common adverse event of Viral infection.

Since the elderly more often suffer from multiple background diseases and are more prone to infections (e.g., herpes zoster and severe influenza or COVID-19), the MAH was requested to discuss the safety of the SC 240 mg dosage in the elderly and if any changes to Product Information are needed regarding use of the higher dose in the elderly. The MAH responded that there were only 2 subjects in study SC-P13 3.8 aged >65 with dose escalation to 240 mg SC. One of the two experienced infections (respiratory tract infection and latent tuberculosis) and one experienced no TEAEs. For comparison, in the entire study population more than 1/3 of those with dose escalation experienced TEAEs classified as infection. It is known from previous scientific data that the elderly are more at risk of serious infections during infliximab treatment; but there exists no definitive information if the risk is associated with the circulating level of infliximab. Since the increased risk of infections is already covered in the SmPC Sections 4.4 and 4.8, it is agreed that no amendment is warranted in Section 4.2, which refers to Sections 4.4 and 4.8 regarding this risk in the elderly.

During the maintenance phase, systemic injection reactions (SIR) were reported for 12 (4.1%) and 4 (2.9%) patients in the CT-P13 SC 120 mg and placebo SC arms of study CT-P13 3.7 (UC), respectively. Grade 3 SIR was reported for 3 (1.0%) patients in the CT-P13 SC 120 mg arm and 1 (0.7%) patient in the placebo SC arm. One patient in each treatment arm experienced SIR that led to study drug discontinuation. In study CT-P13 3.8 (CD), SIRs were reported for 3 (1.3%) and 1 (1.0%) patients in the CT-P13 SC 120 mg and placebo SC arms, respectively. All events were grade 1 in severity and non-serious. No action was taken with the study drug and all patients recovered without receiving treatment for the SIR. No cases of delayed hypersensitivity were reported in either phase 3 study. Localised injection site reactions (ISR) occurred during the maintenance phase of study CT-P13 3.7 in 10/296 (3.4%) of UC patients in the CT-P13 SC 120 mg arm and 3/140 (2.1%) in placebo SC arm, respectively. All events were grade 1 or 2 in severity, non-serious, and did not lead to study drug discontinuation. For study CT-P13 3.8, localised ISR were reported for 14/238 (5.9%) and 1/107 (1.0%) patients in the CT-P13 SC 120 mg and placebo SC groups, respectively. All localized ISRs were grade 1 or 2 in intensity and most patients' localised ISR recovered in both treatment groups. No serious localised ISRs were reported.

As a conclusion, all safety concerns were satisfactorily resolved by the MAH's response to the RSI. The MAH has withdrawn the applications for switching from high dose IV infliximab to 120 mg SC Remsima and for dose escalation to 240 mg SC in subjects with ulcerative colitis. Safety of the dose escalation from the 120 mg SC dose to the 240 mg SC dose in subjects with Crohn's disease not responding adequately to the lower dose has been demonstrated by the multiple additional analyses provided by the MAH. The Product Information has been updated to include COVID-19 as an example of viral infections in the list of adverse events.

9. PRAC advice

N/A

10. Risk management plan

The MAH submitted an updated RMP version (v 16.1, DLP 31 Mar 2023 and version 16.2, DLP 23 Oct 2023) with this application. The (main) proposed RMP changes were the following:

Part I: Product(s) Overview was updated to propose the new posologies for SC formulation of CD and UC indications

Part II: Module SV – Post-authorisation experience was updated with data for IV and SC formulations. Clinical trial exposure was updated as studies CT-P13 SC 3.7 and 3.8 were completed.

Part II: Module SVII – Identified and potential risks – Postmarketing experience section has been updated to replace originator's data with Remsima Inflectra's data. TEAE tables were updated with data from completed studies CT-P13 3.7 and 3.8.

Part III: Studies CT-P13 3.7 and 3.8 were removed from the additional pharmacovigilance plan as they were completed and all sections of Part III were updated accordingly. Pharmacovigilance Plan (including post-authorisation safety studies) synopsis contents and milestones regarding Study CT-P13 4.8 from additional pharmacovigilance plan were updated.

Part VI: Summary of the risk management plan was updated based on changes mentioned above.

The Annexes were updated to reflect the completed additional pharmacovigilance actions.

CHMP comment

No changes to the safety specification were proposed. Based on the data provided, this can be endorsed. Most of the changes in the RMP are related to update of patient exposure data and updates of the characterisation data of the safety concerns. The numbers of ADR cases of different events were updated with numbers of events reported for Remsima/inflectra, instead of Remicade and updated with data from completed studies CT-P13 3.7 and 3.8. The updated data does not change the characterisation of the safety concerns. The pharmacovigilance plan and the RMP was updated throughout to reflect the completion of the additional pharmacovigilance actions. In addition, the Applicant has updated the presentation of the Additional pharmacovigilance activity Study CT-P13 SC 4.8 (An observational, prospective cohort study to evaluate safety of Remsima® Subcutaneous in patients with Rheumatoid Arthritis, Ankylosing Spondylitis, Psoriatic Arthritis and Psoriasis) The aim of the study is to collect further safety information on patients treated with Remsima SC with regard to long-term safety. The main change is that subcutaneous loading dose may be used in RA patients. The study milestones have also been updated. The protocol has been finalised 18 Oct 2022, FPFV occurred 13 Jan 2023. No changes to the planned final report of 3Q 2027 were proposed in this submission. The changes to the RMP v.16.2 are considered acceptable.

10.1. Overall conclusion on the RMP

☒The changes to the RMP are acceptable.

11. Changes to the Product Information

Please refer to attached annotated product information.

12. Request for supplementary information

12.1. Major objections

Please see Section 13 for 1st round RSI questions and assessment.

12.2. Other concerns

Please see Section 13 for 1st round RSI questions and assessment.

RMP aspects

None.

13. Assessment of the responses to the request for supplementary information

13.1. Major objections

Clinical aspects

Dose escalation in UC/CD

Question 1

There is not enough evidence to support the claim on dose escalation from SC 120mg to 240mg in case of loss of response in either of the indications. The study design of both studies 3.7 and 3.8 is inadequate to answer the question on relevant efficacy and safety of this dose increase. The MAH provided virtually no details to enable assessment of the totality of data and sufficient safety of the dose increase has not been demonstrated.

It is known that the C_{trough} levels are manyfold higher in all weight categories with the SC 120mg dosing compared to those achieved with IV administered Remsima. In previous studies on UC and CD, the steady state C_{trough} of infliximab has been around 6-8 microg/l with the double IV dose of 10 mg/kg. In studies 3.7 and 3.8, the normal SC dose of 120mg gave median C_{trough} concentrations of 13-16 microg/l. Hence, already the 120mg SC dose gives rise to considerably higher trough concentrations than those achieved with the highest approved (as described in section 5.1 of the SPC) IV dosing. With the proposed 240mg SC dosing the C_{trough} levels would be even higher. There is very limited amount of safety data on the exposures achieved with the 240mg SC maintenance dose and no long-term data. The MAH should either remove from the SPC the statement of increasing the dose to 240mg at loss of response, or further justify that the benefit/risk of the claimed 240mg dose is positive in all proposed indications. (See also list of OCs).

Summary of the MAH's response

First of all, the Applicant would like to withdraw the proposed dose adjustment from CT-P13 SC 120 mg to 240 mg for patients with loss of response (LoR) in UC indication, and would like to pursue the dose adjustment in CD indication only. Consequently, responses to questions about dose adjustment in UC indication (Questions 11-15, 18-22 and 24) are omitted in this submission package. The Applicant wishes to pursue approval of CT-P13 SC dose adjustment for patients with LoR in CD indication based on the result of Study CT-P13 3.8 (CSR CT-P13 3.8).

Baseline Characteristics

In Study CT-P13 3.8, there was no meaningful difference between the subgroups of patients with and without dose adjustment in terms of baseline characteristics (Section 5.3.5.3 Post-hoc Table 2.219).

Efficacy Following Dose Adjustment

As previously discussed in Section 2.7.3.4.3 (SN0264), the proportions of patients achieving co- primary and key secondary efficacy endpoints depending on the treatment assignment and dose adjustment were calculated (Table 1). Compared to the Placebo SC group, higher proportion of patients achieved co-primary and key secondary endpoints in the subgroup of patients who adjusted the dose from CT-P13 SC 120 mg to 240 mg. Although the proportions of patients achieving endoscopic response and endoscopic remission at Week 54 in the CT-P13 SC 120 mg with dose adjustment subgroup are lower compared to the CT-P13 SC 120 mg without dose adjustment subgroup, they were still higher than the proportions in the Placebo SC group. Also, for all other co- primary and key secondary endpoints, the proportions of patients achieving those endpoints for the CT-P13 SC 120 mg with dose adjustment subgroup were similar to the proportions for the CT-P13 SC 120 mg without dose adjustment subgroup and markedly higher than the proportions for the Placebo SC group. Especially, 61.5% of patients with dose adjustment regained clinical response (based on CDAI-100).

Moreover, as presented in Response to Question 36, for patients who adjusted the dose, reductions in the CDAI and SES-CD scores were observed after the dose adjustment, suggesting that increase of CT-P13 SC dose to 240 mg has effect on patients who initially responded but then lost response.

Moreover, as discussed in Response to Question 35, the efficacy of patients who met loss of response (LoR) criteria and received adjusted dose were compared to the efficacy of patients who met LoR criteria but did not receive adjusted dose in the CT-P13 SC group. The results showed that greater proportion of patients achieved co-primary and key secondary endpoints when patients who met LoR criteria received adjusted dose of CT-P13 SC 240 mg. Therefore, dose adjustment from CT-P13 SC 120 mg to 240 mg is considered as a rescue therapy for patients who meet LoR criteria.

3 Safety Following Dose Adjustment

As previously discussed in Section 2.7.4.2.1.4.3.2 (SN0264), no noticeable difference was observed between the subgroups with dose adjustment and without dose adjustment in the incidence rates of TESAE, TEAE leading to study drug discontinuation and TEAESIs (SIR, delayed hypersensitivity, localised ISR, infection, malignancy) during the Maintenance Phase of Study CT-P13 3.8 (Table 2.7.4- 23 [SN0264]).

To further examine safety profile of patients with dose adjustment, the Applicant conducted post- hoc analyses including all safety data up to Week 102 regardless of switching from placebo to CT- P13 SC (120 mg) and dose adjustment from CT-P13 SC 120 mg or Placebo SC to 240 mg (Section 5.3.5.3 Post-hoc Table 3.114). The adverse events occurred on or after the first administration of each treatment are included in the corresponding treatment group. As discussed in detail in Response to Question 42, the results showed that there was no significant difference in the number of events by 100 persons year (PY) between each dose of CT-P13 SC 120 mg, 240 mg and placebo. The number of patients with at least 1 TEAE, TESAE, TEAE leading to study drug discontinuation or TEAESI with exposure adjusted rate by 100 PY were comparable between the groups.

Moreover, considering that the mean and median duration of treatment for patients who received CT-P13 SC 240 mg are 58.9 weeks and 68.1 weeks, respectively, and 73 patients received CT-P13 SC 240 mg as maintenance treatment for at least 44 weeks in Study CT-P13 3.8, the post-hoc analysis result sufficiently represents long-term safety profile of CT-P13 SC 240 mg. Study drug exposure in Safety Population of Study CT-P13 3.8 is presented in Table 2 (from the response document).

Table 75. Summary of Study Drug Exposure in Study CT-P13 3.8: Safety Population

	Placebo (N=105)	CT-P13 SC 120 mg (N=275)	CT-P13 SC 240 mg (N=105)
Duration of Treatment (weeks)			
Mean (SD)	29.9 (15.87)	69.0 (32.98)	58.9 (27.99)
Median (Min, Max)	35.0 (4, 51)	94.4 (4, 113)	68.1 (5, 96)
Subjects Treated by Duration of Treatment			
≥ 1 dose	105	275	105
≤ 4 weeks	0	1	0
> 4 to ≤ 20 weeks	45	34	17
> 20 to < 44 weeks	17	30	15
≥ 44 weeks	43	210	73

Source: Section 5.3.5.3 Post-hoc Table 3.113
Note: Duration of treatment (weeks) is calculated as (the last visit date - date of first administration of each treatment +1)/7. For patients with any change in treatment due to entering extension phase or dose adjustment, the duration of previous treatment is calculated as (date of first administration of later treatment - date of first administration of each treatment)/7.
N = the number of patients administered at least one dose for each treatment.
Abbreviation: SD, standard deviation

As presented in Response to Question 46, pooled analyses including all available CT-P13 SC clinical studies were conducted to examine safety profile of CT-P13 SC 240 mg. These results also support that there is no significant difference between the long-term safety profiles of CT-P13 SC 120 mg and CT-P13 SC 240 mg. Also, the result of the analysis comparing the events occurring prior to dose adjustment vs after dose adjustment in both CT-P13 SC and Placebo groups showed that the number of adverse events did not significantly increase after dose adjustment in general.

4 Conclusion

The efficacy and safety results from Study CT-P13 3.8 support positive benefit and risk ratio for dose adjustment from CT-P13 SC 120 mg to 240 mg for CD patients with loss of response. The subgroup of patients in CT-P13 SC 120 mg group with dose adjustment showed greater proportions of patients achieving the co-primary and key secondary endpoints compared to the Placebo SC group. In terms of safety, no notable difference was observed between the subgroups with and without dose adjustment in the CT-P13 SC 120 mg group. Also, the proposed dose adjustment would provide another treatment option for patients with LoR. Therefore, based on the benefit-risk assessment, the totality of the CT-P13 SC programme supports that the proposed dose adjustment from CT-P13 SC 120 mg to 240 mg for CD patients who initially showed response but then lost response has favourable benefit-risk ratio.

Assessment of the MAH's response

Data in Crohn's disease (including data provided in response to other questions)

A total of 41 patients in the CT-P13 SC 120 mg group and 48 patients in the placebo group experienced LoR prior to Week 54. Among these patients, 34/41 (82.9%) in CT-P13 SC 120 mg group and 41/48 (85.4%) in placebo group received adjusted dose while 7 patients in each group remained on the initially assigned treatment. A few patients received adjusted dose despite not being eligible for the dose adjustment, 5/182 (2.7%) in CT-P13 SC 120 mg group and 4/57 (7.0%) in placebo group. This protocol violation seems to be driven by the clinicians' desire to improve the treatment for poor responders but exposes poor adherence to GCP. However, the frequency of these protocol violations is small enough not to pursue the issue further.

Among the 34 patients with dose adjustment in the CT-P13 SC 120 mg group 17 (50%) patients achieved clinical remission by CDAI and 7 (20.6%) patients achieved endoscopic response at Week 54. On the other

hand, in the 7 patients who experienced a LoR but did not receive a dose adjustment, regain of clinical remission by CDAI occurred in 1/7 (14.3%) and endoscopic response re-emerged in 3 (42.9%) of these patients on initial active treatment. Regain of response occurred in 21/34 (61.8%) patients with a dose escalation while patients who lost response but remained on active treatment had a renewed response in 2 (28.6%) cases. Spontaneous regain of response and remission was also seen in patients who remained on placebo (3 and 1 patients, respectively).

Although the numbers are small, it can be concluded that spontaneous regain of response is not negligible. However, regain of response according to CDAI is more common and the improvement in absolute CDAI score is more pronounced in patients with a dose adjustment than in those who remained on initial treatment despite a LoR.

A clear difference between patients who experienced LoR and those who did not is seen in terms of serum drug concentration before LoR. This finding supports the theory of loss of response being associated with suboptimal drug concentrations.

Based on the submitted data, the 240 mg SC dose is overall associated with a closely similar safety profile as the 120 mg SC dose in subjects with CD. There were somewhat more infections with the 240 mg dose (table 8.2.1.2). However, the number of treatment-emergent serious adverse events (TESAE) was similar: 28/275 (10.2%, PY 7.70) during use of CT-P13 120 mg SC and 7/105 (6.7%, PY 5.91) during use of CT-P13 240 mg SC. Furthermore, injections-site reactions were more frequent with the higher dose, but this was expected since the 240 mg SC regimen included two injections instead of only one.

The mean and median duration of treatment for patients who received CT-P13 SC 240 mg were 58.9 weeks and 68.1 weeks, respectively, and 73 patients received CT-P13 SC 240 mg as maintenance treatment for at least 44 weeks. Therefore, the post-hoc analysis result is considered to sufficiently represent long-term safety profile of CT-P13 SC 240 mg in subjects with CD.

Data in Ulcerative colitis

The question on dose escalation in UC is no longer relevant.

Conclusion

In CD patients, loss of response is associated with lower drug concentrations.

Regain of response according to CDAI is more common and the improvement in absolute CDAI score is more pronounced in patients with a dose adjustment than in those who remained on initial treatment despite a LoR. Although the groups are not comparable, the totality of data is sufficiently compelling in terms of magnitude and consistency to support a dose increase in patients who lost response. A majority of patients in the active treatment arm who received a dose adjustment had a positive outcome 16 weeks after the dose increase.

The long-term safety profile of 240mg SC is sufficiently identified. The 240 mg SC dose is overall associated with a closely similar safety profile as the 120 mg SC dose in subjects with CD.

The major objection is resolved as sufficient data on safety was provided but some other concerns remain before the data presented in the SPC can be approved.

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

No need to update overall conclusion and impact on benefit-risk balance

SC induction in UC/CD

Question 2

The MAH's justifications for the proposed SC induction regimen in treatment of CD and UC are not sufficient (see section 6.3 of the assessment report). The concentration-time profile and exposure parameters following the SC regimen will not match those following the approved IV regimen. Therefore, efficacy and safety of the proposed SC induction regimen should be demonstrated in a clinical study or, if modelling and simulation approach is utilized, the MAH should A) very robustly demonstrate which exposure parameter(s) and exposure level(s) drive the efficacy and safety of infliximab in induction treatment of moderately to severely active Crohn's disease, fistulising active Crohn's disease, and moderately to severely active ulcerative colitis, and B) demonstrate that these exposure levels will be achieved with the proposed SC induction regimen in all body weight categories. (See also OC / Clinical pharmacology / Population PK model).

Summary of the MAH's response

The Applicant would like to withdraw the proposed SC induction dosing regimen (240 mg at Week 0 followed by 120 mg at Weeks 1, 2, 3 and 4) followed by SC maintenance treatment (120 mg Q2W) from the grouped variation for CD and UC indications. This is mainly due to lack of clinical data to support the SC induction dosing regimen. Consequently, responses to Questions 2 and 6-9 are omitted in this response to RSI package.

Assessment of the MAH's response

The proposed SC induction dosing regimen for CD and UC indications was withdrawn from the grouped variation application procedure.

Conclusion

Issue resolved as questions related to this variation are no longer relevant.

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance

Switch from high IV dose to SC dose in CD

Question 3

The provided data does not justify the proposed amendment which implies that sufficient information on switching from higher than 5 mg/kg IV doses to SC Remsima is available in Crohn's disease. The MAH should either remove the amendment from the SPC, or further justify that the available information is sufficient to support maintenance of the positive benefit-risk balance after a switch in CD patients treated with an approved (as described in section 5.1 of the SPC) high IV dose. The usual rate of relapses in a comparable population could be used as reference. (See also OC)

Summary of the MAH's response

The Applicant would like to withdraw the proposed switching from high-dose (>5 mg/kg) IV maintenance to SC maintenance treatment from the grouped variation for CD and UC indications. This is mainly due to

lack of clinical data to support the switching from high-dose (5 mg/kg) IV maintenance to SC maintenance treatment.

Consequently, responses to Questions 3 and 41 are omitted in this response to RSI package.

Assessment of the MAH's response

The proposed switching from high-dose IV maintenance to SC maintenance was withdrawn from the grouped variation application procedure.

Conclusion

Issue resolved as questions related to this variation are no longer relevant.

Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

13.2. Other concerns

Clinical aspects

Bioanalytics

Question 4

ADA-method: The partial validation with new SA plates provided by Roche was performed only in healthy human serum. Since the clinical studies are performed with ulcerative colitis and Crohn's disease patients, the Applicant is requested to evaluate matrix interference of corresponding disease serum unless otherwise justified.

Summary of the MAH's response
Matrix interference in ulcerative colitis and Crohn's disease serum was evaluated as additional method validation. Ten individual pre-dose samples each from Studies CT-P13 3.7 and CT-P13 3.8 were randomly selected and evaluated unspiked and spiked with low and high level of surrogate positive control (HCA233, BioRad®). All the results met the acceptance criteria specified in the method validation plan.

Assessment of the MAH's response
MAH performed matrix interference studies in ulcerative colitis and Crohn's disease serum as was requested. The provided data met the acceptance criteria and no matrix interference was observed. This point is considered resolved.

Conclusion

Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

Question 5

Bioanalytical report of CT-P13 plasma concentrations: The Applicant is requested to provide full ISR data once available.

Summary of the MAH's response

The full incurred sample reanalysis (ISR) for Study CT-P13 3.7 and Study CT-P13 3.8 have been performed and the results are provided in Appendix 16.1.13 of W102 CSR CT-P13 3.7 (ROPH) and Appendix 16.1.13 of W102 CSR CT-P13 3.8 (RNEM), respectively.

Assessment of the MAH's response

The full ISR data has been provided and is considered acceptable.

Conclusion
Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

Clinical pharmacology

Question 6

Population PK model: According to Section 5.1.1.1 of the population PK/PD report, PK measurements from 3114 subjects were available for PK model development and after exclusions PK measurements from 2998 subjects were included in the population PK model development. According to Table 13 Summary of continuous covariates and Table 14 Summary of categorical covariates, 3017 subjects were included in the population PK model development. Please clarify the discrepancy. In addition, please provide summary tables of continuous and categorical covariates for the final unblinded dataset.

Summary of the MAH's response

The Applicant withdrew the proposed SC induction dosing regimen followed by SC maintenance treatment from the grouped variation for CD and UC indications. Consequently, responses to Questions 2 and 6-9 are omitted in this response to RSI package.

Assessment of the MAH's response

The proposed SC induction dosing regimen for CD and UC indications was withdrawn from the grouped variation application procedure. Questions related to this variation are no longer relevant.

Conclusion

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance

Question 7

Population PK model: ADA and NAb were significant covariates in the population PK model. The MAH should confirm that immunogenicity samples (ADA and NAb) from studies CT-P13 1.6, 1.10, 1.11, 3.5, 3.7, and 3.8 were measured using the same methods, or if the methods were not the same that the results of the methods are comparable.

Summary of the MAH's response

The Applicant withdrew the proposed SC induction dosing regimen followed by SC maintenance treatment from the grouped variation for CD and UC indications. Consequently, responses to Questions 2 and 6-9 are omitted in this response to RSI package.

Assessment of the MAH's response

The proposed SC induction dosing regimen for CD and UC indications was withdrawn from the grouped variation application procedure. Questions related to this variation are no longer relevant.

Conclusion

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance

Question 8

Population PK model: The scope of the variation application is to add induction regimen for subcutaneously administered Remsima in treatment of CD and UC, i.e., the MAH proposes a new dosing regimen for the first 6 weeks of treatment. This period is not adequately shown in the presented pcVPC plots. Additional pcVPC plots should be provided for the final updated PK model (run5102) for time periods 6 weeks after the first dose and 6 weeks after the last dose. Binning should be selected carefully to avoid artefacts in the plots. Plots for the whole dataset should be stratified at least by route of administration, SC dose, and immunogenic response (unknown/no/yes). In addition, separate plots should be provided for patients with CD and UC (stratified by route of administration).

Summary of the MAH's response

The Applicant withdrew the proposed SC induction dosing regimen followed by SC maintenance treatment from the grouped variation for CD and UC indications. Consequently, responses to Questions 2 and 6-9 are omitted in this response to RSI package.

Assessment of the MAH's response

The proposed SC induction dosing regimen for CD and UC indications was withdrawn from the grouped variation application procedure. Questions related to this variation are no longer relevant.

Conclusion

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance

Question 9

Population PK model: The model appears to have significant model misspecifications according to the pcVPCs stratified by route of administration (Figure 6.2.2.9) which should be addressed.

a. The median profile for the observed data is not adequately described by the model predictions. Infliximab may have non-linear PK with respect to dose/concentration and/or time (i.e., target-mediated drug disposition) which is not accounted for. The Applicant should address this limitation by exploring model(s) for non-linear PK and update the final model as appropriate.

b. The variability (i.e., outer percentiles) is over-predicted for the IV route and under-predicted for the SC route, which is problematic considering that the Applicant propose to use the PK model to support a new SC induction regimen. Potential differences in variability between IV and SC is an important aspect for assessing the new SC induction regimen. The SC dosing may display higher variability than IV due to variability in rate and extent of absorption from the subcutaneous injection site. The Applicant should resolve the misspecification in variability, for example by exploring inter-individual variability in KA and/or F and update the SC induction regimen predictions.

Summary of the MAH's response

The Applicant withdrew the proposed SC induction dosing regimen followed by SC maintenance treatment from the grouped variation for CD and UC indications. Consequently, responses to Questions 2 and 6-9 are omitted in this response to RSI package.

Assessment of the MAH's response

The proposed SC induction dosing regimen for CD and UC indications was withdrawn from the grouped variation application procedure. Questions related to this variation are no longer relevant.

Conclusion

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance

Efficacy

Study CT-P13 3.7

Question 10

The protocol assumptions differ to a large degree from what was observed in the study. In the protocol a 45% response rate in the placebo arm was expected whereas the results show a response rate of 20.8%. Furthermore, in the protocol a 15% delta was expected which would have translated into 60% response rate in the active arm. This is also notably lower (43%) though the expected delta was observed. The Applicant should discuss whether the difference in the expected vs observed results is due to low number of true responders or whether the dose escalation/switch to placebo allowed in the protocol, or some other

reason, explains the difference. The response may refer to the OC in the efficacy section related to categories for non-responders.

Summary of the MAH's response

Historical data used for the assumption was ACT1 study (Rutgeerts et al., 2005) and Study CT-P13 1.6 Part 2 (CSR CT-P13 1.6 Part 2). Although there were a few aspects of the two reference studies that did not exactly match Study CT-P13 3.7, those studies were selected due to limitation of available historical data at the time of Study CT-P13 3.7. For assumption, clinical remission rate of CT-P13 SC 120 mg group was assumed by result of CTP13 at Week 30 (64.4%, 38/59) in Study CT-P13 1.6 Part 2 which was most up-to-date data at the time of Study CT-P13 3.7 sample size assumption. In Study CT-P13 1.6 Part 2, clinical remission rate of CT-P13 intravenous (IV) group and CT-P13 subcutaneous (SC) group was 58.1% (18/31) and 71.4% (20/28), respectively. Clinical remission rate of Study CT-P13 1.6 Part 2 was based on partial Mayo score among patients who showed clinical response based on partial Mayo score of IV induction (at Week 6) whereas clinical remission rate of Study CT-P13 3.7 was based on modified Mayo score among patients who showed clinical response based on modified Mayo score of IV induction (at Week 10). The modified Mayo score consists of the stool frequency, rectal bleeding and endoscopic subscores, whereas the partial Mayo score consists of the stool frequency, rectal bleeding subscore and physician's global assessment (PGA).

Study CT-P13 1.6 Part 2 was an open-label study and only biologic naïve patients were included in this study which could have caused higher clinical remission rate compared to blinded Study CT-P13 3.7 which included patients with previous exposure of biologics or JAK inhibitors. Applying different criteria of clinical remission and eligibility in each study could have had impact on lower clinical remission rate of Study of CT-P13 3.7.

Considering that different criteria of clinical remission and eligibility were applied, clinical remission rate of CT-P13 SC 120 mg group in Study CT-P13 3.7 was estimated as 60% by conservative assumption. For assumption of clinical remission rate of Placebo group, delta was assumed by using ACT1 study, due to lack of historical data of subcutaneous placebo. Though 18% delta was observed in ACT1 study, 15% delta was estimated due to difference in regimen. In ACT1 study, placebo was administered during both induction and maintenance periods while in Study CT-P13 3.7, CT-P13 IV was administered during induction period and placebo was administered during maintenance period. Based on 60% clinical remission rate of CT-P13 SC 120 mg group and 15% delta, 45% clinical remission rate of Placebo group was applied on Study of CT-P13 3.7. Though observed clinical remission rate of Placebo SC group (20.8%) in the Study CT-P13 3.7 is lower than expected, it is similar compared to clinical studies of other drugs (Feagan et al., 2013; Sands et al., 2019), where 16%, and 24% of clinical remission rate in Placebo group were observed, respectively.

Additionally, Study CT-P13 3.7 considered patients with dose adjustment as non-responder which could have had impact on lower clinical remission rate for both CT-P13 SC 120 mg group and Placebo group.

The Applicant had limited historical sources with data for CT-P13 SC and Placebo SC at the time of study protocol development, thus the Applicant inevitably chose ACT1 and Study CT-P13 1.6 Part 2 for sample size assumption despite the differences described above.

Assessment of the MAH's response

The MAH argues that limited data was available at the time of study planning. This argument cannot be fully supported as treatment of this indication with the same MoA has been established for a long time.

As the MAH states, it appears that the lower absolute number of responders could be linked to the fact that

patients whose dose was escalated were automatically counted as non-responders. This further confirms the impression that the impact of dose escalation in both active and placebo groups on the overall robustness of the results was not adequately considered at the planning stage of the study. This impacts the robustness of the results at Week 54.

Conclusion

Issue not pursued further.

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

No need to update overall conclusion and impact on benefit-risk balance

Question 11

One analysis was included in the SAP to assess dose escalation: In addition, for the descriptive comparison of the treatment effect between patients with and without dose adjustment to CT-P13 SC 240 mg prior to Week 54 within CT-P13 SC treatment group, the primary endpoint was summarized by patients with and without dose adjustment in CT-P13 SC treatment group using frequency table without the statistical test. In this analysis, remitter was determined as per remission criteria regardless of dose adjustment. This analysis is, however, not included in the submitted dossier which is rather surprising considering the intended changes to the SmPC. This analysis should be provided.

Summary of the MAH's response

The Applicant would like to withdraw the proposed dose adjustment from CT-P13 SC 120 mg to 240 mg for UC patients with loss of response from the grouped variation for CD and UC indications. This is mainly due to lack of clinical data to statistically support the proposed dose adjustment for UC indication.

Consequently, responses to Questions 11-15, 18-22 and 24 are omitted in this response to RSI package.

Assessment of the **MAH's response**

The requested analysis was not provided. The results are covered by other questions and, hence, these tables do not need to be provided.

Conclusion

Issue resolved.

☐Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

Question 12

The Applicant is requested to provide a Figure of Patient Disposition which outlines for how many patients the dose was escalated at/after week 22.

Summary of the MAH's response

The Applicant would like to withdraw the proposed dose adjustment from CT-P13 SC 120 mg to 240 mg for

UC patients with loss of response from the grouped variation for CD and UC indications. This is mainly due to lack of clinical data to statistically support the proposed dose adjustment for UC indication.

Consequently, responses to Questions 11-15, 18-22 and 24 are omitted in this response to RSI package.

Assessment of the MAH's response

The requested Figure of Patient Disposition was not provided. Although the proposal for dose escalation was dropped for UC indication, the figure would have been relevant for assessment of the week 54 outcome. However, as only W22 data will be acceptable in the SPC, the issue is not pursued further.

Conclusion

Issue resolved.

Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

Question 13

It should be clarified how patients with progressive disease, who discontinued the study, differed from patients who received a dose increase. If possible, the differentiation should be displayed in the flow chart Figure of Patient Disposition.

Summary of the MAH's response

The Applicant would like to withdraw the proposed dose adjustment from CT-P13 SC 120 mg to 240 mg for UC patients with loss of response from the grouped variation for CD and UC indications. This is mainly due to lack of clinical data to statistically support the proposed dose adjustment for UC indication.

Consequently, responses to Questions 11-15, 18-22 and 24 are omitted in this response to RSI package.

Assessment of the MAH's response

The proposed dose escalation in UC patients with loss of response was withdrawn from the grouped variation application procedure. Questions related to this variation are no longer relevant.

Conclusion

Issue resolved

Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

Question 14

Baseline characteristics should be tabulated for patients who required/received dose escalation and compared to those who did not.

Summary of the MAH's response

The Applicant would like to withdraw the proposed dose adjustment from CT-P13 SC 120 mg to 240 mg for UC patients with loss of response from the grouped variation for CD and UC indications. This is mainly due to lack of clinical data to statistically support the proposed dose adjustment for UC indication.

Consequently, responses to Questions 11-15, 18-22 and 24 are omitted in this response to RSI package.

Assessment of the MAH's response

The proposed dose escalation in UC patients with loss of response was withdrawn from the grouped variation application procedure. Questions related to this variation are no longer relevant.

Conclusion

Issue resolved.

Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

Question 15

There are no tables depicting the details of the non-responder category at Week 54. The MAH should provide tables outlining the number of patients who were: a) non-responder according to the clinical criteria b) dose was escalated/switch to active c) discontinuation before Week 54 d) missing data e) incomplete data f) any other reason and corresponding combination categories.

Summary of the MAH's response

The Applicant would like to withdraw the proposed dose adjustment from CT-P13 SC 120 mg to 240 mg for UC patients with loss of response from the grouped variation for CD and UC indications. This is mainly due to lack of clinical data to statistically support the proposed dose adjustment for UC indication.

Consequently, responses to Questions 11-15, 18-22 and 24 are omitted in this response to RSI package.

Assessment of the MAH's response

The requested table was not provided. Although the proposal for dose escalation was dropped for UC indication, data on baseline characteristics for the main subgroups would have been relevant for assessment of the week 54 outcome. However, as only W22 data will be acceptable in the SPC, the issue is not pursued further.

Conclusion

Issue resolved.

Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

Question 16

Male and female patients achieved remission and response at week 54 with equal frequency in the CT-P13 SC 120 mg treatment arm. However, in the placebo arm, women seemed to achieve response almost twice as often as men and the difference between treatment and placebo was not as pronounced. According to corticoid-free remission, there was no clear difference between Remsima and placebo among women (38% of women in the treatment arm and 35% in the placebo arm were remitters at 54 weeks). The MAH should discuss whether this reflects a true gender difference in placebo response or if the different criteria leading to classification as a non-responder (corticosteroid use, dose increase, missing value) could have caused a discrepancy between sexes.

Summary of the MAH's response

In Study CT-P13 3.7 conducted in patients with ulcerative colitis (UC), there were fewer patients in the Placebo SC group compared to CT-P13 SC group. Small number of patients in the Placebo SC group may have had impact on the difference in clinical remission and response rate between male and female subgroups in the Placebo SC group. Also, patients with dose adjustment prior to Week 54 or patients with incomplete or missing modified Mayo score at Week 54 were considered as nonremitter/ non-responder for the primary and key secondary endpoints. The criteria for classification as a non-remitter/non-responder were the same for all enrolled patients (regardless of treatment or gender), however, more male patients were considered as non-remitter/non-responder. This may have had impact on the difference in clinical remission and response rate between male and female subgroups in the Placebo SC group as more male patients were considered as non-responder due to incomplete or missing modified Mayo score at Week 54 and dose adjustment prior to Week 54.

Total number of patients randomized in CT-P13 SC group and Placebo SC group was 294 and 144, respectively, and the number of patients in Placebo SC group were almost half of CT-P13 SC 120 mg group. Also, the number of male and female patients in the CT-P13 SC group was 163 and 131, respectively, and the number of male and female patients in the placebo SC group was 83 and 61, respectively. Similarly, male and female patients of Placebo SC group was almost a half of CT-P13 SC group. As Placebo SC group had small number of patients, there were limitations for interpreting the results. Small number of patients could have caused impact on the difference in clinical remission and response rate between male and female subgroups in the Placebo SC group.

The number of patients who had dose adjustment prior to Week 54 or with incomplete or missing modified Mayo score at Week 54 in the Placebo SC group was 57/83 (68.7%) in males and 34/61 (55.7%) in females, respectively. In CT-P13 SC 120 mg group, the number of patients who had dose adjustment prior to Week 54 or with incomplete or missing modified Mayo score at Week 54 was 53/163 (32.5%) in males and 39/131 (29.8%) in females, and difference in clinical remission and response rate between male and female was not observed. Dose adjustment and discontinuation from the study in the Placebo SC arm was allowed by investigator's judgement, regardless of treatment or gender. Total of dose adjustment prior to Week 54 and incomplete or missing values per the Statistical Analysis Plan of Study CT-P13 3.7 occurred more in male compared to female patients.

Lower clinical remission and clinical response rates in males compared to females in the Placebo SC group was shown in Table 1 and Table 2. As mentioned by CHMP, there was no clear difference in corticosteroid-free remission at Week 54 between CT-P13 SC 120 mg group and Placebo SC group among female patients (Table 3). However, this result was obtained only by chance due to the small number of patients are analysed for the corticosteroid-free remission. Only the patients who was treated with oral corticosteroid at baseline were included in the analysis. Also, in corticosteroid-free remission, the difference between the CT-P13 SC group and Placebo SC group in male and female was 26.3 and 4.2, respectively, which is within the difference (95% CI) of 17.3 [3.1, 28.9] between the CT-P13 SC group and Placebo SC group in total all-randomized population (Table 3).

Although a difference was seen in clinical remission and response rates between the male and female in the Placebo SC group, Applicant believes this was not a true gender difference. It might be a coincidental finding due to small number of patients in Placebo SC group and difference in number of patients classified as non-remitter/non-responder in male and female patients in the Placebo SC group based on the factors mentioned above.

Assessment of the MAH's response

The Applicant has provided the requested tables. As the difference between male and female is prominent in the placebo group, it is not linked to the MoA of the active treatment. It may not be a full chance finding; however, the difference does not appear to question the efficacy of CP-P13 in male and female patients.

Conclusion

Issue resolved

Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

Question 17

According to the label, available data suggest that clinical response is usually achieved within 14 weeks in the treatment of UC. This recommendation stems from the initial IV formulation and dosing intervals. The MAH is invited to discuss, whether another time point could be introduced with the current and newly proposed SC regimen.

Summary of the MAH's response

The Applicant would like to keep the time point for decision on continuation of treatment within 14 weeks of the infliximab treatment for UC.

As a biosimilar to Remicade, CT-P13 intravenous (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). After EC approval of CT-P13 IV, a subcutaneous formulation with the same active pharmaceutical ingredient (API) as CT-P13 IV has been developed (CT-P13 SC), and CT-P13 subcutaneous (SC) is also approved for treatment of same indications including UC as CT-P13 IV in line extension EMA/CHMP/548703/2019.

Compared to clinical response rate based on total Mayo score at Week 8 in ACT1 and ACT2 combined study (66.9%), clinical response rate based on total Mayo score at Week 10 in intent to treat population of Study CT-P13 3.7 (78.1%) showed similar result (Table 4). Considering that Week 8 in ACT1 and ACT2 study and Week 10 in Study CT-P13 3.7 are both the first visit after 3 induction doses, the Applicant believes that it is reasonable to compare Week 8 from ACT 1 and 2 studies and Week 10 from Study CT-P13 3.7.

As mentioned above, CT-P13 IV was approved as biosimilar to Remicade and Study CT-P13 1.6 demonstrated clinical similarity between CT-P13 IV and CT-P13 SC. In the Study CT-P13 3.7, clinical response rate after 3rd dosing of Infliximab IV 5mg/kg was similar to clinical response rate of ACT1 and ACT2 studies. Therefore, the Applicant would like to apply identical timepoints to observe achieved clinical response as the previously submitted label for CT-P13 SC (Table 5).

Table 76: Currently Approved and Proposed Table from the Label

Currently Approved	Proposed
Available data suggest that the clinical response is usually achieved within 14 weeks of treatment, i.e. 2 intravenous infusions and 4 subcutaneous injections (see section 5.1). Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within this time period.	Available data suggest that the clinical response is usually achieved within 14 weeks of treatment, ~~i.e. 2 intravenous infusions and 4 subcutaneous injections~~ (see section 5.1). Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within this time period.

Assessment of the MAH's response

It is acceptable not to change the approved wording.

Conclusion

Issue resolved.

Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

Question 18

The MAH should clarify how many patients in each treatment arm were eligible for a dose increase before Week 54 and how many got it. The data should be presented by sex, body weight, disease severity, drug concentration and ADA status. It should also be clarified which weeks the dose increase was initiated at, i.e for how long the patients were exposed to the higher dose.

Summary of the MAH's response

The Applicant would like to withdraw the proposed dose adjustment from CT-P13 SC 120 mg to 240 mg for UC patients with loss of response from the grouped variation for CD and UC indications. This is mainly due to lack of clinical data to statistically support the proposed dose adjustment for UC indication.

Consequently, responses to Questions 11-15, 18-22 and 24 are omitted in this response to RSI package.

Assessment of the MAH's response

The requested level of detail is no longer needed as the proposal for dose escalation was withdrawn.

Conclusion

Issue resolved.

Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

Question 19

The MAH should describe how the disease activity evolved among those who stayed on initial treatment regimen versus those who had a dose escalation. The analysis should be conducted for patients for whom

dose was escalated/not escalated and patients who were eligible for dose escalation but did not escalate/did escalate. Did regain of response occur in patients who continued on placebo? Spontaneous fluctuation of the disease should be discussed and comparison should be made to patients who did not escalate and to historical controls. The MAH should provide spaghetti plots (overlay and individual) where time point of dose escalation is standardized in the middle of the graph and 4 visits before and after dose escalation are included.

Summary of the MAH's response

The Applicant would like to withdraw the proposed dose adjustment from CT-P13 SC 120 mg to 240 mg for UC patients with loss of response from the grouped variation for CD and UC indications. This is mainly due to lack of clinical data to statistically support the proposed dose adjustment for UC indication.

Consequently, responses to Questions 11-15, 18-22 and 24 are omitted in this response to RSI package.

Assessment of the MAH's response

The requested level of detail is no longer needed as the proposal for dose escalation was withdrawn.

Conclusion

Issue resolved.

Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

Question 20

The MAH claims that for patients who adjusted the dose, the reduction in the efficacy scores was observed from their following scheduled visit after the first dose adjustment. Appropriate data should be provided to support this claim.

Summary of the MAH's response

The Applicant would like to withdraw the proposed dose adjustment from CT-P13 SC 120 mg to 240 mg for UC patients with loss of response from the grouped variation for CD and UC indications. This is mainly due to lack of clinical data to statistically support the proposed dose adjustment for UC indication.

Consequently, responses to Questions 11-15, 18-22 and 24 are omitted in this response to RSI package.

Assessment of the MAH's response

The requested level of detail is no longer needed as the proposal for dose escalation was withdrawn.

Conclusion

Issue resolved.

Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

Question 21

Did the groups (i.e., patients for whom dose was escalated/not escalated and patients who were eligible for dose escalation but did not escalate/did escalate) differ in terms of compliance with the protocol or other parameters which could describe their well-being in addition to the primary endpoint?

Summary of the MAH's response

The Applicant would like to withdraw the proposed dose adjustment from CT-P13 SC 120 mg to 240 mg for UC patients with loss of response from the grouped variation for CD and UC indications. This is mainly due to lack of clinical data to statistically support the proposed dose adjustment for UC indication.

Consequently, responses to Questions 11-15, 18-22 and 24 are omitted in this response to RSI package.

Assessment of the MAH's response

The requested level of detail is no longer needed as the proposal for dose escalation was withdrawn.

Conclusion

Issue resolved.

Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

Question 22

Did loss of response or regain of response correlate with PK and/or ADA titres? Did the subjects needing dose escalation have lower concentrations of CT-P13 during the induction treatment (placebo group) and during induction and maintenance treatment (CT-P13 group)? Did the subjects who regained response have higher concentrations of CT-P13 compared to those who did not? Was the need for dose escalation or failure to regain response associated with high ADA titres? Were high ADA titres associated with low drug concentrations?

Summary of the MAH's response

The Applicant would like to withdraw the proposed dose adjustment from CT-P13 SC 120 mg to 240 mg for UC patients with loss of response from the grouped variation for CD and UC indications. This is mainly due to lack of clinical data to statistically support the proposed dose adjustment for UC indication.

Consequently, responses to Questions 11-15, 18-22 and 24 are omitted in this response to RSI package.

Assessment of the MAH's response

The proposal for dose escalation was withdrawn and the question is no longer relevant for dose escalation. However, the data could influence a previously approved paragraph on immunogenicity in SPC section 4.8. As a clear correlation between loss of response and ADA titre was seen in CD, it is expected that ADA significantly influences also the efficacy in UC. The paragraph on immunogenicity in SPC section 4.8 needs to be justified or amended taking into account the new available data from study 3.7. The correlation

between loss of response and ADA status, median ADA titres and drug concentrations should be presented for both indications in tables where subgroups 1 and 3 are pooled and compared to subgroups 2 and 4, as defined in responses to Q 34.

Conclusion

Issue not resolved.

Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

Question 23

An analysis according to principal stratum estimand should be provided.

Summary of the MAH's response

As per the Agency's request, for the assessment of treatment effects within principal stratum composed by the target population where the intercurrent event would not occur, the analysis of primary and key secondary endpoints was conducted excluding patients who experienced dose adjustment prior to Week 54 (81 and 70 patients with dose adjustment in CT-P13 SC 120 mg and Placebo SC groups, respectively), where the dose adjustment was considered as the only intercurrent event in Study CT-P13 3.7 (Table 6).

The proportion of patients who achieved primary and key secondary endpoints was numerically higher in the CT-P13 SC 120 mg group than in the Placebo SC group. Regarding corticosteroid-free remission, no notable difference was seen between treatment groups. However, there is a limitation in interpreting results due to small sample size of patients with oral corticosteroid at baseline among patients who did not experience dose adjustment prior to Week 54. Additionally, despite the small number of patients, the difference (5.6%) in corticosteroid-free remission between treatment groups in the target population (which is a subset of All-randomized population) falls within the 95% CI (3.1%, 28.9%) of the difference in corticosteroid-free remission between treatment groups in the All-randomized population (W54 CSR CT-P13 3.7 Sections 11.4.1.1 and 11.4.1.2 [SN0264]).

In conclusion, the results for the primary and key secondary endpoints according to principal stratum estimand showed a consistent trend with the findings from the main analysis in the All-randomized population.

Table 77 Proportion of Patients Achieving Primary and Key Secondary Endpoints (principal stratum estimand): All-Randomized Population

	CT-P13 SC 120 mg (N=294)	Placebo (N=144)	Difference (95% CI)[1]	P-value[2]
Clinical remission at Week 54	127/213 (59.6%)	30/74 (40.5%)	17.1 (3.7, 29.4)	0.0094
Clinical response at Week 54	158/213 (74.2%)	45/74 (60.8%)	11.1 (-1.1, 23.8)	0.0673
Endoscopic-histologic mucosal improvement at Week 54	105/213 (49.3%)	24/74 (32.4%)	15.0 (1.8, 26.9)	0.0216
Corticosteroid-free remission at Week 54	44/77 (57.1%)	11/23 (47.8%)	5.6 (-16.9, 27.1)	0.6289

Sources: Section 5.3.5.3. Post-hoc Tables 2.227, 2.228, 2.229 and 2.230
Note: Analysis is stratified by Use of treatment with oral corticosteroids at Week 0 (used or not used) and Clinical remission at Week 10 (remitter or non-remitter by modified Mayo score). Except corticosteroid-free remission at Week 54, percentages are calculated using the number of patients without dose adjustment to CT-P13 SC 240 mg prior to Week 54 as the denominator.
Clinical remission is defined as modified Mayo score with a stool frequency subscore of 0 or 1, rectal bleeding subscore of 0, and endoscopic subscore of 0 or 1.
Clinical response is defined as a decrease in modified Mayo score from baseline of at least 2 points and at least 30%, with an accompanying decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1 point.
Endoscopic-histologic mucosal improvement is defined as an absolute endoscopic subscore of 0 or 1 point from modified Mayo score and an absolute Robarts Histopathology Index (RHI) score of 3 points or less with an accompanying laminal propria neutrophils and neutrophils in epithelium subscore of 0 point.
Corticosteroid-free remission is defined as being in clinical remission by modified Mayo score in addition to not requiring any treatment with corticosteroid for at least 8 weeks at Week 54, among the patients who used oral corticosteroids at baseline. Analysis is stratified by Use of treatment with oral corticosteroids at Week 0 (used or not used) and Clinical remission at Week 10 (remitter or non-remitter by modified Mayo score). Percentages are calculated by using the number of patients who used oral corticosteroids at baseline without dose adjustment to CT-P13 SC 240 mg prior to Week 54 as the denominator.
[1] The difference of proportions between two treatment groups estimated using CMH (Cochran-Mantel-Haenszel) weights, and the 95% stratified Newcombe CI with CMH weights are presented.
[2] The nominal p-value from stratified CMH test is presented in descriptive purpose.

Assessment of the MAH's response

It appears that Table 6 in MAH´s response is basically just an analysis restricted to patients with no dose escalation. This does not correspond to principal stratum estimand. The results are challenging to interpret because the groups are not comparable. However, the results do demonstrate the large overall impact of dose escalation on week 54 results and how the clinical response/remission data is actually largely replaced by whether dose was escalated/patients in the placebo arm switched to active treatment.

Conclusion

Issue not pursued further.

Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

Question 24

The MAH should discuss how the fact that patients and investigators were effectively unblinded at the time of dose escalation, impacts the results.

Summary of the MAH's response

The Applicant would like to withdraw the proposed dose adjustment from CT-P13 SC 120 mg to 240 mg for UC patients with loss of response from the grouped variation for CD and UC indications. This is mainly due to lack of clinical data to statistically support the proposed dose adjustment for UC indication.

Consequently, responses to Questions 11-15, 18-22 and 24 are omitted in this response to RSI package.

Assessment of the MAH's response

The requested discussion was not provided. Although the proposal for dose escalation was dropped for UC indication, the question on blinding would have been relevant for assessment of the week 54 primary outcome. However, as only W22 data will be acceptable in the SPC, the issue is not pursued further.

Conclusion

Issue not pursued further.

Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

Study CT-P13 3.8

Question 25

The proposed update of section 4.2 for Remsima SC includes a harmonisation of posologies between active Crohn's disease and fistulising active Crohn's disease but many patients with active fistulising CD were excluded from the study. Taking into account the exclusion criteria, the MAH should discuss how well the current study results and resulting amendments to the SPC are applicable to patients with active fistulising CD.

Summary of the MAH's response

Fistula is one of the complications in patients with Crohn's disease (CD), with approximately one third of CD patients experiencing fistulas during their disease course (Schari *et al*., 2017). TNFα signalling is known to be involved in mucosal damage as well as ulcer and fistula development through stimulation of macrophages, neutrophils and myofibroblasts, ultimately leading to tissue damage, remodeling and secondary effects on tissue damage (Di Sabatino *et al*., 2007). Therefore, infliximab is effective for both fistulising CD (fCD) and CD through its mechanism of inhibiting TNFα signalling. Infliximab was approved with the same dose for both indications.

CT-P13 subcutaneous (SC) has the same active pharmaceutical ingredient (infliximab) as CT-P13 intravenous (IV) and the totality of evidence from a number of studies including Studies CT-P13 1.6, CT-P13 3.7 and CT-P13 3.8 demonstrates that CT-P13 SC is as effective as CT-P13 IV as maintenance treatment.

Suggested therapeutic threshold of infliximab for IBD treatment is determined to be 5 μg/mL according to the guideline on therapeutic drug monitoring in inflammatory bowel disease (IBD) (Feuerstein *et al*., 2017). The optimal trough level of infliximab in patient with perianal fCD also identified as >7.1 μg/mL for both fistula healing and closure (Plevris *et al*., 2020). In Study CT-P13 3.8, trough concentration range of CT-P13 SC was shown from 13.3 to 14.8 μg/mL in patients with CD. The proposed dosing regimens of CT-P13 SC for fCD, which is the same as for CD, are expected to achieve and maintain the therapeutic thresholds at least one year.

Considering the mechanism of action and the therapeutic threshold of both fCD and CD, CT-P13 SC is expected to be effective in both fCD and CD. Therefore, the posology of CT-P13 SC approved for IBD indication is applicable for patients with fCD.

Assessment of the MAH's response

No harmonisation of posologies between active Crohn's disease and fistulising active Crohn's disease is proposed anymore. Therefore, the question is no longer relevant.

The newly included possibility to use a 3 IV induction regimen in addition to the 2 IV induction regimen is a minor amendment for which the small differences in the indications are not relevant. Therefore, the 3 IV regimen can be applied also to the fCD although such patients were not included in the clinical study.

Conclusion

Issue resolved.

☐Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

Question 26

In the protocol, a 2% response rate in placebo has been assumed for endoscopic response at Week 54. In the end 17.9% response rate was observed. The difference between the assumed (basically no responders) and observed (a meaningful proportion of responders) cannot be neglected because it reflects that either the study population or the behavior of the endpoint (potentially including data analysis), or something else, is not as expected. The MAH should elaborate on the potential root cause(s) for this finding.

Summary of the MAH's response

Since there was no historical data from infliximab for the endoscopic response at Week 54, historical data from study conducted with adalimumab was used for examination of the statistical power (Feagan *et al*., 2018) and the following limitations described below could have caused the difference between the assumed and observed response rate in Placebo SC group.

While only patients who had clinical response (by CDAI-100) to induction therapy was randomized and included in the analysis in Study CT-P13 3.8, all randomized patients were involved in the analysis regardless of patient's clinical response to the adalimumab induction therapy in the historical study of adalimumab (Rutgeerts *et al*., 2012). Given that the long-term efficacy of anti-TNF alpha treatment is not expected for patients who had not initial clinical response, those randomized patients who had no initial response may have affected the result in the low response rate of placebo group in the historical study of adalimumab.

According to the definition of endoscopic response in Study CT-P13 3.8, patients who had 50% reduction from baseline in SES-CD were classified as a responder. However, a patient with the same degree of SES-CD reduction who would have been classified as responder in Study CT-P13 3.8 was classified as non-responder in the historical adalimumab study because the endoscopic response was defined as more than 50% reduction from baseline in SES-CD. In other words, the endoscopic response standard for historical adalimumab study was slightly more conservative than Study CT- P13 3.8, thus, this difference in the endpoint definition may have had impact and led to lower assumed response rate for Placebo SC group in the study protocol as it was based on the historical adalimumab study.

Additionally, the literature reports that use of non-biologic agents such as MTX, AZA in CD studies also led to some degree of endoscopic response. For instance, in systematic review (Picco *et al.*, 2019), rates of endoscopic response in non-biologic treated patients could range between 8-30%. Therefore, some concomitant immunomodulatory therapies also contribute to the response rates. However, the use of concomitant immunomodulatory therapy was balanced between treatment groups in Study CT-P13 3.8. The treatment effect for SES-CD response between CT-P13 SC and placebo was 34.6 at Week 54 and was statistically and clinically meaningful supporting the superiority of the CT-P13 SC.

Assessment of the MAH's response

The MAH argues that the difference stems from the fact that at the planning stage the MAH had used an adalimumab study as reference which included responders and non-responders in the analysis.

Conclusion

The issue is not pursued further.

Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

Question 27

One analysis was included in the SAP to assess dose escalation: In addition, for the descriptive comparison of the treatment effect between patients with and without dose adjustment to CT-P13 SC 240 mg prior to Week 54 within CT-P13 SC treatment group, the primary endpoint was summarized by patients with and without dose adjustment in CT-P13 SC treatment group using frequency table without the statistical test. In this analysis, remitter was determined as per remission criteria regardless of dose adjustment. This analysis is, however, not included in the submitted dossier which is rather surprising considering the intended changes to the SmPC. This analysis should be provided.

Summary of the MAH's response

The Applicant would like to clarify that results for the questioned analysis included in the statistical analysis plan (SAP) for dose escalation assessment was submitted in the following parts of the dossier:

1. W54 CSR CT-P13 3.8 Post-text Tables 14.2.1.1Z and 14.2.1.2Z [SN0264]
2. W54 CSR CT-P13 3.8 Sections 11.4.1.1.1.2 and 11.4.1.1.2.2 [SN0264]
3. CTD Module 2.7.3 Section 4.3 [SN0264]

Analyses on the co-primary endpoints (clinical remission based on CDAI score and endoscopic response based on central SES-CD score at Week 54) were summarized for patients with or without dose adjustment in CT-P13 SC 120 mg treatment group using frequency table without statistical test. For these analyses on the treatment effect in patients with dose adjustment, remitter/responder was determined as per remission/response criteria regardless of dose adjustment. The results table for these analyses in All-randomized Population were presented in CSR CT-P13 3.8 Post-text Tables 14.2.1.1Z and 14.2.1.2Z, respectively, as included in the SAP.

Assessment of the MAH's response

The analysis provided is extremely simplistic considering the fundamental impact of dose escalation to the

results at Week 54. It does show that in the active arm there were 39 patients whose dose was escalated and 21 of them where responders at week 54. Of note, in the primary analysis, all 39 were counted as non-responders although 5 of the patients never lost response but received a dose increase anyway.

Conclusion

Issue not pursued further.

Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

Question 28

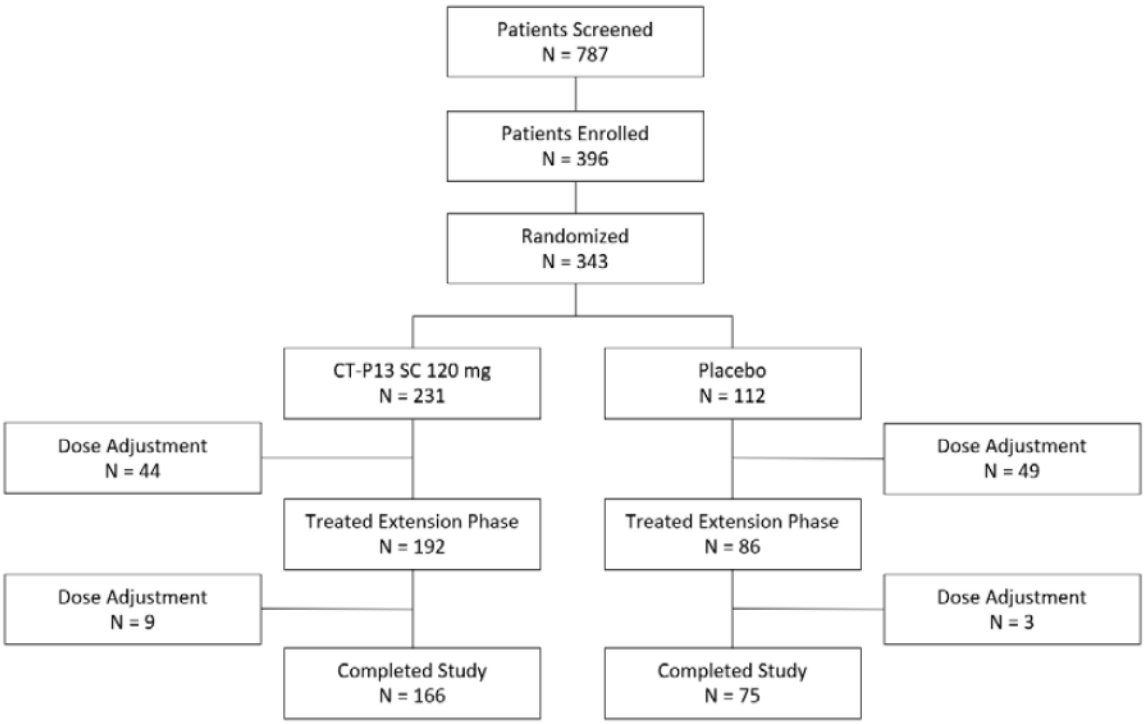
The Applicant is requested to provide a Figure of Patient Disposition which outlines for how many patients the dose was escalated at/after week 22.

Summary of the MAH's response

In Study CT-P13 3.8, dose adjustment to CT-P13 SC 240 mg was allowed from Week 22 through Week 102 when the patient met loss of response criteria defined in the protocol. In the Maintenance Phase, dose was adjusted at least once for a total of 93 (27.1%) patients (44 [19.0%] and 49 [43.8%] patients in the CT-P13 SC 120 mg and Placebo groups, respectively) in all-randomised population. In the Extension Phase, a total of 12 (3.5%) patients (9 [3.9%] and 3 [2.7%] patients in the CT-P13 SC 120 mg and Placebo groups, respectively) had dose adjustment at least once for the first time in all-randomised population. In the whole Treatment Period up to Week 102, dose was adjusted at least once for a total of 105 (30.6%) patients (53 [22.9%] and 52 [46.4%] patients in the CT-P13 SC 120 mg and Placebo groups, respectively).

The number of dose adjusted patients for the safety population is reported in the W54 and Final clinical study reports (CSRs). In the Maintenance Phase, dose was adjusted at least once for a total of 93 (27.1%) patients (45 [18.9%] and 48 [45.7%] patients in the CT-P13 SC 120 mg and Placebo groups, respectively) in safety population. In the whole Treatment Period up to Week 102, dose was adjusted at least once for a total of 105 (30.6%) patients (54 [22.7%] and 51 [48.6%] patients in the CT-P13 SC 120 mg and Placebo groups, respectively) in safety population.

As per request, the Applicant has identified the distribution of patients with dose adjustment at/after Week 22 in all-randomised population, and a flow-chart outlining the number and proportion of patients with dose adjustment at/after Week 22 is provided in Figure 1.



Sources: Final CSR CT-P13 3.8 Post-text Table 14.1.1 and Section 5.3.5.3 Post-hoc Table 2.238
Abbreviation: SC, subcutaneous

Figure 37: Flow Chart of Patient Disposition of Study CT-P13 3.8: All-randomised Population

Assessment of the MAH's response

The number of patients with dose adjustment has been presented as requested. The numbers do not fully comply with the response to 27 and it would have been appreciated is this would have been proactively discussed.

Conclusion

Issue resolved.

☐Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

Question 29

It should be clarified how patients with progressive disease who discontinued the study differed from patients who received a dose increase. If possible, the differentiation should be displayed in the flow chart Figure of Patient Disposition.

Summary of the MAH's response

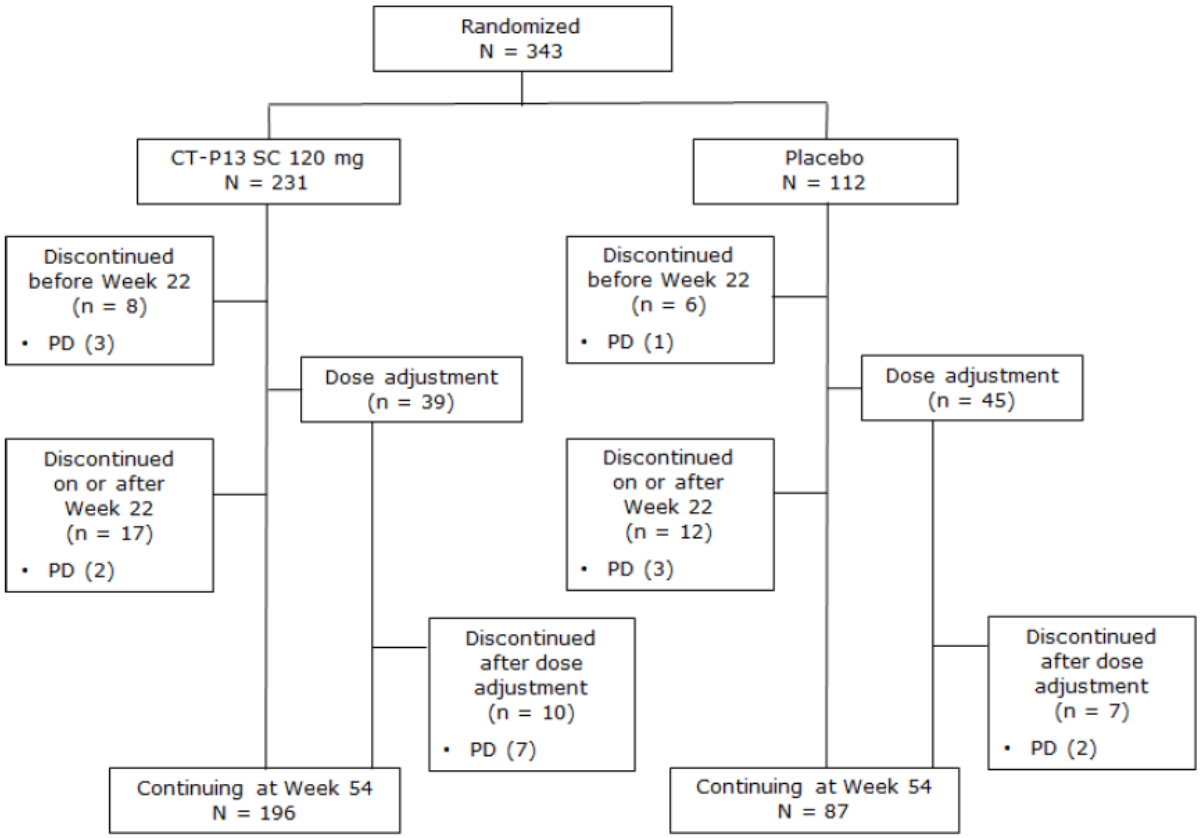
According to the protocol of Study CT-P13 3.8, dose adjustment was provided to patients who met the loss

of response (LoR) criteria from Week 22. The protocol specified the definition of LoR as an increase in Crohn's disease activity index (CDAI) of ≥100 points from the Week 10 CDAI score with a total score ≥220. Disease progression was decided by the investigator if the disease had worsened continuously or if the patient was considered to lack the benefit of study continuation. Dose adjustment and disease progression had different indicators and were independently decided. In other words, the patient could be discontinued by disease progression even after receiving an adjusted dose.

As requested, the Applicant provides the flow chart of patient disposition regarding discontinuation for all-randomised population (Figure 2).

In all-randomised population, 8 patients discontinued before Week 22 in CT-P13 SC 120 mg group. A total of 39 patients in CT-P13 SC 120 mg group had received adjusted dose before Week 54 visit. Among patients who discontinued on or after Week 22, 10 patients discontinued (7 patients by disease progression as primary reason) after dose adjustment and 17 patients discontinued (2 patients by disease progression as primary reason) without dose adjustment.

In placebo group, 6 patients discontinued before Week 22. A total of 45 patients had received adjusted dose before Week 54 visit. Among patients who discontinued on or after Week 22, 7 patients discontinued (2 patients by disease progression as primary reason) after dose adjustment and 12 patients discontinued (3 patients by disease progression as primary reason) without dose adjustment.



Note: The number of patients who discontinued during the maintenance phase was counted up to the Week 54 visit.
Source: Section 5.3.5.3 Post-hoc Table 3.117
Abbreviations: PD, progressive disease; SC, subcutaneous.

Figure 38: Flow Chart of Patient Disposition of Study CT-P13 3.8: All-randomised Population

Assessment of the MAH's response

The MAH has explained that dose adjustment and disease progression had different indicators and were independently decided. It is still not entirely clear why some patients with disease progression were not offered a dose escalation but were discontinued instead. However, as this was the case only for 2 patients in each treatment arm, it has no impact on final conclusions and the issue will not be pursued further.

The flow chart provided in Q28 shows that 44 patients received dose adjustment while the flow chart provided in Q29 shows 39 patients receiving dose adjustment. The difference should be clarified.

Conclusion

Issue not resolved.

Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

Question 30

There is a discrepancy in the reported number of patients analysed. It is stated that 11 patients with major protocol deviation were excluded from the PP population, only one of whom was in the CT-P13 arm.

However, in Table 10-2 of the CSR (Table 7.2.3.1 of the AR) it is stated that 7 major protocol deviations occurred in the CT-P13 arm and 4 in the placebo arm. The numbers should be clarified and aligned.

Summary of the MAH's response

The discrepancy as noted by the Agency is caused by the different definition of population analysis in Study CT-P13 3.8.

The all-randomized population was analysed according to the planned treatment group (i.e, randomized treatment group) which was assigned at Week 10 randomly, while safety and per- protocol (PP) population were analysed according to the actual treatment group. The actual treatment group was assigned according to their treatment actually administered during the double-blind maintenance phase, even if there was a discrepancy between the treatment actually administered and the randomized group. If there was a patient with such a discrepancy, the patient receiving at least one dose of CT-P13 SC prior to initiation of dose adjustment during the double-blind maintenance phase was treated as CT-P13 SC 120 mg group. All other patients were treated as placebo group as per statistical analysis plan (SAP) Study CT-P13 3.8 Section 5.4, and as reported in CSR Study CT-P13 3.8 Section 9.7.1.2 Population of analysis. Therefore, the number of patients reported in each treatment group was different between all-randomized population based on randomized treatment group (CT-P13 SC 120 mg group: 231 patients; Placebo group: 112 patients) and safety population based on actual treatment group (CT-P13 SC 120 mg group: 238 patients; Placebo group: 105 patients) even if the total number of patients was the same in both analysis populations.

A total of 11 patients were counted as major protocol deviation in Table 10-2 (Major Protocol Deviations) from the CT-P13 3.8 CSR, and 7 and 4 patients were classified as CT-P13 SC 120 mg group and placebo group based on the 'all-randomized population', respectively. However, based on the safety population (actual treatment group which was the same analysis criteria of PP population), 8 and 3 patients were classified as CT-P13 SC 120 mg group and placebo group since one patient in placebo group based on all-randomized population received at least one dose of CT-P13 SC during the maintenance phase. This means the actual treatment group for this patient was CT-P13 SC 120 mg group.

The applicant would like to stress that the number of patients excluded from each treatment group in PP population should be compared with safety population not with the all-randomized population. Since the PP population was based on actual treatment group like safety population, 238 patients would be included in CT-P13 SC 120 mg group in PP population if there was no major protocol deviation. However, the number of patients with major protocol deviation in CT-P13 SC 120 mg group based on actual treatment group was 8 (Table 7). Given that 8 of 238 patients in CT-P13 SC 120 mg group are required to be excluded from the PP population, the number of patients in CT-P13 SC 120 mg group in PP population should be 230. As a result, the results in Table 11-1 Population of analysis from the CSR of Study CT-P13 3.8 are correct.

Assessment of the MAH's response

The discrepancies have been clarified and a table with more detailed descriptions of the major protocol deviations was provided in the response document.

Conclusion

Issue resolved.

Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

Question 31

Baseline characteristics should be tabulated for patients who required/received dose escalation and compared to those who did not.

Summary of the MAH's response

As per request, baseline characteristics of patients in Study CT-P13 3.8 by dose adjustment status is presented below in Table 8. In Study CT-P13 3.8, there was no meaningful difference between the subgroups of patients who required or received dose adjustment compared to those who did not, in terms of baseline characteristics.

Table 78 (Truncated for brevity): Baseline Characteristics by Dose Adjustment Status in Study CT-P13 3.8: All-randomised Population

	With Dose Adjustment[1]		Not Required / Not Dose Adjusted	
	CT-P13 SC 120 mg (N'=39)	Placebo (N'=45)	CT-P13 SC 120 mg (N'=177)	Placebo (N'=53)
Screening BMI (kg/m^2)				
n	39	45	177	53
Mean (SD)	24.410 (5.0903)	22.475 (4.7291)	23.073 (4.2419)	22.732 (4.1938)
Median (min, max)	24.050 (16.95, 34.54)	21.460 (15.93, 34.72)	22.480 (14.2, 34.61)	22.210 (16.04, 33.75)
Previous exposure to biologic agent and/or JAK inhibitors, n (%)				
Used	3 (7.7%)	5 (11.1%)	19 (10.7%)	3 (5.7%)
Not used	36 (92.3%)	40 (88.9%)	158 (89.3%)	50 (94.3%)
Use of Treatment with oral corticosteroids at Week 0, n (%)				
Used	22 (56.4%)	22 (48.9%)	69 (39.0%)	17 (32.1%)
Not used	17 (43.6%)	23 (51.1%)	108 (61.0%)	36 (67.9%)

[1] With Dose Adjustment Group includes subgroup of patients regardless of whether the LoR criteria are met.

Assessment of the MAH's response

The only baseline characteristic where some difference was seen between the subgroups of patients who received dose adjustment compared to those who did not was the use of oral corticosteroids at baseline. Among patients who received a dose escalation the use of oral corticosteroids was more frequent at baseline compared to those who did not require a dose increase. This difference was seen in both treatment groups and could possibly reflect a more severe form of disease among those who lost response.

The basis for assessment of the efficacy of an escalated dose would have been comparison between the outcome following dose escalation versus no dose escalation in patients who lost response. Therefore, baseline characteristics should have been provided for all subgroups 1-4 as defined in Q 34. However, as no randomisation occurred, the groups are not comparable in any case. Some unknown factors lead to different decisions regarding dose escalation among patients who lost response but these factors and their impact on the primary outcome cannot be reliably assessed. Therefore, this issue is not pursued further.

Conclusion

Issue not pursued further.

Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

Question 32

There are no tables depicting the details of the non-responder category at Week 54. The MAH should provide tables outlining the number of patients who were: a) non-responder according to the clinical criteria b) dose was escalated/switch to active c) discontinuation before Week 54 d) missing data e) incomplete data f) any other reason and corresponding combination categories.

Summary of the MAH's response

In Protocol Study CT-P13 3.8, non-remitter or non-responder were defined as below.

For the efficacy endpoints *related remission or response, the following patients were considered as non-remitter or non-responder:*

- *Patients who did not met th*e remission or response criteria
- Patients with missing or incomplete data for the evaluation of each endpoint at their scheduled visit of interest, even after applying the data handling rule
- Patients with dose adjustment to CT-P13 SC 240 mg prior to their scheduled visit of interest

As requested by the Agency, the Applicant analysed the non-remitter or non-responder at Week 54 with detailed reasons. Patients with two or more reasons for being considered as non-remitter/non- responder are included in one of the reasons in following order; c) discontinuation before Week 54 –

b) dose escalation or switch to CT-P13 SC from placebo – e) incomplete data – d) missing data – a) non-remitter/non-responder according to the criteria – f) any other reason.

Incomplete data and missing data were categorized by following rules. Incomplete data is the case when data was collected in CDAI diary but there were invalid data for more than 4 days (or at least 1 day at screening) or when at least 1 component of CDAI score is missing. Missing data is the case when data was collected as 'No' in CRF, thus the evaluation was not conducted.

Since the patients who had dose adjustment prior to Week 54 were considered as non-remitter or non-responder at Week 54 in the analysis of co-primary endpoints and key secondary endpoints, patients who were considered as non-remitter or non-responder at Week 54 are summarised for co-primary endpoints and key secondary endpoints. The results are presented in Table 9 for co-primary endpoints and Table 10 for key secondary endpoints.

The most frequent reason for being considered as non-remitter or non-responder in co-primary endpoints analysis for each endpoint were 'Dose escalation or switch to CT-P13 SC from placebo' and 'Non-responder according to the clinical criteria' for clinical remission (based on CDAI) and endoscopic response (based on SES-CD [Central]), respectively. The proportion of patients who were non-remitter or non-responder due to 'Dose escalation or switch to CT-P13 SC from placebo' was higher in placebo group, which led to much higher proportion of non-remitter/non-responder in placebo group. This result also suggests that patients in the placebo group had higher chance of loss of response and dose escalation as a result of receiving placebo instead of CT-P13 SC. Similar results were observed for key secondary endpoints.

Table 79: Number of Patients who were Non-remitter/Non-responder for Co-primary Endpoints at Week 54 in Study CT-P13 3.8: All-randomised Population

Endpoint Non-remitter/non-responder Reason for non-remitter/non-responder	CT-P13 SC (N=231)	Placebo (N=112)	Total (N=343)
Clinical Remission (Based on CDAI) [1]	**144 (62.3%)**	**36 (32.1%)**	**180 (52.5%)**
Non-remitter	**87 (36.7%)**	**76 (67.9%)**	**163 (47.5%)**
Discontinuation before Week 54	34 (14.7%)	21 (18.8%)	55 (16.0%)
Dose escalation or switch to CT-P13 SC from placebo	29 (12.6%)	40 (35.7%)	69 (20.1%)
Incomplete data	0	0	0
Missing data	0	0	0
Non-remitter according to the clinical criteria	24 (10.4%)	15 (13.4%)	39 (11.4%)
Endoscopic Response (Based on SES-CD [Central]) [2]	**118 (51.1%)**	**20 (17.9%)**	**138 (40.2%)**
Non-responder	**113 (48.9%)**	**92 (82.1%)**	**205 (59.8%)**
Discontinuation before Week 54	34 (14.7%)	21 (18.8%)	55 (16.0%)
Dose escalation or switch to CT-P13 SC from placebo	29 (12.6%)	40 (35.7%)	69 (20.1%)
Incomplete data	0	0	0
Missing data	7 (3.0%)	3 (2.7%)	10 (2.9%)
Non-responder according to the clinical criteria	43 (18.6%)	28 (25%)	71 (20.7%)

Sources: W54 CSR CT-P13 3.8 Post-text Tables 14.2.1.1, 14.2.1.2 [SN0264] and Section 5.3.5.3 Post-hoc Table 2.220
Note: A patient with two or more reasons for non-responder/non-remitter is included in one of the reasons in following order; c) discontinuation before Week 54 – b) dose escalation or switch to CT-P13 SC from placebo – e) incomplete data – d) missing data – a) non-remitter/non-responder according to the criteria – f) any other reason. There were no cases due to 'any other reason.'
[1] Clinical remission is defined as an absolute CDAI score of less than 150 points.
[2] Endoscopic response is defined as a 50% decrease in SES-CD score from the baseline value.
Abbreviations: CDAI, Crohn's disease activity index; SES-CD. simplified endoscopic activity score for Crohn's disease

Assessment of the MAH's response

As expected, the proportion of patients who were non-remitter or non-responder due to 'Dose escalation or switch to CT-P13 SC from placebo' was higher in the placebo group. The difference in proportion of remitters/responders at week 54 is mainly driven by the automatic classification as a non-remitter in case of a dose escalation. While it is not known how many of the patients who received a dose escalation could have been responders at week 54 despite the loss of response at or after week 22, some indication of the possibility of renewed response is seen in the answer to Q35: In both treatment arms, there were 7 patients who met the loss of response criteria but did not receive a dose adjustment. Of these patients, one patient in each group (14.3%) was in clinical remission at week 54. Hence, the ability to regain response is possible but not frequent.

Overall, it is clearly visible that the non-remmitter and non-responser categories consist mainly of other categories than no clinical response. The impact of intercurrent events on the overall results is large. In the active arm the most frequent ICEs are discontinuation and dose escalation (14.7% and 12.6%). In the placebo group, the most common ICE is dose escalation (36%) followed by discontinuation (19%), that is, more than half of the patients in the placebo group had an ICE before reaching the timepoint of the primary analysis. Hence, the inclusion of possibility for dose escalation in the protocol, does not allow for accurate assessment of the primary endpoint of interest. Afterall, this was a placebo controlled study because there is the possibility to maintain a response without any treatment after induction until week 54 and responder-status can also fluctuate over time.

Nevertheless, the difference in proportion of remitters is considered clinically meaningful and the magnitude of the difference sufficiently large such that the results can be overall concluded to be relevant to be included in Section 5.1. However, in the SPC, the MAH should include information that dose escalated patients were non-responders. See annotated SPC.

Conclusion

Issue resolved.

Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

Question 33

According to the current label, available data suggest that clinical response is usually achieved within 6 weeks in the treatment of CD and 14 weeks in the treatment of fistulising CD. With the current variation, the MAH proposes to change the timing for decision on continuation of treatment to 10 weeks for both CD and fistulising CD. Since patients with active fistulising CD were excluded, Study CT-P13 3.8 cannot directly support this change for all fistulising CD. Furthermore, no discussion on this aspect of the amended wording was provided in the dossier. The MAH should provide scientific justification for the newly proposed time frame for decision making in both CD and fistulising CD. It should also be noted that decision after 6 weeks of treatment is still recommended with IV Remsima in CD and that this wording for IV is bound by the originator wording.

Summary of the MAH's response

The Applicant would like to keep the timepoint for the decision on the continuation of infliximab treatment for CD within 6 weeks.

The clinical response rates of CT-P13 IV at Week 6 in Study CT-P13 3.8 were as high as clinical response rates of Infliximab historical Study (i.e., SONIC Study; Colombel *et al*, 2010) and the results are provided in Table 11.

Table 80: Proportion of Patients Achieving CDAI-70 Response and CDAI-100 Response Based on CDAI in Study CT-P13 3.9 and SONIC (Infliximab historical)

Study	CT-P13 3.8	SONIC	
Dosage	CT-P13 IV 5mg/kg	IFX 5mg/kg (Monotherapy)	IFX 5mg/kg + AZA (Combined therapy)
	Number (%) of patients		
CDAI -70 response at Week 6	308/396 (77.8)	109/169 (64.5)	125/169 (74.0)
CDAI -100 response at Week 6	271/396 (68.4)	92/169 (54.4)	107/169 (63.3)

Source: Section 5.3.5.3 Post hoc table 2.221, Supplement to Colombel *et al*. 2010.
Note: Percentages are calculated by using the total number of patients in the ITT Population as the denominator and the total number of responders as numerators in Study CT-P13 3.8.
Abbreviations: AZA, azathioprine; CDAI, crohn's disease activity index; IFX, infliximab; IV, intravenous.

As mentioned above, CT-P13 IV was approved as biosimilar to Remicade and Study CT-P13 1.6 demonstrated clinical similarity between CT-P13 IV and CT-P13 SC. In the Study CT-P13 3.8, clinical response rate at Week 6 was similar to the clinical response rate of SONIC study. Therefore, the Applicant would like to apply identical timepoints to observe achieved clinical response as the previously submitted label for CT-P13 SC (Table 12).

Assessment of the MAH's response

Only the timepoint related to the CD indication was discussed in the response. Based on the presented results it is acceptable to maintain the 6 weeks for CD. No new data on fistulising CD has been presented and therefore it is endorsed to keep the approved wording, i.e 14 weeks before decision on continuation.

Conclusion

Issue resolved.

Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

Question 34

The MAH should clarify how many patients in each treatment arm were eligible for a dose increase before Week 54 and how many got it. The data should be presented by sex, body weight, disease severity, drug concentration and ADA status. It should also be clarified which weeks the dose increase was initiated at, i.e for how long the patients were exposed to the higher dose.

Summary of the MAH's response

In Study CT-P13 3.8, dose adjustment to CT-P13 SC 240 mg was allowed from Week 22 when the patient met loss of response (LoR) criteria defined in the protocol. The LoR was defined as an increase in Crohn's disease activity index (CDAI) of ≥100 points from the Week 10 CDAI score with a total score ≥220.

Of 343 patients for all-randomised population, 328 (95.6%) patients who had CDAI score on or after Week 22 visit including Unscheduled and End of study visit are categorised into 4 subgroups according to LoR and dose adjustment from Week 22 prior to Week 54; patients with dose adjustment meeting LoR (subgroup 1), patients with dose adjustment not meeting LoR (subgroup 2), patients without dose adjustment meeting LoR (subgroup 3), patients without dose adjustment not meeting LoR (subgroup 4).

The number of patients in each subgroup and summary of sex, body weight, disease severity, pre- dose serum concentration and anti-drug antibody (ADA) status according to 4 subgroups are provided in Table 13.

A total of 41 patients in CT-P13 SC 120 mg group and 48 patients in placebo group experienced LoR (subgroups 1 and 3). Among these patients, 34/41 (82.9%) in CT-P13 SC 120 mg group and 41/48 (85.4%) in placebo group received adjusted dose (subgroup 1). In contrast, 182 patients in CT-P13 SC 120 mg group and 57 patients in placebo group did not meet LoR criteria (subgroups 2 and 4). Among these patients, 5/182 (2.7%) in CT-P13 SC 120 mg group and 4/57 (7.0%) in placebo group received adjusted dose but were not eligible for the dose adjustment (subgroup 2).

In both CT-P13 SC 120 mg group and placebo group, sex, and body weight show no notable differences among the subgroups. Disease severity with mean CDAI score collected at specific timepoint for each subgroup (at dose adjustment visit for subgroups 1 and 2, at first occurrence of LoR for subgroup 3, and at Week 22 visit for subgroup 4) are similarly highest in subgroups 1 and 3, followed by subgroup 2, and lowest in subgroup 4. This trend is similar between CT-P13 SC 120 mg group and placebo group. The mean pre-dose serum concentration analysed in subgroup 1 (at dose adjustment visit) of CT-P13 SC 120 mg group shows the lowest, followed by subgroup 3 (at first occurrence of LoR), subgroup 2 (at dose adjustment visit) and subgroup 4 (at Week 22 visit) in CT- P13 SC 120 mg group. The patients who experienced LoR (subgroups 1 and 3) show higher disease severity and lower pre-dose serum concentration compared to the patients who did not experience LoR and not received adjusted dose (subgroup 4) in CT-P13 SC 120 mg group. In addition, the patients who received adjusted dose without LoR (subgroup 2) also show higher disease severity and lower pre-dose serum concentration compared to the patients of subgroup 4 in CT-P13 SC 120 mg group. However, these results should be interpreted taking into account the number of patients in subgroups 2 and 3. Since the serum concentrations in placebo group shown in Table 13 were collected during maintenance phase, when placebo

group received placebo SC, interpretation by subgroups would be unnecessary. The serum concentrations by subgroups of placebo group are analysed for Induction Phase treating CT-P13 IV in Response to Question 38. There was no notable difference of ADA positive rate across the subgroups.

The visit for first dose adjustment before Week 54 visit and duration of dose adjustment for subgroups 1 and 2 are summarised in Table 14. In subgroup analysis, the visit of the most patients received their first dose adjustment at Week 22 visit, when the dose adjustment was first allowed. No meaningful trend was observed in mean durations of exposure to adjusted dose in subgroups of CT-P13 SC 120 mg group and placebo group; 20.1 weeks and 28.0 for subgroup 1, 31.0 weeks and 27.1 weeks for subgroup 2, respectively.

Table 81: Summary of Demographics, CDAI score, Pre-dose Serum Concentration, ADA Status by Dose Adjustment Status in Study CT-P13 3.8: All-randomised Population

		CT-P13 SC (N=223)				Placebo (N=105)			
		subgroup 1 (N' = 34)	subgroup 2 (N' = 5)	subgroup 3 (N' = 7)	subgroup 4 (N' = 177)	subgroup 1 (N' = 41)	subgroup 2 (N' = 4)	subgroup 3 (N' = 7)	subgroup 4 (N' = 53)
Gender									
male	n (%)	20 (58.8)	3 (60)	2 (28.6)	105 (59.3)	26 (63.4)	1 (25)	4 (57.1)	34 (64.2)
female	n (%)	14 (41.2)	2 (40)	5 (71.4)	72 (40.7)	15 (36.6)	3 (75)	3 (42.9)	19 (35.8)
Screening weight (kg)	mean (SD)	71.71 (20.767)	69.94 (21.003)	60.34 (11.327)	68.57 (14.526)	68.90 (16.480)	66.83 (20.371)	71.17 (17.862)	66.88 (13.721)
CDAI score	mean (SD)	283.47 (68.404)	194.66 (58.432)	293.51 (60.668)	77.74 (60.017)	295.64 (53.045)	152.35 (57.310)	301.57 (80.402)	78.11 (56.805)
Change from baseline, CDAI score	mean (SD)	-32.71 (61.995)	-151.60 (54.567)	-46.90 (86.438)	-231.02 (80.718)	-19.22 (62.997)	-118.05 (51.631)	-16.79 (121.254)	-222.95 (69.885)
Serum concentration (ng/mL)	mean (SD)	8547.0 (8436.42)	13260.0 (7983.92)	12235.7 (8142.46)	15509.1 (8725.68)	696.9 (2177.42)	143.3 (59.45)	100.0 (0.00)	385.9 (698.93)
ADA status									
positive	n (%)	20 (58.8)	4 (80)	4 (57.1)	79 (44.6)	28 (68.3)	3 (75)	5 (71.4)	38 (71.7)
negative	n (%)	14 (41.2)	1 (20)	3 (42.9)	98 (55.4)	13 (31.7)	1 (25)	2 (28.6)	15 (28.3)

Source: Section 5.3.5.3 Post-hoc Table 1.171

Note: Loss of response (LoR) is defined as following: an increase in CDAI of >=100 points from the Week 10 CDAI score with a total score >=220. The patients who have at least one CDAI result on or after Week 22 including Unscheduled and EOS visit are categorised according to LoR and dose adjustment from Week 22 prior to Week 54. Percentages are calculated using the number of patients in each subgroup as denominator. When the result for corresponding visit was missing, the latest result before the visit was used instead.

4 subgroups were categorised among the patients who had CDAI score on or after Week 22 visit including Unscheduled and End of study visit; patients with dose adjustment meeting LoR (subgroup 1), patients with dose adjustment not meeting LoR (subgroup 2), patients without dose adjustment meeting LoR (subgroup 3), patients without dose adjustment not meeting LoR (subgroup 4). CDAI score, pre-dose serum concentration and ADA status include data that were collected at dose adjustment for subgroups 1&2, collected at first occurrence of LoR for subgroup 3, and collected at Week 22 for subgroup 4.

N': the number of patients in the subgroup

Abbreviations: ADA, anti-drug antibody; CDAI, Crohn's disease activity index; LoR, Loss of response; SC, subcutaneous; SD, standard deviation.

Assessment of the MAH's response

A total of 41 patients (18%) in the CT-P13 SC 120 mg group and 48 patients (46%) in the placebo group experienced LoR (subgroups 1 and 3) by week 54. Among these patients, 34/41 (82.9%) in CT-P13 SC 120 mg group and 41/48 (85.4%) in placebo group received adjusted dose (subgroup 1).

In the CT-P13 SC 120 mg group, those who experienced LoR were more often ADA positive compared to those who maintained response. Referring to the answer to Q31, patients who experienced LoR may have had a more treatment resistant form of CD at baseline since the use of oral corticosteroids was more frequent among those who received a dose escalation at baseline compared to those who did not require a dose increase. However, patients who received dose escalation are not the same as the LoR group as patients who received dose escalation also included patients without a loss of response by prespecified criteria.

Loss of response was obviously accompanied by high CDAI scores but also patients who did not meet the criteria for LoR but received a dose increase anyway had markedly higher CDAI scores than those who continued on the previous dose. The decision to increase the dose for these patients is a protocol violation which seems to have been driven by the clinicians' desire to improve the treatment for poor responders,

but it exposes poor adherence to GCP. Such violations occurred in 9/328 patients (2.7%). The frequency is small enough not to pursue the issue further.

Patients who had a LoR but did not receive a dose adjustment were more often female but did not seem to differ from those who did receive a dose adjustment in any of the other reported aspects. However, as no randomisation occurred and the decision to increase the dose was based on un documented factors, the groups (subgroups 1 and 3) are not comparable.

A clear difference between patients who experienced LoR and those who did not is seen in terms of serum drug concentration at loss of response. This finding supports the theory of loss of response being associated with suboptimal drug concentrations.

Most patients received their first dose adjustment at Week 22 visit, when the dose adjustment was first allowed.

Conclusion

Issue resolved.

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

No need to update overall conclusion and impact on benefit-risk balance

Question 35

The MAH should describe how the disease activity evolved among those who stayed on initial treatment regimen versus those who had a dose escalation. The analysis should be conducted for patients for whom dose was escalated/not escalated and patients who were eligible for dose escalation but did not escalate/did escalate. Did regain of response occur in patients who continued on placebo? Spontaneous fluctuation of the disease should be discussed and comparison should be made to patients who did not escalate and to historical controls. The MAH should provide spaghetti plots (overlay and individual) where time point of dose escalation is standardized in the middle of the graph and 4 visits before and after dose escalation are included.

Summary of the MAH's response

For the assessment of disease activity, mean actual Crohn's disease activity index (CDAI) score at newly defined baseline (hereafter referred to as the "baseline") and Week 54 were evaluated. The baseline was newly defined as the visit of dose adjustment for subgroups 1 and 2, visit of occurrence of LoR from Week 22 for subgroup 3 and Week 22 for subgroup 4, respectively.

Although the small number of people in subgroup 3 should be interpreted with caution, the dose adjustment might induce higher improvement in disease activity than spontaneous recovery. (Table 15)

Table 82: CDAI Score for Patients by Dose Adjustment Status in Study CT-P13 3.8: All-randomised Population

CDAI score		CT-P13 SC (N=223)				Placebo (N=105)			
		subgroup 1 (N' = 34)	subgroup 2 (N' = 5)	subgroup 3 (N' = 7)	subgroup 4 (N' = 177)	subgroup 1 (N' = 41)	subgroup 2 (N' = 4)	subgroup 3 (N' = 7)	subgroup 4 (N' = 53)
Baseline	n	34	5	7	177	41	4	7	53
	mean (SD)	283.47 (68.404)	194.66 (58.432)	293.51 (60.668)	77.74 (60.017)	295.64 (53.045)	152.35 (57.310)	301.57 (80.402)	78.11 (56.805)
Week 54	n	24	5	4	164	36	3	5	46
	mean (SD)	105.77 (77.704)	94.42 (107.064)	258.23 (136.908)	77.63 (70.374)	98.91 (70.199)	81.40 (70.520)	227.68 (176.350)	102.42 (94.688)
Week 54 Change from baseline	n	24	5	4	164	36	3	5	46
	mean (SD)	-163.93 (74.396)	-100.24 (131.430)	-31.35 (117.949)	1.18 (61.615)	-193.58 (89.517)	-98.47 (52.017)	-57.98 (210.789)	27.33 (101.950)

Source: Section 5.3.5.3 Post-hoc Table 2.223

Note: Loss of response (LoR) is defined as following: an increase in CDAI of >=100 points from the Week 10 CDAI score with a total score >=220. The patients who have at least one CDAI result on or after Week 22 including Unscheduled and EOS visit are categorised according to LoR and dose adjustment from Week 22 prior to Week 54.

Four subgroups; patients with dose adjustment meeting LoR (subgroup 1), patients with dose adjustment not meeting LoR (subgroup 2), patients without dose adjustment meeting LoR (subgroup 3), patients without dose adjustment not meeting LoR (subgroup 4). When the result for corresponding visit was missing, the latest result before the visit was used instead for all subgroups.

Baseline for each subgroup was defined as following:

- With/Without LoR and With Dose Adjustment (subgroup 1 and 2) - Visit of Dose adjustment
- With LoR and Without Dose Adjustment (subgroup 3) - Visit of first occurrence of LoR from Week 22
- Without LoR and Without Dose Adjustment (subgroup 4) - Week 22

N': the number of patients in the subgroup

Abbreviations: CDAI, Crohn's disease activity index; SC, subcutaneous; SD, standard deviation.

There were no available historical data for the comparison for spontaneous fluctuation of the disease activity score (before/after meeting LoR criteria) depending on the dose adjustment status. However, the Applicant found the same trend with Study CT-P13 3.8 in Remicade historical data (D'Haens G *et al.,* 2018 and Katz L *et al.,* 2012) that doubling the infliximab IV dose (5 mg/kg every 8 weeks → 10 mg/kg every 8 weeks) for patients who had LoR would induce regain clinical response, although it is inappropriate to directly compare the efficacy results of dose adjustment due to the difference of study design.

In the CT-P13 SC 120 mg group, most of co-primary/key secondary endpoints results were higher in patients with dose adjustment (subgroup 1 and 2) than patients without dose adjustment meeting LoR criteria (subgroup 3), except for endoscopic response and endoscopic remission at Week 54. (Table 16)

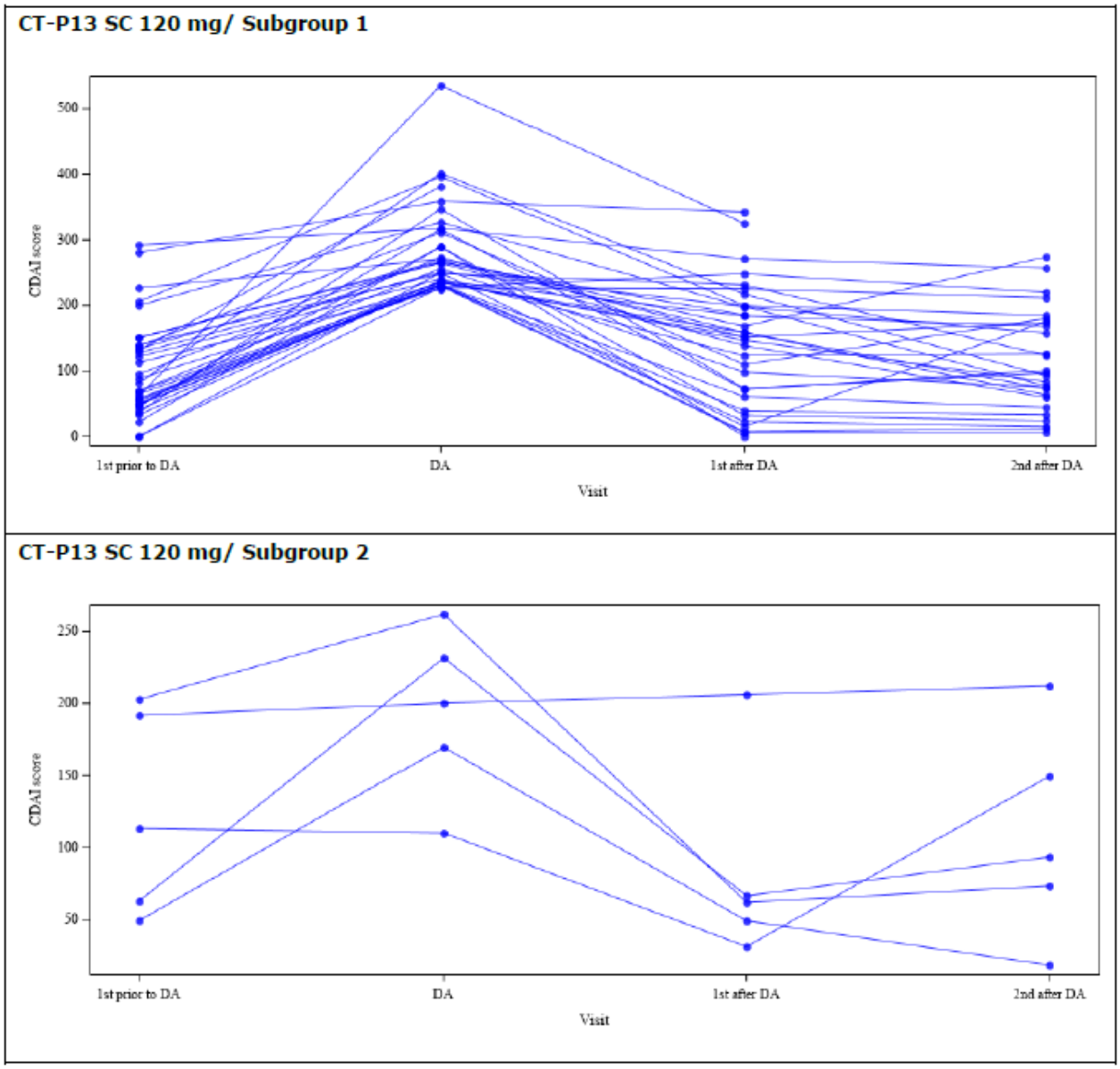
Table 83: Proportions of Patients Achieving Co-primary and Key Secondary Endpoints by Dose Adjustment Status: All-randomised Population

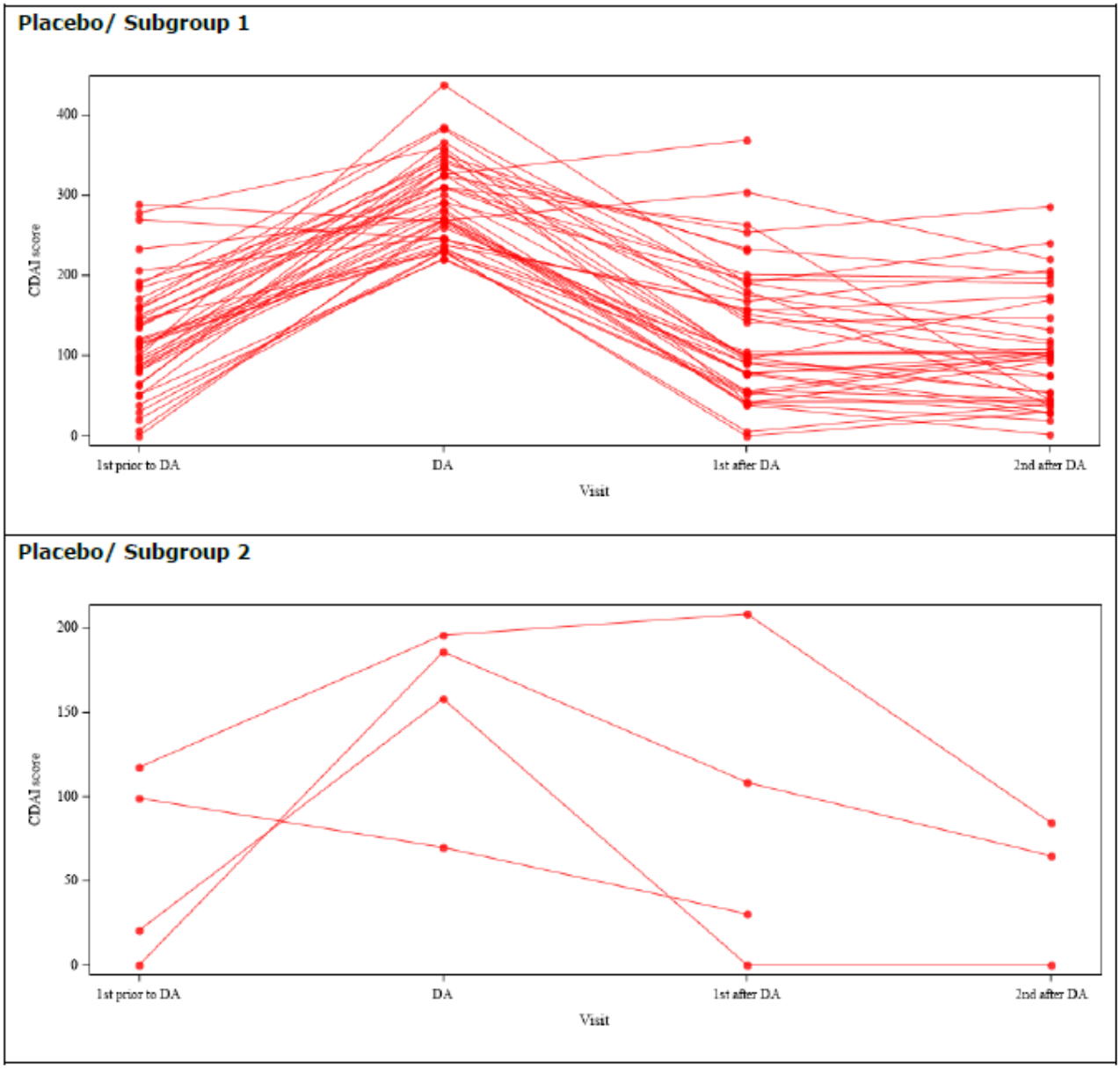
	CT-P13 SC (N=223)				Placebo (N=105)			
	subgroup 1 (N' = 34)	subgroup 2 (N' = 5)	subgroup 3 (N' = 7)	subgroup 4 (N' = 177)	subgroup 1 (N' = 41)	subgroup 2 (N' = 4)	subgroup 3 (N' = 7)	subgroup 4 (N' = 53)
Co-primary endpoints								
Clinical Remission (Based on CDAI) at Week 54	17 (50%)	4 (80%)	1 (14.3%)	143 (80.8%)	27 (65.9%)	3 (75%)	1 (14.3%)	35 (66.0%)
Endoscopic Response at Week 54	7 (20.6%)	4 (80%)	3 (42.9%)	115 (65.0%)	24 (58.5%)	1 (25%)	3 (42.9%)	17 (32.1%)
Key secondary endpoints								
Regained clinical response (CDAI-100) at Week 54	21 (61.8%)	3 (60%)	2 (28.6%)	150 (84.7%)	31 (75.6%)	3 (75%)	3 (42.9%)	40 (75.5%)
Clinical remission (Based on AP/SF) at Week 54	17 (50%)	3 (60%)	1 (14.3%)	130 (73.4%)	29 (70.7%)	3 (75%)	1 (14.3%)	34 (64.2%)
Endoscopic remission at Week 54	3 (8.8%)	2 (40%)	2 (28.6%)	78 (44.1%)	13 (31.7%)	1 (25%)	2 (28.6%)	10 (18.9%)
Corticosteroid-free remission at Week 54	5/17 (29.4%)	2/5 (40%)	0/5	40/69 (58.0%)	11/19 (57.9%)	1/3 (33.3%)	0/2	10/17 (58.8%)

Source: Section 5.3.5.3 Post-hoc Table 2.222

An analysis of overlay and individual spaghetti plots of CDAI score at the time of dose adjustment and 4 visits before and after dose adjustment for subgroup 1 and 2 for CT-P13 SC and placebo groups are provided in Figure 3. Overall, the CDAI scores of patients with dose adjustment showed decreasing trend compared to the visit of the dose adjustment in both subgroup 1 and 2 in the CT-P13 SC group. Similar trend of results was observed in the placebo group as well.

Figure 39: CDAI Score versus Time by Dose Adjustment Status





Source: Section 5.3.5.3 Post-hoc Figure 2.051
Note: LoR is defined as following: an increase in CDAI of >=100 points from the Week 10 CDAI score with a total score >=220. The patients who have at least one CDAI result on or after Week 22 including Unscheduled and EOS visit are categorised according to LoR and dose adjustment from Week 22 prior to Week 54. Two subgroups; patients with dose adjustment meeting LoR (subgroup 1), patients with dose adjustment not meeting LoR (subgroup 2). Two CDAI results prior to dose adjustment and 2 results after dose adjustment excluding EOS are displayed for each patient. The CDAI result at the time of the dose adjustment is the result right before the dose adjustment according to protocol.
Abbreviations: CDAI, Crohn's disease activity index; DA, dose adjustment; LoR, loss of response; SC, subcutaneous.

Assessment of the MAH's response

Among the 34 patients with dose adjustment in the CT-P13 SC 120 mg group 17 (50%) patients achieved clinical remission by CDAI and 7 (20.6%) patients achieved endoscopic response at Week 54. On the other hand, in the 7 patients who experienced a LoR but did not receive a dose adjustment, regain of clinical remission by CDAI occurred in 1/7 (14.3%) and endoscopic response re-emerged in 3 (42.9%) of these patients on initial active treatment. Regain of response occurred in 21/34 (61.8%) patients with a dose

escalation while patients who lost response but remained on active treatment had a renewed response in 2 (28.6%) cases. Spontaneous regain of response and remission was also seen in patients who remained on placebo (3 and 1 patients, respectively).

Although the numbers are small, it can be concluded that spontaneous regain of response is not negligible. However, regain of response according to CDAI is more common and the improvement in absolute CDAI score is more pronounced in patients with a dose adjustment than in those who remained on initial treatment despite a LoR. There is no clear difference between dose adjusted LoR and dose maintained LoR patients in terms of endoscopic response but the number of patients who regain endoscopic response after LoR is small and does not permit conclusions.

Based on the provided spaghetti plots, the loss of response was usually not seen at the previous visit before DA (usually week 14). Improvement in CDAI scores was usually seen 8 weeks after DA and was usually maintained for the next 8 weeks. Some patients did not respond at all to the DA and some lost response again after a brief improvement but overall, a majority of patients in the active treatment arm who received a DA had a positive outcome 16 weeks after DA.

Conclusion

Although spontaneous regain of response does occur, regain of response is more common and the improvement in absolute CDAI score seems to be more pronounced in patients with a dose adjustment than in those who remained on initial treatment despite a LoR. A majority of patients in the active treatment arm who received a dose adjustment had a positive outcome 16 weeks after the dose increase.

Issue resolved.

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

No need to update overall conclusion and impact on benefit-risk balance

Question 36

The MAH claims that for patients who adjusted the dose, the reduction in the efficacy scores was observed from their following scheduled visit after the first dose adjustment. Appropriate data should be provided to support this claim.

Summary of the MAH's response

Overlay and individual spaghetti plots of CDAI score before and after dose adjustment for patients with dose adjustment are provided in Question 35. Overall, the CDAI scores of patients with dose adjustment generally decreased after the dose adjustment.

For assessment of change in scores for patients with dose adjustment, mean actual CDAI or SES-CD score of patients who had efficacy measurements at both first dose adjustment visit (just before first adjusted dose treatment) and Week 54 was evaluated. Compared to the first dose adjustment visits, patients with dose adjustment from CT-P13 SC 120 mg to CT-P13 SC 240 mg had almost a half reduction in mean CDAI score at Week 54, and approximately 20% reduction in mean SES-CD score after dose adjustment.

Table 84: Change in Mean CDAI and SES-CD Score for Patients with Dose Adjustment in CT-P13 SC 120 mg Group in Study CT-P13 3.8: All-randomised Population

Endpoint	First visit of dose adjustment (just before first adjusted dose treatment)	Week 54	Mean Change	p-value[1]
CDAI	256.37 (n=28)	105.43 (n=28)	-150.94	<0.0001
SES-CD	7.8 (n=16)	6.5 (n=16)	-1.3	0.1237

Sources: Section 5.3.5.3 Post-hoc Tables 2.123 and 2.124 [SN0264]

Note: The patients with dose adjustment before Week 54 who had efficacy measurements at both dose adjustment visit and Week 54 are included in this summary. For the first visit of dose adjustment, the CDAI and SES-CD scores are measured just before the first dose adjustment.

[1] P-value for difference in the mean of actual value between dose adjustment visit and Week 54 visit within treatment group was obtained by paired t-test.

Abbreviations: CDAI, Crohn's disease activity index; SES-CD, simplified endoscopic activity score for Crohn's

Change in disease activity scores for patients by dose adjustment status were summarised in Question 35.

The time to achieve clinical response and clinical remission is provided in Table 19.

Table 85: Time to Achieve Clinical Remission/Clinical Response after Dose Adjustment: All-Randomised Population

		CT-P13 SC 120mg (N=231)
Time to achieve clinical remission (days)	n	27
	Mean (SD)	74.7 (34.73)
Time to achieve clinical response (days)	n	26
	Mean (SD)	65.2 (29.92)

Assessment of the MAH's response

Based on the plots provided in Q 35 it is agreed that CDAI scores of patients with dose adjustment generally decreased after the dose adjustment and the change was usually seen at the first scheduled visit after the dose adjustment.

Conclusion

Issue resolved

Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

Question 37

Did the groups (i.e., patients for whom dose was escalated/not escalated and patients who were eligible for dose escalation but did not escalate/did escalate) differ in terms of compliance with the protocol or other parameters which could describe their well-being in addition to the primary endpoint?

Summary of the MAH's response

Table 86: Major Protocol Deviation by Dose Adjustment Status in Study CT-P13 3.8: All-randomised Population

	CT-P13 SC 120 mg (N=231)	Placebo (N=112)
	Number (%) of patients	
Major protocol deviation	7/231 (3.0%)	4/112 (3.6%)
Patients with dose adjustment meeting LoR (Subgroup 1)	0/34 (0%)	1/41 (2.4%)
Patients with dose adjustment not meeting LoR (Subgroup 2)	1/5 (20%)	0/4 (0%)
Patients without dose adjustment meeting LoR (Subgroup 3)	0/7 (0%)	0/7 (0%)
Patients without dose adjustment not meeting LoR (Subgroup 4)	6/177 (3.4%)	3/53 (5.7%)

Source: Section 5.3.5.3 Post-hoc Table 3.118
Note: A patient was not summarised in this table, since he was excluded from all populations due to significant GCP non-compliance of the 3001 site. LoR is defined as following: an increase in CDAI of ⩾100 points from the Week 10 CDAI score with a total score ⩾220. The patients who have at least one CDAI result on or after Week 22 including Unscheduled and EOS visit are categorised according to LoR and dose adjustment from Week 22 prior to Week 54. Four subgroups; patients with dose adjustment meeting LoR (subgroup 1), patients with dose adjustment not meeting LoR (subgroup 2), patients without dose adjustment meeting LoR (subgroup 3), patients without dose adjustment not meeting LoR (subgroup 4).
Percentages are calculated using the number of patients in each subgroup as denominator.
Abbreviations: CDAI, Crohn's disease activity index; EOS, end of study; LoR, loss of response; SC, subcutaneous.

Table 87: Number of Patients who Achieved Clinical Remission by PGS at Week 54 by Dose Adjustment Status in Study CT-P13 3.8: All-randomised Population

	CT-P13 SC 120 mg (N=231)	Placebo (N=112)
	Number (%) of patients	
Patients with dose adjustment meeting LoR (Subgroup 1)	16/34 (47.1%)	32/41 (78.0%)
Patients with dose adjustment not meeting LoR (Subgroup 2)	3/5 (60%)	2/4 (50%)
Patients without dose adjustment meeting LoR (Subgroup 3)	1/7 (14.3%)	3/7 (42.9%)
Patients without dose adjustment not meeting LoR (Subgroup 4)	138/177 (78.0%)	37/53 (69.8%)

Assessment of the MAH's response

There was no relation between dose adjustment status and protocol compliance or patient's well-being.

Conclusion

Issue resolved

Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

Question 38

Did loss of response or regain of response correlate with PK and/or ADA titres? Did the subjects needing dose escalation have lower concentrations of CT-P13 during the induction treatment (placebo group) and during induction and maintenance treatment (CT-P13 group)? Did the subjects who regained response have higher concentrations of CT-P13 compared to those who did not? Was the need for dose escalation or failure to regain response associated with high ADA titres? Were high ADA titres associated with low drug concentrations?

Summary of the MAH's response

Loss of Response and PK (Pre-dose Serum Concentration) and/or Immunogenicity (ADA Titer)

As requested by the agency, post-hoc analysis was performed to see the correlation between loss of response (LoR) and PK level by analysing the pre-dose concentration of infliximab at major timepoints by dose adjustment status (Table 88). Data for induction phase were collected at Week 10. Data for maintenance phase were collected at dose adjustment for subgroup 1&2, were collected at first occurrence of LoR for subgroup 3, and were collected at Week 22 for subgroup 4.

Table 88: Pre-dose Serum Concentration at Major Timepoints by Dose Adjustment status

		CT-P13 SC (N=223)				Placebo (N=105)			
		subgroup 1 (N' = 34)	subgroup 2 (N' = 5)	subgroup 3 (N' = 7)	subgroup 4 (N' = 177)	subgroup 1 (N' = 41)	subgroup 2 (N' = 4)	subgroup 3 (N' = 7)	subgroup 4 (N' = 53)
Induction phase	n	34	5	6	174	41	4	7	52
	Mean (SD)	10796.2 (5673.33)	10522.8 (7141.18)	9064.0 (6837.88)	13074.6 (7623.11)	13794.7 (8094.16)	11282.5 (6676.81)	13608.6 (4686.06)	15532.5 (8543.96)
Maintenance phase	n	34	5	7	177				
	Mean (SD)	8547.0 (8436.42)	13260.0 (7983.92)	12235.7 (8142.46)	15509.1 (8725.68)	-	-	-	-

Source: Section 5.3.5.3 Post-hoc Table 1.175

Note: All concentrations (ng/mL) BLQ after study drug exposure are set equal to LLoQ. Pre-dose concentrations (ng/mL) are included in this summary. LoR is defined as following: an increase in CDAI of >=100 points from the Week 10 CDAI score with a total score >=220. The patients who have at least one CDAI result on or after Week 22 including Unscheduled and EOS visit are categorised according to LoR and dose adjustment from Week 22 prior to Week 54. Four subgroups; patients with dose adjustment meeting LoR (subgroup 1), patients with dose adjustment not meeting LoR (subgroup 2), patients without dose adjustment meeting LoR (subgroup 3), patients without dose adjustment not meeting LoR (subgroup 4). When the result for corresponding visit in Maintenance Phase was missing, the latest result before the visit was used instead. Data for induction phase were collected at Week 10. Data for maintenance phase were collected at dose adjustment for subgroup 1&2, were collected at first occurrence of LoR for subgroup 3, and were collected at Week 22 for subgroup 4.

N': the number of patients in the subgroup

Abbreviations: BLQ, below the lower limit of quantification; CDAI, Crohn's disease activity index; LLoQ, lower limit of quantification; LoR, loss of response; SC, subcutaneous; SD, standard deviation.

Table 89: ADA Titer at Major Timepoint by Dose Adjustment Status

		CT-P13 SC (N=223)				Placebo (N=105)			
		subgroup 1 (N' = 34)	subgroup 2 (N' = 5)	subgroup 3 (N' = 7)	subgroup 4 (N' = 177)	subgroup 1 (N' = 41)	subgroup 2 (N' = 4)	subgroup 3 (N' = 7)	subgroup 4 (N' = 53)
Maintenance phase	n	21	4	5	80	28	3	5	38
	Mean (SD)	2553.0 (9949.98)	1323.0 (2520.00)	441.0 (707.17)	695.6 (2500.15)	294.0 (433.40)	231.0 (290.98)	138.6 (69.01)	363.6 (878.21)

Source: Section 5.3.5.3 Post-hoc Table 1.176

Clinical Response Regain and PK (Pre-dose Serum Concentration) and/or Immunogenicity (ADA Titer)

In CT-P13 SC 120 mg group, the mean pre-dose concentration of patients who regained CDAI-100 response (at Week 54) was higher than patients who did not regained CDAI-100 response (at Week 54) at both dose adjustment visit and Week 54 visit. But the increase of mean pre-dose concentration from initiation of dose adjustment to Week 54 was much higher in patients who regained CDAI-100 response (at Week 54) than in patients who did not regain CDAI-100 response (at Week 54).

In both treatment groups, higher increase of mean/median PK level has been shown for patients who regained clinical response than in patients who did not regain clinical response.

Table 90: Pre-dose Concentration (ng/mL) by Clinical Response Regain

		CT-P13 SC 120 mg (N=231)		Placebo (N=112)	
		Regained CDAI-100 response	Not regained CDAI-100 response	Regained CDAI-100 response	Not regained CDAI-100 response
At Dose adjustment visit	n	24	15	34	11
	Mean (SD)	11590.4 (8028.09)	5248.5 (7777.68)	222.0 (260.59)	1963.5 (4041.38)
At Week 54 visit	n	24	13	34	10
	Mean (SD)	21951.7 (14692.14)	12224.6 (15944.66)	28993.2 (16721.02)	12499.5 (13174.55)

Source: Section 5.3.5.3 Post-hoc Table 1.173
Note: Only patients having dose adjustment prior to Week 54 are summarised. The latest result before initiation of dose adjustment was used for Dose Adjustment Visit. Missing data at Week 54 was carried forward from the last non-missing value after initiation of dose adjustment.
All concentrations (ng/mL) BLQ after study drug exposure are set equal to LLoQ. Pre-dose concentrations (ng/mL) are included in this summary.
Abbreviations: BLQ, below the lower limit of quantification; CDAI, Crohn's disease activity index; LLoQ, lower

The post-hoc analysis was performed to see the correlation between ADA titer and the regain of response by analysing the ADA titer by the clinical response regain for patients with dose adjustment (Table 25).

The mean ADA titer was increased from initiation of dose adjustment visit to Week 54 visit for patients who regained CDAI-100 response at Week 54 in both treatment groups.

For patient who did not regain CDAI-100 response, mean ADA titer was decreased from initiation of dose adjustment visit to Week 54 visit in CT-P13 120 mg group. However, in Placebo group, mean ADA titer was increased from initiation of dose adjustment visit to Week 54 visit.

There was no consistent trend between clinical response regain and ADA titer. However, it is important to interpret the findings based on ADA titer and clinical response regain with caution due to the limited number of patients in each group.

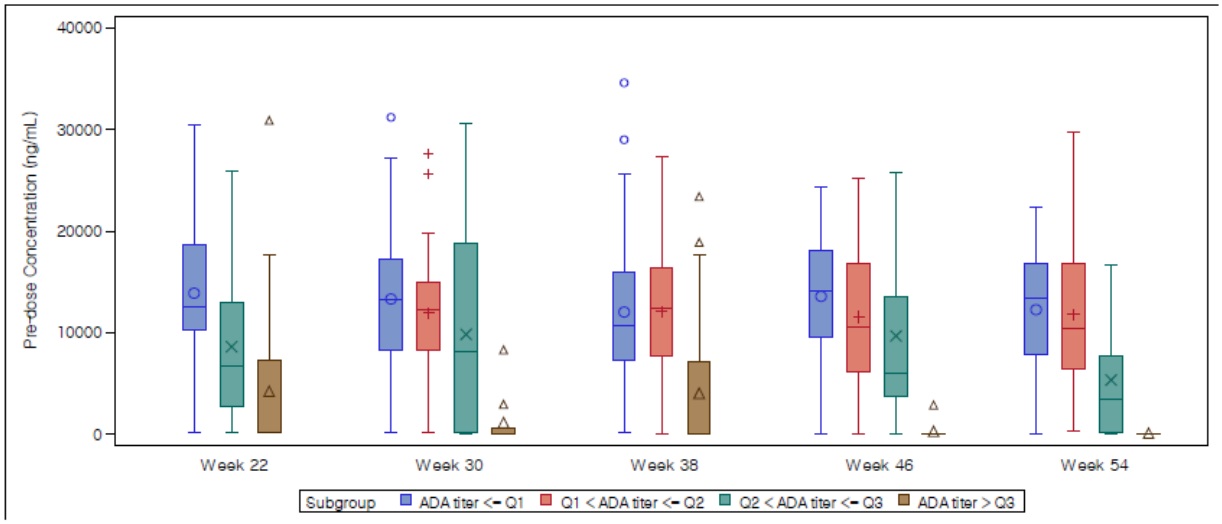
Table 91: ADA Titer by Clinical Response Regain

		CT-P13 SC 120 mg (N=231)		Placebo (N=112)	
		Regained CDAI-100 response	Not regained CDAI-100 response	Regained CDAI-100 response	Not regained CDAI-100 response
ADA titer at Dose adjustment visit	n	14	11	23	8
	Mean (SD)	3411.0 (12237.77)	1013.7 (1478.41)	251.1 (369.61)	393.8 (551.02)
ADA titer at Week 54 visit	n	15	11	17	7
	Mean (SD)	9493.4 (35492.43)	868.6 (810.24)	436.1 (1209.45)	7425.0 (17077.20)

Source: Section 5.3.5.3 Post-hoc Table 1.174
Note: Only patients having dose adjustment prior to Week 54 are summarised. The latest post-treatment result before initiation of dose adjustment was used for Dose Adjustment Visit. Missing data at Week 54 was carried forward from the last non-missing value after initiation of dose adjustment.
Abbreviations: CDAI, Crohn's disease activity index; SC, subcutaneous; SD, standard deviation.

PK (Pre-dose Serum Concentration) and Immunogenicity (ADA Titer)

Box plot of pre-dose concentration by visit-based ADA titer quartile (Table 26) is provided in Figure 4. As shown in Figure 4, there was a trend for pre-dose concentration to decrease as ADA titer increases in the CT-P13 SC 120 mg group.



Source: Section 5.3.5.3 Post-hoc Figure 1.017

Note: All below the lower limit of quantifications after study drug exposure were set to Lower Limit of Quantification (LLoQ). The patients who have ADA result and pre-dose concentration are categorised by ADA titer quartile at each visit in the Pharmacokinetic population. For patients with dose adjustment, data collected before initiation of dose adjustment are included in this figure.

The 25th and 50th percentiles are the same at Week 22, and the 50th and 75th percentiles are the same at Week 38.

Abbreviations: ACE, affinity capture elution; ADA, anti-drug antibody; ECL, electrochemiluminescence; MSD, Meso Scale Discovery; SC, subcutaneous.

Figure 40: Box plot of Pre-dose Concentration by Visit-based ADA Titer Quartile

Assessment of the MAH's response

Patients who never lost response had slightly higher drug concentrations after the induction phase at week 10 compared to those who lost response. A slight difference in the same direction was seen even among those who continued on placebo. Based on the numerical values, higher concentrations after induction might be correlated with a better maintenance of response but the groups are still fairly comparable at week 10 in terms of PK.

Samples collected at LoR, or at week 22 if no LoR occurred, indicate a correlation between LoR and lower drug concentrations. For proper statistical comparison of drug concentrations, subgroups 1 and 3 should have been pooled and compared to the pooled subgroups 2 and 4. Patients with dose adjustment despite not meeting LoR criteria (subgroup 2) had lower drug concentrations compared to subgroup 4 at both induction phase and maintenance phase. These patients also had higher (worse) CDAI scores. Since subgroup 2 only includes 5 patients and these patients were not treated according to protocol, the results of subgroup 2 are difficult to interpret.

The MAH has presented a table comparing drug concentrations among dose adjusted responders at week 54 to dose adjusted non-responders at week 54. According to table 24 drug concentrations are higher among responders. However, since the table compares all dose adjusted patients and not only those who had a loss of response, the term "regained response" is not accurate, and the results do not answer the original question. To enable meaningful assessment of the correlation between regain of response and drug concentrations the MAH should have present a table including only LoR patients.

Mean ADA titres were substantially higher among patients who lost response compared to those who did not. Again, pooled results of subgroups 1 and 3 should have been compared to pooled results of subgroups 2 and 4 but the presented numbers indicate correlation between high ADA titres and LoR. Table 25, depicting ADA titres in relation to regain of response does not enable meaningful interpretation for two

reasons. Patients with and without LoR were pooled together and patients without any ADA seem to have been excluded. While it seems that loss of response could be due to a more pronounced development of ADAs and lower drug concentrations as a result, it is still unclear whether failure to regain response is correlated with high ADA titres.

From the box plot it is evident that higher ADA titres have a higher impact on drug concentrations. But it is not known how a dose increase affects the development of ADA. Some studies have shown that higher drug concentrations might counteract the development of ADAs but it is not known whether this is true for patients who have already developed high titres of ADA. While increasing the dose may be a solution to LoR in the short term, it is not known whether or how fast the development of new ADAs will neutralise the potential benefit of such a dose adjustment. Moreover, as loss of response frequently results from high ADA titres and decreased drug concentrations, the drug concentrations are not expected to be doubled after a dose increase among patients who lost response.

Conclusion

PK analysis by subgroups indicate a correlation between lower drug concentrations and LoR. This association does not seem to be entirely driven by any imbalance in concentrations at baseline (after induction). It seems that loss of response is often due to a more pronounced development of ADAs (higher titres) and lower drug concentrations as a result.

It is still unclear how drug concentrations developed among those with a dose increase and for how long patients with high ADA titres at dose adjustment could maintain a potential benefit from a higher dose. However, as these are not an issues which could affect the wording in SPC, they will not be pursued further.

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

No need to update overall conclusion and impact on benefit-risk balance

Question 39

An analysis according to principal stratum estimand should be provided.

Summary of the MAH's response

An analysis according to principal stratum estimand should be provided.

Summary of the MAH's response

As per Agency's request, for the assessment of treatment effects within principal stratum composed by the target population where the intercurrent event would not occur, the analysis of co-primary and key secondary endpoints was conducted excluding patients who experienced dose adjustment prior to Week 54 (39 and 35 patients with dose adjustment in CT-P13 SC 120 mg and Placebo SC groups, respectively), where the dose adjustment was considered as the only intercurrent event in Study CT-P13 3.8 (Table 27).

The proportion of patients who achieved co-primary and key secondary endpoints was numerically higher in the CT-P13 SC 120 mg group than in the Placebo SC group. Regarding corticosteroid-free remission at Week 54, no notable difference was seen between treatment groups. However, there is a limitation in interpreting results due to small sample size of patients with oral corticosteroid at baseline among patients who did not experience dose adjustment prior to Week 54. Additionally, despite the small number of

patients, the difference (6.3%) in corticosteroid-free remission at Week 54 between treatment groups in the target population (which is a subset of All-randomized population) falls within the 95% CI (1.1%, 32.5%) of the difference in corticosteroid-free remission at Week 54 between treatment groups in the All-randomized population (W54 CSR CT-P13 3.8 Sections 11.4.1.1 and 11.4.1.2 [SN0264]).

In conclusion, the results for the co-primary and key secondary endpoints according to principal stratum estimand showed a consistent trend with the findings from the main analysis in the All- randomized population.

Table 92: Proportion of Patients Achieving Co-primary and Key Secondary Endpoints (Principal Stratum Estimand): All-Randomized Population

	CT-P13 SC 120 mg (N=231)	Placebo (N=112)	Difference (95% CI)[1]	P-value[2]
Clinical remission at Week 54	144/192 (75%)	36/67 (53.7%)	23.3 (10.1, 36.4)	0.0002
Endoscopic response at Week 54	118/192 (61.5%)	20/67 (29.9%)	33.3 (19.4, 45.1)	<.0001
CDAI-100 response at Week 54	152/192 (79.2%)	43/67 (64.2%)	17.0 (4.8, 30.0)	0.0041
Clinical remission based on AP and SF at Week 54	131/192 (68.2%)	35/67 (52.2%)	17.4 (3.9, 30.8)	0.0074
Endoscopic Remission at Week 54	80/192 (41.7%)	12/67 (17.9%)	24.7 (11.7, 35.1)	0.0003
Corticosteroid-free remission at Week 54	40/77 (51.9%)	10/22 (45.5%)	6.3 (-16.3, 28.2)	0.5784

Source: Section 5.3.5.3. Post-hoc Tables 2.231, 2.232, 2.233, 2.234. 2.235 and 2.236
Note: Analysis is stratified by Previous exposure to biologic agents and/or JAK inhibitors (used or not used), Use of treatment with oral corticosteroids at Week 0 (used or not used) and Clinical remission at Week 10 (remitter or non-remitter by CDAI score). Except corticosteroid-free remission at Week 54, percentages are calculated using the number of patients without dose adjustment to CT-P13 SC 240 mg prior to Week 54 as the denominator.
Clinical remission is defined as an absolute CDAI score of less than 150 points.
Endoscopic response is defined as a 50% decrease in SES-CD score from the baseline value.
CDAI-100 response is defined as a decrease in CDAI score of 100 points or more from the baseline value.
Clinical remission is defined as an average worst daily abdominal pain (AP) score of ≤1 (using 4-point scale) and an average daily loose/watery stool frequency (SF) score of ≤3 (of Type 6 or Type 7 on BSFS) with no worsening in either average score compared with the baseline value.
Endoscopic remission is defined as an absolute SES-CD score of ≤4 and at least 2-point reduction from the baseline value with no Segment sub-score of >1.
Corticosteroid-free remission at Week 54 is defined as being in clinical remission (by an absolute CDAI score of <150) in addition to not receiving corticosteroids for at least 8 weeks prior to Week 54, among the patients who used oral corticosteroids at Baseline. Percentages are calculated by using the number of patients who used oral corticosteroids at baseline without dose adjustment to CT-P13 SC 240 mg prior to Week 54 as the denominator.
[1] The difference of proportions between two treatment groups estimated using CMH (Cochran-Mantel-Haenszel) weights, and the 95% stratified Newcombe CI with CMH weights are presented.
[2] The nominal p-value from stratified CMH test is presented in descriptive purpose.

Assessment of the MAH's response

The Question was for a principal stratum estimand and the MAH has just provided a table within the principal stratum which is not what was requested.

Overall, the results for the co-primary and key secondary endpoints in patients without dose escalation were in line with the findings from the main analysis. Corticosteroid-free remission was only calculated among the patients who used oral corticosteroids at baseline. The study protocol is not crystal clear on this point, but it seems that corticosteroids as rescue medication were only allowed for patients with

corticosteroid use at baseline. Therefore, corticoid free remission is not comparable to other endpoints as the analysed population is completely different.

Conclusion

Issue not pursued further.

Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

Question 40

The MAH should discuss how the fact that patients and investigators were effectively unblinded at the time of dose escalation, impacts the results.

Summary of the MAH's response

In Study CT-P13 3.8, dose escalation was permitted when a patient met the defined loss of response criteria outlined in the study protocol (*Section 5.2 Treatment Administered* of the protocol). Since Study CT-P13 3.8 was double blind study, the blinding for the study group assignment for

Maintenance Phase were remained until Final CSR (for Week 102 results) was generated (*Section*

5.6 Blinding of the protocol). During dose escalation, a patient received a double injection of active study drug (CT-P13 SC), regardless of which arm the patient was assigned before the dose escalation. This process ensured that neither the patient nor the investigator was aware of the patient's initial study arm assignment, thus preserving blinding throughout the study.

While patients and investigators were aware of the administration of active drug (CT-P13 SC 240mg) during dose escalation, potentially impacting patient-self reported outcomes, CELLTRION points that the influence on the efficacy of CT-P13 240 mg administration, treated as an open-label intervention, was very limited. The assessment of efficacy was supported by objective measures such as the CDAI score, encompassing parameters like the number of liquid stools, hematocrit results, disease complications of Crohn's disease (CD), and the SES-CD, which is scored based on colonic conditions using objective standards (Vuitton *et al.*, 2016). In addition, there were no notable differences in safety between the CT-P13 SC 120 mg administration and CT-P13 SC 240 mg administration as CELLTRION reported in Response to Question 46.

In light of these considerations, CELLTRION asserts that the dose escalation did not impact the study procedure or results in terms of study blindness.

Assessment of the MAH's response

While some of the components of the CDAI score can be considered objective, others are not (e.g. average abdominal pain rating, general well being). Furthermore, the real problematic issue is that because dose escalation was allowed, it was possible to knowingly switch a placebo patient to active treatment. Indeed, the results at Week 54 are a combination of the actual, intended primary endpoint and the number of patients with dose escalation/switch to active treatment which makes the results difficult to interpret.

Nevertheless, the difference in proportion of remitters is considered clinically meaningful and the magnitude of the difference sufficiently large such that the results can be overall concluded to be relevant to be included in Section 5.1 even if there was some bias involved.

Conclusion

Issue resolved.

Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

REMSWITCH study

Question 41

Other indications than RA and CD have not been mentioned in the SPC 4.2 paragraph on switching from high dose IV. While it is understood by the regulator that this paragraph only mentions the indications where higher IV doses are approved (as described in SPC 5.1), it is considered confusing for non-regulators. As the data on switching is still considered insufficient for all indications, it is proposed to delete any reference to indications and to amend the paragraph, as follows:

There is insufficient information regarding switching to the subcutaneous formulation of Remsima in patients who received the intravenous infusions of infliximab in doses higher than the initial maintenance dose (see section 5.1).

Summary of the MAH's response

The Applicant would like to withdraw the proposed switching from high-dose (>5 mg/kg) IV maintenance to SC maintenance treatment from the grouped variation for CD and UC indications. This is mainly due to lack of clinical data to support the switching from high-dose (5 mg/kg) IV maintenance to SC maintenance treatment. Thus, the Applicant has reverted the paragraph about switching from IV formulation to SC formulation to the previous paragraph as follows:

There is insufficient information regarding the switching of patients who received the intravenous infusions of infliximab higher than 3 mg/kg for rheumatoid arthritis or 5 mg/kg for Crohn's disease every 8 weeks to the subcutaneous formulation of Remsima.

Consequently, responses to Questions 3 and 41 are omitted in this response to RSI package.

Assessment of the MAH's response

The Applicant did not address the request to amend the wording of the paragraph on switching from high dose IV to SC. However, the issue is not pursued further as the variation was withdrawn.

Conclusion

Issue resolved

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

No need to update overall conclusion and impact on benefit-risk balance

Safety

Question 42

The MAH has not described in detail the populations for the comparison between placebo and CT-P13 SC and between the 120 mg and 240 mg doses and how exposure time for each dose was accounted for in the analyses. Therefore, the currently submitted safety data is not considered robust. The MAH informs that for the active arm group with dose adjustment, all data were collected regardless of dose adjustment for CT-P13 SC 120 mg group and for the placebo arm, data collected before initiation of dose adjustment to 240 mg were included in both phase 3 studies. Are the data from subjects who were switched from placebo to active treatment with 240 dose omitted? If so, analyses should be repeated with all subjects using 240 mg dose included, also those from the comparator arm. Are the data for subjects with dose escalation only from the period when the patient used that dose or from the entire study duration? How was different duration of use of different doses addressed in the analyses? The data on dose escalation should be analysed also separately for subjects with UC and CD for confirmation of safety in each indication.

Summary of the MAH's response

As described in Section 2.7.4.1.1.2.1.2 (SN0264) Data Presentation for Adverse Events, for patients with dose adjustment from Studies CT-P13 3.7 and CT-P13 3.8, all data collected regardless of dose adjustment for the CT-P13 SC 120 mg group and data collected before initiation of dose adjustment for the Placebo group were included in the summary tables, which was considered as a conservative approach for the comparison of safety profile between the patients exposed to CT-P13 SC and placebo.

Thus, treatment-emergent adverse events (TEAEs) that occurred after dose adjustment (i.e., TEAEs that occurred after administration of CT-P13 SC 240 mg) in the Placebo group were omitted from the summary tables as the purpose of these tables were to compare the safety profile of CT-P13 SC and Placebo.

For the analysis of dose adjustment in Study CT-P13 3.8 (Section 2.7.4.2.1.4.3.2 [SN0264]), the comparison of safety profile was made within the CT-P13 SC 120 mg group between patients with dose adjustment (from CT-P13 SC 120 mg to 240 mg dose) and patients without dose adjustment (maintained CT-P13 SC 120 mg dose). The data for both subgroups were from the entire duration of the Maintenance Phase.

Per the comment from CHMP, the safety data are re-analysed to include the data of all patients exposed to study treatment (Placebo, CT-P13 SC 120 mg or CT-P13 SC 240 mg), regardless of treatment phase and treatment group. The re-analysis includes the Extension Phase and data collected after dose adjustment from patients in the Placebo arm. All reported TEAEs have been categorised into following subgroups based on the actual treatment the patients received (i.e., Safety Population):

- Placebo: Events reported on or after the date of Week 10 study drug administration and before dose adjustment to CT-P13 SC 240 mg or switch to CT-P13 SC 120 mg at Week 56 in the Placebo group
- CT-P13 SC 120 mg: Events reported on or after the date of Week 10 study drug administration and before dose adjustment to CT-P13 SC 240 mg in the CT-P13 SC 120 mg group and events reported after switch to CT-P13 SC 120 mg at Week 56 and before dose adjustment to CT-P13 SC 240 mg in the Placebo group

CT-P13 SC 240 mg: Events reported after dose adjustment from CT-P13 SC 120 mg to 240 mg in the CT-P13 SC 120 mg arm and placebo to CT-P13 SC 240 mg in the Placebo group

Also, to take into account the different duration of use for each treatment (Placebo, CT-P13 SC 120 mg and CT-P13 SC 240 mg), the incidence rates per 100 Person Year (PY) is calculated by multiplying a hundred to the number of patients divided by total person year, which is sum of study duration of each patient. Person year for each treatment and patient is calculated as follows:

- (Last Visit Date – Date of First Administration Date of Each Treatment + 1)/365.25

For patients with any change in treatment due to entering the Extension Phase or dose adjustment, the duration of previous treatment is calculated as follows:

- (Date of First Administration of Later Treatment – Date of First Administration of Each Treatment)/365.25

The analysis is performed only for patients with Crohn's disease (CD) as the Applicant would like to withdraw the proposed dose adjustment from CT-P13 SC 120 mg to 240 mg for patients with ulcerative colitis (UC).

Comparative safety analyses were performed for the following events that were reported during the Maintenance and Extension Phase of Study CT-P13 3.8: TEAEs, treatment-emergent serious adverse events (TESAEs), TEAEs leading to study drug discontinuation and TEAEs of special interest (TEAESIs) with each TEAESI category analysed separately. The events that occurred on or after the first administration of each treatment are included in each treatment group. The number of patients with at least 1 TEAE, TESAE, TEAE leading to study drug discontinuation or TEAESI with exposure adjusted rate by 100 PY are presented in Table 1 below by subgroups of CT-P13 SC 120 mg, CT-P13 SC 240 mg and Placebo.

The number of patients reported with localised ISR by 100 PY was higher for CT-P13 SC 240 mg (6.75) compared to Placebo (1.66) and CT-P13 SC 120 mg (4.95); however, this was expected given that patients with dose adjustment to CT-P13 SC 240 mg were given 2 injections instead of 1. Also, localised ISRs reported in patients exposed to CT-P13 SC 240 mg were grade 1 or 2 in severity and majority of the events were resolved within the same day of onset without requiring treatment (Final CSR CT-P13 3.8 Listing 16.2.7.6).

The number of patients reported with infection by 100 PY was also higher for CT-P13 SC 240 mg (33.74) compared to Placebo (31.55) and CT-P13 SC 120 mg (28.88). However, most events were grade 1 or 2 infections which were unrelated to the study drug and the number of patients reported with study drug-related infection by 100 PY for CT-P13 SC 240 mg (4.22) was lower than Placebo (9.96) or similar to CT-P13 SC 120 mg (4.40). Also, there was no notable difference in the number of patients with TESAE of infection by 100 PY between the 3 subgroups (1.66 for Placebo, 3.30 for CT-P13 SC 120 mg, 2.53 for CT-P13 SC 240 mg) (Section 5.3.5.3 Post-hoc Table 3.122)

Overall, the results showed that there was no significant difference in the number of events by 100 PY between each dose of 120 mg and 240 mg and placebo, supporting that no safety risk is expected from the higher dose of CT-P13 SC 240 mg.

Table 93: Summary of Safety by the Dosage of Study Drug in Study CT-P13 3.8 (Maintenance Phase + Extension Phase): Safety Population

	Placebo (N=105, PY=60.22)	CT-P13 SC 120 mg (N=275, PY=363.58)	CT-P13 SC 240 mg (N=105, PY=118.54)
	Number (%, 100PY) of Patients with ≥ 1 Event		
TEAE	64 (61.0%, 106.27)	202 (73.5%, 55.56)	67 (63.8%, 56.52)
TESAE	8 (7.6%, 13.28)	28 (10.2%, 7.70)	7 (6.7%, 5.91)
TEAE Leading to Study Drug Discontinuation	5 (4.8%, 8.30)	14 (5.1%, 3.85)	5 (4.8%, 4.22)
SIR	1 (1.0%, 1.66)	3 (1.1%, 0.83)	0
Delayed Hypersensitivity	0	0	0
Localised ISR	1 (1.0%, 1.66)	18 (6.5%, 4.95)	8 (7.6%, 6.75)
Infection	19 (18.1%, 31.55)	105 (38.2%, 28.88)	40 (38.1%, 33.74)
Malignancy	1 (1.0%, 1.66)	0	0

Source: Section 5.3.5.3 Post-hoc Table 3.114
Abbreviations: ISR, injection site reaction; PY, person year; SIR, systemic injection reaction; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event

Moreover, considering that the mean and median duration of treatment for patients who received CT-P13 SC 240 mg are 58.9 weeks and 68.1 weeks, respectively, and 73 patients received CT-P13 SC 240 mg as maintenance treatment for at least 44 weeks (Section 5.3.5.3 Post-hoc Table 3.113), the post-hoc analysis result sufficiently represents long-term safety profile of CT-P13 SC 240 mg.

Also per the comment from CHMP, the pooled analysis of the CT-P13 SC 120 mg dose and 240 mg dose for all approved indications of SC administered Remsima and analysis comparing TEAEs occurring prior to dose adjustment (CT-P13 SC 120 mg) vs after dose adjustment (from CT-P13 SC 120 mg to 240 mg) within the CT-P13 SC group and TEAEs occurring prior to dose adjustment (Placebo) vs after dose adjustment (from Placebo to CT-P13 SC 240 mg) within the Placebo group are provided in Response to Question 46.

Assessment of the MAH's response

The Applicant withdraws the proposed dose adjustment from CT-P13 SC 120 mg to 240 mg for patients with ulcerative colitis (UC). Hence, the requested additional analyses were performed by the Applicant only for patients with Crohn's disease (CD), comparing the safety profile of the 120 mg SC and 240 mg SC doses of CT-P13 and placebo.

The re-analyses performed by the Applicant include the data of all patients exposed to study treatment (Placebo, CT-P13 SC 120 mg or CT-P13 SC 240 mg) in Study CT-P13 3.8, regardless of treatment phase and treatment group.

The number of patients reported with localised ISR by 100 PY was higher for CT-P13 SC 240 mg (6.75) than CT-P13 SC 120 mg (4.95) (for Placebo 1.66). However, it is agreed with the Applicant that this was expected as patients with dose adjustment to CT-P13 SC 240 mg were given two injections instead of one.

The number of patients reported with infection by 100 PY was also higher for CT-P13 SC 240 mg (33.74) compared to Placebo (31.55) and CT-P13 SC 120 mg (28.88) in Study CT-P13 3.8. It is noteworthy that in all groups, the TEAE classified as Infection were as often classified to be unrelated as related to treatment (Table 3.1.2.2, CTD Module 5, Section 5.3.5.3 copied below). The number of patients by 100 PY with TEAE classified as unrelated was also higher in subjects administered CT-P13 SC 240 mg (33.74) than 120 mg (26.95) or placebo (26.75); hence, assessment of relatedness has obviously not been accurate.

There was no notable difference in the number of patients with TESAE of infection by 100 PY between the 3 subgroups, but the actual numbers of subjects are too low for firm conclusions (table 1 of the response and table 3.1.2.2 below).

Table 94 Summary of Infection by the Dosage of Study Drug/ Safety Population

Number (%, 100PY) of Patients With at Least One Event	Placebo (N=105, PY=60.22)	SC 120 mg (N=275, PY=363.58)	SC 240 mg (N=105, PY=118.54)
TEAE classified as Infection	19 (18.1%, 31.55)	105 (38.2%, 28.88)	40 (38.1%, 33.74)
Related	6 (5.7%, 9.96)	16 (5.8%, 4.40)	5 (4.8%, 4.22)
Grade 1	4 (3.8%, 6.64)	5 (1.8%, 1.38)	2 (1.9%, 1.69)
Grade 2	2 (1.9%, 3.32)	10 (3.6%, 2.75)	3 (2.9%, 2.53)
Grade 3	0	1 (0.4%, 0.28)	0
Unrelated	16 (15.2%, 26.57)	98 (35.6%, 26.95)	40 (38.1%, 33.74)
Grade 1	6 (5.7%, 9.96)	39 (14.2%, 10.73)	24 (22.9%, 20.25)
Grade 2	7 (6.7%, 11.62)	49 (17.8%, 13.48)	13 (12.4%, 10.97)
Grade 3	2 (1.9%, 3.32)	9 (3.3%, 2.48)	1 (1.0%, 0.84)
Grade 4	1 (1.0%, 1.66)	1 (0.4%, 0.28)	2 (1.9%, 1.69)
TESAE classified as Infection	1 (1.0%, 1.66)	12 (4.4%, 3.30)	3 (2.9%, 2.53)
Related	0	1 (0.4%, 0.28)	0
Grade 3	0	1 (0.4%, 0.28)	0
Unrelated	1 (1.0%, 1.66)	11 (4%, 3.03)	3 (2.9%, 2.53)
Grade 2	0	3 (1.1%, 0.83)	0
Grade 3	0	7 (2.5%, 1.93)	1 (1.0%, 0.84)
Grade 4	1 (1.0%, 1.66)	1 (0.4%, 0.28)	2 (1.9%, 1.69)

Note: At each level of summarization, patients are counted once using the most severe event if they reported one or more events. The event is considered to be related if the relationship is defined as 'Possible', 'Probable', 'Definite'. The intensity is defined as Grade 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Life-threatening, 5 = Death.

The adverse events occurred on or after the first administration of each treatment are included in each treatment group. The number of patients per 100 PY is presented along with percentages in parentheses. The person year for each patient is calculated as the (last visit date - date of first administration of each treatment +1)/365.25. For patients with any change in treatment due to entering extension phase or dose adjustment, the duration of previous treatment is calculated as (date of first administration of later treatment - date of first administration of each treatment)/365.25.

N= The number of patients administered at least one dose for each treatment, PY= Person Year.

As a conclusion, in Study CT-P13 3.8, the incidence of TEAE classified as infection was slightly higher per PY with the 240 mg SC dose than with placebo or the 120 mg SC dose, but the difference was small. All TEAE were markedly more frequent in the placebo group vs. both active groups, raising the question if a great part of reported TEAEs represented symptoms of the disease. Nevertheless, the data support the MAH's claim that there was no significant difference in the number of events by 100 PY between each dose of 120 mg and 240 mg.

Conclusion

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

No need to update overall conclusion and impact on benefit-risk balance

Question 43

For both pivotal trials, discrepant numbers are given in the figures and tables on disposition of patients vs. the summary tables on subjects discontinuing treatment due to adverse events during the induction and maintenance phases of the studies. The Applicant is requested to clarify the root cause of these discrepancies and to confirm numbers of subjects who discontinued treatment due to adverse events during the induction and maintenance phases of studies CT-P13 37 and CT-P13 38. Details of TEAEs leading to discontinuation should be reported separately for the induction and maintenance periods of both studies.

Summary of the MAH's response

The MAH clarifies that the discrepant numbers between the patient disposition summary and the summary of treatment-emergent adverse event (TEAE) leading to study drug discontinuation were mainly due to the different source of data and analysis method according to Statistical Analysis Plan (SAP) of both pivotal studies.

Summaries of patient discontinuation in the Induction and Maintenance Phases of Studies CT-P13 3.7 and CT-P13 3.8 are provided in Table 2, Table 3, Table 4 and Table 5 of the MAH's response document, respectively, and the reasons for discrepancy are provided in each section. The information is not copied here for brevity.

Assessment of the MAH's response

Sufficient clarifications were received for the discrepancies noted between the disposition figures and tables vs. summary tables on subjects discontinuing treatment due to AEs.

Conclusion

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

No need to update overall conclusion and impact on benefit-risk balance

Question 44

It is noteworthy that even in the placebo arms, 15.0 % and 14.3 % of subjects in studies CT-P13 3.7 and CT-P13 3.8, respectively, experienced TEAEs that were considered to be related to study drug. Hence, the observed TEAEs obviously overlap with symptoms of the medical conditions of the subjects; or the TEAEs in the placebo arm may have occurred after switch from placebo to active treatment with the 240 mg dose. The MAH should clarify if the TEAEs related to study drug occurred in the placebo group during placebo treatment or during active treatment with **CT-P13 after dose adjustment.**

Summary of the MAH's response

For both Study CT-P13 3.7 and Study CT-P13 3.8, only data collected before initiation of dose adjustment for Placebo SC group were included in Treatment-Emergent Adverse Event (TEAE) summary tables as per Statistical Analysis Plan (SAP) of Study CT-P13 3.7 and SAP of Study CT-P13 3.8. Thus, the study drug-related TEAEs reported in 15.0% and 14.3% of subjects in Studies CT-P13 3.7 and CT-P13 3.8, respectively, were not reported after dose adjustment to the 240 mg dose. Since both studies were double-blind during the maintenance period, the investigators reported relatedness of TEAE in the blind state. Most of the TEAEs were considered by the investigator as possibly related to study drug, by the definition suggesting that treatment with the study drug caused or contributed to the AE, i.e., the event follows a reasonable temporal sequence from the time of study drug administration or follows a known response pattern to the study drug but could also have been produced by other factors.

Assessment of the MAH's response

The MAH has sufficiently clarified the issue.

Conclusion

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

No need to update overall conclusion and impact on benefit-risk balance

Question 45

The MAH should clarify for both pivotal studies the numbers of the adverse reactions which occurred more frequently in active than placebo arms but are nevertheless not proposed to be included in the SmPC. The MAH should discuss the potential relatedness of these ADRs with the medication and justify for each adverse reaction why they are not proposed to be included in the SmPC or alternatively, add them in the proposed SmPC. If the ADRs seen with the SC treatment have not occurred with the IV treatment and are added in the tabulated list in Section 4.8, they should be marked with an asterisk referring to a clarifying footnote.

Summary of the MAH's response

The adverse reactions listed in Table 1 - Adverse reactions in clinical studies and from post-marketing experience of intravenous infliximab in section 4.8 of the SmPC were initially proposed as identical as those in the SmPC of original medication of infliximab.

To identify and evaluate adverse events that were more prevalent than placebo, aiming to determine if their addition to the SmPC is warranted, CELLTRION has listed the TEAEs reported for at least 1% of patients in the CT-P13 SC 120 mg group and at a higher rate than the Placebo SC group (Table 6). This table was analysed from pooled studies (Study CT-P13 3.7 and Study CT-P13 3.8) in accordance with the EMA Guideline on SmPC. This guideline emphasizes that the frequency of adverse reactions should be derived from pooled placebo-controlled studies, as outlined in Revision 2, 2009.

TEAEs reported for less than 1% of patients in the CT-P13 SC 120 mg group were intentionally excluded from the table due to their low reported rate, deemed insufficient to consider potential relatedness to subcutaneously administered Remsima.

Data in Table 6 from pooled studies include adverse events that occurred prior to dose adjustment from CT-P13 SC 120 mg or placebo to CT-P13 SC 240 mg during the Maintenance Phase. This approach ensures a direct comparison of the safety profile between the two groups while excluding the impact of dose adjustment.

Among TEAEs listed in Table 6, five TEAEs by preferred term (PT) (thrombocytosis, large intestine polyp, Blood creatine phosphokinase increased, arthritis and haematuria) were identified as not being listed in Section 4.8 of the SmPC. However, after thorough assessment on causal relationship between the medicinal product and the adverse events, it was deemed unnecessary to add them to the SmPC. Those TEAEs are presented along with justifications regarding their potential relatedness with the medication. Overall, CELLTRION asserts the rationale for maintaining the list of AEs in Section 4.8 of the SmPC based on these justifications.

Table 95: TEAEs Reported for at Least 1% of Patients in the CT-P13 SC Treatment Arm and at Higher Rate than the Placebo Group (Study CT-P13 3.7+3.8)

System Organ Class Preferred Term	CT-P13 SC 120 mg (N=534)	Placebo SC (N=245)	Justification
Blood and lymphatic system disorders			
Leukopenia	8 (1.5%)	1 (0.4%)	Listed in the tabulated list in Section 4.8 of SmPC as Common adverse event and the frequency or severity of the reaction was not changed.
Neutropenia	10 (1.9%)	2 (0.8%)	Listed in the tabulated list in Section 4.8 of SmPC as Common adverse event and the frequency or severity of the reaction was not changed.
Thrombocytosis	9 (1.7%)	4 (1.6%)	All cases were considered unrelated to the study drug by the investigator and occurred in both CT-P13 SC 120 mg and Placebo SC groups at a similar rate. Thus, thrombocytosis is not proposed to be added in the tabulated list in Section 4.8 of SmPC.
Gastrointestinal disorders			
Abdominal pain upper	9 (1.7%)	1 (0.4%)	Listed in the tabulated list in Section 4.8 of SmPC as Very common adverse event of abdominal pain and the frequency or severity of the reaction was not changed.
Diarrhoea	13 (2.4%)	3 (1.2%)	Listed in the tabulated list in Section 4.8 of SmPC as Common adverse event and the frequency or severity of the reaction was not changed.
Large intestine polyp	6 (1.1%)	1 (0.4%)	All cases were considered unrelated to the study drug by the investigator. Most of the case occurred in UC (For UC, 5 [1.7%] and 1 [0.7%] patient in CT-P13 SC 120 mg and Placebo SC, respectively and for CD, 1 [0.4%] patient in CT-P13 SC 120 mg only), which indicates potential relation with UC. Thus, large intestine polyp is not proposed to be added in the tabulated list in Section 4.8 of SmPC.
Nausea	10 (1.9%)	3 (1.2%)	Listed in the tabulated list in Section 4.8 of SmPC as Very Common adverse event and the frequency or severity of the reaction was not changed.
General disorders and administration site conditions			
Injection site reaction	21 (3.9%)	4 (1.6%)	Listed in the tabulated list in Section 4.8 of SmPC as Common adverse event and the frequency or severity of the reaction was not changed.
Infections and infestations			
COVID-19	49 (9.2%)	14 (5.7%)	Updated in the tabulated list in Section 4.8 of SmPC as Very Common adverse event of Viral infection (e.g. influenza, herpes virus infection)
Herpes zoster	6 (1.1%)	2 (0.8%)	Considered to be listed in the tabulated list in Section 4.8 of SmPC as Very Common adverse event of Viral infection (e.g. influenza, herpes virus infection) and the frequency or severity of the reaction was not changed.
Oral herpes	10 (1.9%)	1 (0.4%)	Considered to be listed in the tabulated list in Section 4.8 of SmPC as Very Common adverse event of Viral infection (e.g. influenza, herpes virus infection) and the frequency or severity of the reaction was not changed.
Pharyngitis	10 (1.9%)	0	Considered to be listed in the tabulated list in Section 4.8 of SmPC as Very Common adverse event of Viral infection (e.g. influenza, herpes virus infection) and the frequency or severity of the reaction was not changed.
Urinary tract infection	13 (2.4%)	4 (1.6%)	Listed in the tabulated list in Section 4.8 of SmPC as Common adverse event and the frequency or severity of the reaction was not changed.
Injury, poisoning and procedural complications			
Injection related reaction	12 (2.2%)	5 (2.0%)	Injection related reaction is systemic injection reaction caused by subcutaneous treatment which is identical to Infusion related reaction by intravenous treatment. Thus, it is considered to be listed in the tabulated list in Section 4.8 of SmPC as Very Common adverse event of Infusion-related reaction and the frequency or severity of the reaction was not changed.
Investigations			
Alanine aminotransferase increased	18 (3.4%)	3 (1.2%)	Considered to be listed in the tabulated list in Section 4.8 of SmPC as Common adverse event of transaminases increased and the frequency or severity of the reaction was not changed.
Aspartate aminotransferase increased	8 (1.5%)	2 (0.8%)	Considered to be listed in the tabulated list in Section 4.8 of SmPC as Common adverse event of transaminases increased and the frequency or severity of the reaction was not changed.
Blood creatine phosphokinase increased	16 (3.0%)	7 (2.9%)	The events occurred in both CT-P13 SC 120 mg and Placebo SC groups at a similar rate. Thus, blood creatine phosphokinase increased is not proposed to be added in the tabulated list in Section 4.8 of SmPC.
Musculoskeletal and connective tissue disorders			
Arthralgia	21 (3.9%)	5 (2.0%)	Listed in the tabulated list in Section 4.8 of SmPC as Common adverse event and the frequency or severity of the reaction was not changed.
Arthritis	6 (1.1%)	0	The events were reported only in the CT-P13 SC 120 mg group; however, all cases were considered unrelated to the study drug by the investigator and reported at a very low rate of 1.1%. Thus, arthritis is not proposed to be added in the tabulated list in Section 4.8 of SmPC.
Back pain	6 (1.1%)	1 (0.4%)	Listed in the tabulated list in Section 4.8 of SmPC as Common adverse event and the frequency or severity of the reaction was not changed.
Nervous system disorders			
Dizziness	10 (1.9%)	1 (0.4%)	Listed in the tabulated list in Section 4.8 of SmPC as Common adverse event and the frequency or severity of the reaction was not changed.
Headache	33 (6.2%)	12 (4.9%)	Listed in the tabulated list in Section 4.8 of SmPC as Very Common adverse event and the frequency or severity of the reaction was not changed.
Renal and urinary disorders			
Haematuria	9 (1.7%)	2 (0.8%)	All cases were considered unrelated to the study drug by the investigator and the reported rate was only 0.9% higher in the CT-P13 SC 120 mg group compared to the Placebo SC group. Thus, haematuria is not proposed to be added in the tabulated list in Section 4.8 of SmPC.
Skin and subcutaneous tissue disorder			
Rash	7 (1.3%)	3 (1.2%)	Listed in the tabulated list in Section 4.8 of SmPC as Common adverse event and the frequency or severity of the reaction was not changed.
Vascular disorders			
Hypertension	14 (2.6%)	2 (0.8%)	Listed in the tabulated list in Section 4.8 of SmPC as Common adverse event and the frequency or severity of the reaction was not changed.

Note: At each level of summarisation, patients are counted once if they reported one or more events

Assessment of the MAH's response

The submitted information from pooled placebo-controlled studies on TEAEs reported for at least 1% of patients in the CT-P13 SC 120 mg group and at a higher rate than the Placebo SC group is considered sufficient. The MAH has adequately justified for each observed TEAE the inclusion or omission of that AE from the table in Section 4.8 of the SmPC. Based on these data, no change is warranted on the table except for Covid-19, which was added in the updated tabulated list in Section 4.8 of SmPC as Very Common adverse event of Viral infection.

Conclusion

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

No need to update overall conclusion and impact on benefit-risk balance

Question 46

The MAH is requested to submit safety analyses for the integrated data for SC administered Remsima in all approved indications separately 1) for subjects who were administered the 120 mg SC dose and 2) for subjects who were administered the 240 mg SC dose in studies CT-P13 3.7 (UC), CT-P13 3.8 (CD), CT-P13 3.5 Part 1 and Part 2 (rheumatoid arthritis, RA) and CT-P13 1.6 Part 1 and Part 2 (UC and CD); and 3) pooled together for both SC doses. Adverse events occurring prior to dose escalation from 120 mg SC to 240 mg SC vs. after dose escalation should be compared, with adjustment for duration of exposure to each dose. The same analysis is requested to be conducted for the patients who originally were administered placebo and were switched to the 240 mg SC dose. The analyses should be performed separately for both of the currently assessed phase 3 studies and for the pooled safety population from all patient trials listed above. The MAH should propose an update to the Product Information based on the results of the analyses described above.

Summary of the MAH's response

Per the comment from CHMP, the pooled analysis of the CT-P13 SC 120 mg and 240 mg doses for all approved indications of SC administered Remsima has been conducted and includes the following final data from each study:

- Study 1.6 Part 1 (CD): CT-P13 SC 120 mg group and CT-P13 SC 240 mg group from Week 6
- Study 1.6 Part 2 (CD/UC): CT-P13 SC 120/240 mg group from Week 6 and CT-P13 IV 5 mg/kg group from Week 30
- Study 3.5 Part 1 (RA): CT-P13 SC 120 mg group from Week 6
- Study 3.5 Part 2 (RA): CT-P13 SC 120 mg group from Week 6 and CT-P13 IV 3 mg/kg group from Week 30
- Study CT-P13 3.7 (UC): CT-P13 SC 120 mg group from Week 10 and Placebo group from Week 56 or after dose adjustment
- Study CT-P13 3.8 (CD): CT-P13 SC 120 mg group from Week 10 and Placebo group from Week 56 or after dose adjustment

Comparative safety analyses were performed for the events that occurred on or after the first administration of each treatment of CT-P13 SC 120 mg or 240 mg. The number of patients with at least 1 treatment-emergent adverse event (TEAE), treatment-emergent serious adverse event (TESAE), TEAE leading to study drug discontinuation or treatment-emergent adverse event of special interest (TEAESI) with exposure adjusted rate by 100 PY are presented in Table 7 by subgroups of CT-P13 SC 120 mg, CT-P13 SC 240 mg

and CT-P13 SC Total. The results showed that there was no significant difference in the number of events by 100 PY between each dose of CT-P13 SC 120 mg and 240 mg from the pooled analysis, indicating that the safety profile of higher dose of CT-P13 SC 240 mg is comparable to the approved dose of 120 mg for SC administered Remsima.

Table 96: Summary of Safety by the Dosage of Study Drug in All CT-P13 SC Studies: Safety Population

	CT-P13 SC 120 mg (N=1056, PY=1106.05)	CT-P13 SC 240 mg (N=342, PY=344.24)	Total (N=1230, PY=1450.30)
	Number (%, 100PY) of Patients with ≥ 1 Event		
TEAE	674 (63.8%, 60.94)	232 (67.8%, 67.39)	835 (67.9%, 57.57)
TESAE	71 (6.7%, 6.42)	29 (8.5%, 8.42)	99 (8.0%, 6.83)
TEAE Leading to Study Drug Discontinuation	40 (3.8%, 3.62)	17 (5.0%, 4.94)	57 (4.6%, 3.93)
SIR	22 (2.1%, 1.99)	8 (2.3%, 2.32)	30 (2.4%, 2.07)
Delayed Hypersensitivity	7 (0.7%, 0.63)	3 (0.9%, 0.87)	10 (0.8%, 0.69)
Localised ISR	99 (9.4%, 8.95)	20 (5.8%, 5.81)	119 (9.7%, 8.21)
Infection	327 (31.0%, 29.56)	117 (34.2%, 33.99)	427 (34.7%, 29.44)
Malignancy	2 (0.2%, 0.18)	3 (0.9%, 0.87)	5 (0.4%, 0.34)

Abbreviations: ISR, injection site reaction; PY, person year; SIR, systemic injection reaction; TEAE, treatment emergent adverse event; TESAE, treatment-emergent serious adverse event

Per the additional comment from CHMP, analysis comparing the events occurring prior to dose adjustment (CT-P13 SC 120 mg) vs after dose adjustment (from CT-P13 SC 120 mg to 240 mg) within the CT-P13 SC group and TEAEs occurring prior to dose adjustment (Placebo) vs after dose adjustment (from Placebo to CT-P13 SC 240 mg) within the Placebo group are provided in Table 8 for Study CT-P13 3.8 and Table 9 for the pooled population. As the Applicant would like to withdraw the proposed dose adjustment from CT-P13 SC 120 mg to 240 mg for patients with ulcerative colitis (UC), the analysis on dose adjustment for the Phase 3 study is performed only for the safety data from Study CT-P13 3.8. For the pooled population, only Studies CT-P13 3.7, CT-P13 3.8 and CT-P13 1.6 Part 2 are included as these are the only studies that allowed dose adjustment to CT-P13 SC 240 mg.

Table 97: Summary of Safety by the Dose Adjustment in Study CT-P13 3.8: Safety Population

	CT-P13 SC 120 mg (N=54, PY=30.82)	CT-P13 SC 240 mg (from SC 120 mg) (N=54, PY=52.58)	Placebo (N=50, PY=17.83)	CT-P13 SC 240 mg (from Placebo) (N=50, PY=65.11)
	Number (%, 100PY) of Patients with ≥ 1 Event			
TEAE	33 (61.1%, 107.07)	34 (63.0%, 64.66)	27 (54%, 151.42)	32 (64%, 49.14)
TESAE	2 (3.7%, 6.49)	4 (7.4%, 7.61)	1 (2%, 5.61)	3 (6%, 4.61)
TEAE Leading to Study Drug Discontinuation	N/A[1]	3 (5.6%, 5.71)	N/A[1]	2 (4%, 3.07)
SIR	1 (1.9%, 3.24)	0	1 (2%, 5.61)	0
Delayed Hypersensitivity	0	0	0	0
Localised ISR	2 (3.7%, 6.49)	4 (7.4%, 7.61)	0	4 (8%, 6.14)
Infection	15 (27.8%, 48.67)	21 (38.9%, 39.94)	5 (10%, 28.04)	19 (38%, 29.18)
Malignancy	0	0	0	0

Note: Excluding TEAEs reported from patients in the Placebo group who switched from Placebo to CT-P13 SC 120 mg at Week 56 then underwent dose adjustment from CT-P13 SC 120 mg to 240 mg during the Extension Phase.
[1] Marked as N/A since TEAE leading to study drug discontinuation can only be reported once for each patient.

Abbreviations: ISR, injection site reaction; PY, person year; SIR, systemic injection reaction; TEAE, treatment emergent adverse event; TESAE, treatment-emergent serious adverse event

Table 98: Summary of Safety by the Dose Adjustment in Studies CT-P13 3.7, CT-P13 3.8 and CT-P13 1.6 Part 2: Safety Population

	CT-P13 3.7 + CT-P13 3.8 + CT-P13 1.6 Part 2		CT-P13 3.7 + CT-P13 3.8	
	CT-P13 SC 120 mg (N=159, PY=74.69)	CT-P13 SC 240 mg (from SC 120 mg) (N=159, PY=153.98)	Placebo (N=126, PY=43.53)	CT-P13 SC 240 mg (from Placebo) (N=126, PY=153.13)
	Number (%, 100PY) of Patients with ≥ 1 Event			
TEAE	93 (58.5%, 124.51)	107 (67.3%, 69.49)	67 (53.2%, 153.93)	92 (73.0%, 60.08)
TESAE	6 (3.8%, 8.03)	14 (8.8%, 9.09)	2 (1.6%, 4.59)	10 (7.9%, 6.53)
TEAE Leading to Study Drug Discontinuation	N/A[1]	8 (5.0%, 5.20)	N/A[1]	8 (6.3%, 5.22)
SIR	3 (1.9%, 4.02)	4 (2.5%, 2.60)	3 (2.4%, 6.89)	3 (2.4%, 1.96)
Delayed Hypersensitivity	0	1 (0.6%, 0.65)	0	0
Localised ISR	8 (5.0%, 10.71)	8 (5.0%, 5.20)	1 (0.8%, 2.30)	8 (6.3%, 5.22)
Infection	34 (21.4%, 45.52)	51 (32.1%, 33.12)	21 (16.7%, 48.25)	50 (39.7%, 32.65)
Malignancy	0	1 (0.6%, 0.65)	0	2 (1.6%, 1.31)

Note: Excluding TEAEs reported from patients in the Placebo group who switched from Placebo to CT-P13 SC 120 mg at Week 56 then underwent dose adjustment from CT-P13 SC 120 mg to 240 mg during the Extension Phase.
[1] Marked as N/A since TEAE leading to study drug discontinuation can only be reported once for each patient.
Abbreviations: ISR, injection site reaction; PY, person year; SIR, systemic injection reaction; TEAE, treatment emergent adverse event; TESAE, treatment-emergent serious adverse event

Other than TEAE leading to study drug discontinuation, the results showed that the number of patients with at least 1 TEAE, TESAE or TEAESI with exposure adjusted rate by 100 PY was not significantly increased after dose adjustment to CT-P13 SC 240 mg for both patients switching from CT-P13 SC 120 mg and placebo.

In both Table 8 and Table 9, TEAE leading to study drug discontinuation appears to occur only after each patient started receiving CT-P13 SC 240 mg, but the comparison between before and after dose adjustment cannot be since each patient can be reported only once with TEAE leading to study drug discontinuation. Also, patients who discontinued from the study while receiving CT-P13 SC 120 mg or placebo did not have the chance for dose adjustment to receive CT-P13 SC 240 mg.

When compared by study treatment, the number of patients reported with TEAE leading to study drug discontinuation by 100 PY was slightly higher for the CT-P13 SC 240 mg group (4.94) compared to the CT-P13 SC 120 mg group (3.62) (Table 7) and similar trend was shown in the analysis for Study CT-P13 3.8 as the number of patients reported with TEAE leading to study drug discontinuation by 100 PY was 8.30, 3.85 and 4.22 for Placebo, CT-P13 SC 120 mg and CT-P13 SC 240 mg subgroups, respectively (Table 1 of Response to Question 42).

As all analyses provided in this response showed that the safety profile of higher dose of CT-P13 SC 240 mg is comparable to the approved dose of CT-P13 SC 120 mg, no proposal is made for an update to the Product Information.

Assessment of the MAH's response

The MAH has submitted the requested analyses: except for that the analysis on dose adjustment for the Phase 3 study was performed only for the safety data from Study CT-P13 3.8, since the MAH would like to withdraw the proposed dose adjustment from CT-P13 SC 120 mg to 240 mg for patients with ulcerative colitis (UC),

In the pooled analysis of all CT-P13 SC studies, there were slightly more TEAE, TESAE, TEAE leading to study drug discontinuation, SIR, delayed hypersensitivity and infections with the 240 mg SC dose than the 120 mg SC dose (Table 7). Regarding malignancy, there were only 2/1056 cases (0.2%, 0.18 100 PY) in the 120 mg SC group and 3/342 cases (0.9%, 0.87 100 PY) in the 240 mg SC group, so interpretation of the difference in incidence of malignancy is futile.

In study CT-P13 3.8, interestingly, there were markedly more TEAE with placebo (54%, 151.42/100 PY)) and CT-P13 120 mg SC (61.1%, 107.07/100 PY) than in subjects with dose escalation from 120 mg to 240 mg SC (63.0%, 64.66/100 PY) or subjects with dose escalation from placebo to 240 mg SC (64%, 49.14/100 PY) (Table 8).

Only studies CT-P13 3.7, CT-P13 3.8 and CT-P13 1.6 Part 2 were included in the pooled analysis, as these are the only studies that allowed dose adjustment to CT-P13 SC 240 mg. In this analysis (table 9) that includes subjects with both CD and UC (from studies CT-P13 3.7, CT-P13 3.8 and CT-P13 1.6), there were also markedly more TEAE in the placebo and CT-P13 120 mg SC groups than in the CT-P13 240 mg SC groups (escalated from 120 mg SC or placebo). However, the incidence of TESAE was larger in the 240 mg SC group escalated from 120 mg SC than in subjects continuing with 120 mg SC and also larger in the 240mg SC group escalated from placebo than in the placebo group. Notably, also infections occurred less often during treatment with CT-P13 240 mg SC (39.7%, 32.65/100 PY when escalation from 120 mg and 39.7%, 32.65/100 PY) than during treatment with CT-P13 120 mg SC (21.4%, 45.54/100 PY) or placebo (16.7 %, 48.25/100 PY).

Overall, the results do not indicate that the safety profile of the 240 mg SC dose would relevantly differ from the safety profile of 120 mg SC of CT-P 13.

Conclusion

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

No need to update overall conclusion and impact on benefit-risk balance

Question 47

COVID-19 should be added in the examples of infections mentioned in parentheses in the table of ADRs in Section 4.8 of the SmPC, together with influenza and herpes virus infection, with an asterisk referring to a footnote describing that these ADRs were seen with the SC administered Remsima.

Summary of the MAH's response

As requested, the Applicant has added COVID-19 as an example of viral infections with the suggested footnote to the table of ADRs in Section 4.8 of SmPC.

Assessment of the MAH's response

Issue resolved.

Conclusion

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

No need to update overall conclusion and impact on benefit-risk balance

Question 48

From tables included in the document "Post-hoc Analyses" (Module 5.3.5.3) it is understood that there were 534 subjects in the pooled analysis for assessment of safety of the doses of 120 mg SC and 240 mg SC, of whom 137 with dose adjustment and 397 without dose adjustment. The MAH is however requested to further clarify the patient populations used for investigating effects of dose escalation in the pooled data set and in the separate analyses of both phase 3 trials. The MAH informs that for the active arm group with dose adjustment, all data were collected regardless of dose adjustment for CT-P13 SC 120 mg group; and for the placebo arm, data collected before initiation of dose adjustment to 240 mg were included. The MAH should clarify if the data from subjects who were switched from placebo to active treatment with 240 dose were omitted? If so, analyses should be repeated with all subjects using 240 mg dose included, also those from the comparator arm. Are the data for subjects with dose escalation only from the period when the patient used that dose or from the entire study duration? The MAH is requested to clarify how different durations of use of different doses were addressed in the analyses?

Summary of the MAH's response

As discussed in Response to Question 42, the comparison of safety profile between patients with dose adjustment (from CT-P13 SC 120 mg to 240 mg dose) and patients without dose adjustment (maintained CT-P13 SC 120 mg dose) was made within the CT-P13 SC group of Study CT-P13 3.8 (Section 2.7.4.2.1.4.3.2 [SN0264]). The data for both subgroups were from the entire duration of the Maintenance Phase.

By including the Extension Phase and data collected after dose adjustment from patients in the Placebo arm and calculating the incidence rates per 100 Person Year (PY), the re-analysis of the safety data include the data of all patients regardless of treatment phase and treatment group and take into account the different duration of each treatment. The results are provided in Response to Question 42 and Response to Question 46.

Assessment of the MAH's response

The submitted analyses are assessed in context of questions 42 and 46. The provided analyses on incidence of AEs during use of either 120 mg Sc, 240 mg SC or placebo per patient year are considered adequate.

Issue resolved.

Conclusion

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

No need to update overall conclusion and impact on benefit-risk balance

Question 49

The data on dose escalation should be analysed also separately for subjects with UC and CD for confirmation of safety in each indication.

Summary of the MAH's response

As the Applicant would like to withdraw the proposed dose adjustment from CT-P13 SC 120 mg to 240 mg for patients with ulcerative colitis (UC), the analysis on dose adjustment is performed only for patients with Crohn's disease (CD). The analysis comparing events occurring prior to dose adjustment (CT-P13 SC 120 mg) vs after dose adjustment (from CT-P13 SC 120 mg to 240 mg) within the CT-P13 SC group and TEAEs occurring prior to dose adjustment (Placebo) vs after dose adjustment (from Placebo to CT-P13 SC 240 mg) within the Placebo group are provided in Table 8 of Response to Question 46.

Assessment of the MAH's response

See assessment of question 46. Issue resolved.

Conclusion

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

No need to update overall conclusion and impact on benefit-risk balance

Question 50

The MAH should also confirm that once the dose was adjusted for a patient, the dose was 240 mg for the rest of the duration of the trial. The numbers of subjects with dose escalation appear to be lower at some visits than the previous visit: was this due to drop-outs or were there subjects who returned to previous dose after having had dose adjustment earlier?

Summary of the MAH's response

Among patients with dose adjustment in Study CT-P13 3.8 (both CT-P13 SC 120 mg and Placebo SC groups), no patients have returned to their previous dose by the decision of the investigator to decrease the dose. The number of patients with dose adjustment appeared to be lower at some visits than the previous visit due to dropouts, dose skip and dosing error (e.g. human error) (CSR CT-P13 3.8 (Week 54) Section 12.1 [SN0264]). The dosing errors were corrected in the subsequent study visit. In all, a total of 93 patients received at least one adjusted dose for the safety population during the Maintenance Phase on or after Week 22 and until Week 54. Among them, 9 patients started the adjusted dose at Week 54, 67 patients maintained the adjusted dose at Week 54 and 17 patients were early terminated before the Week 54 administration.

Assessment of the MAH's response

The requested clarifications were received and are sufficient. Issue resolved.

Conclusion

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

No need to update overall conclusion and impact on benefit-risk balance

Question 51

Since the elderly more often suffer from multiple background diseases and are more prone to infections (e.g., herpes zoster and severe influenza or COVID-19), the MAH is requested to submit data on exposure to the 240 mg dose in subjects aged 65 years and above, and if such subjects exist, safety data in these subjects. The MAH should discuss the safety of the 240 mg dosage in the elderly and if any changes to Product Information are needed regarding use of the higher dose in the elderly.

Summary of the MAH's response

In Study CT-P13 3.8 (Crohn's disease), two patients aged above 65 years received the adjusted dose of CT-P13 SC 240 mg during Treatment Period.

A patient in the CT-P13 SC 120 mg group received the adjusted dose of CT-P13 SC 240 mg from Week 22 until study discontinuation at Week 32. The patient was not reported with any treatment-emergent adverse events (TEAEs) during study participation.

A patient in the Placebo group received the adjusted dose of CT-P13 SC 240 mg from Week 22 until study completion at Week 102. The patient's TEAEs reported during the study treatment period (up to Week 102) are presented in Table 10. The patient was reported with 2 TEAEs of infection and 1 TEAE of blood creatine phosphokinase increased after dose adjustment.

Both events of infection (respiratory tract infection viral and latent tuberculosis) were expected adverse reactions based on the product information of Infliximab. In addition, both events were considered unrelated to study drug by the decision of the investigator. Treatment-emergent adverse event of blood creatine phosphokinase increased was reported as possibly related to study drug after dose adjustment. However, TEAE was reported as grade 1 in intensity and recovered with no action taken.

To summarize, no new safety risk was observed from both elderly patients exposed to the dose of CT-P13 SC 240 mg.

Table 99: Treatment-Emergent Adverse Events of A Patient in Treatment Period of Study CT-P13 3.8

Phase	PT	SOC	Grade	Causality	Action Taken	Outcome
Induction (21 days after Week 2)	Abdominal distension	Gastrointestinal disorders	Grade 1	possible	Dose not changed	Recovered/ resolved
Maintenance (2 days after Week 18)	Crohn's disease	Gastrointestinal disorders	Grade 2	unrelated	Dose not changed	Recovered/ resolved
Maintenance (12 days after Week 26)	Respiratory tract infection viral*	Infections and infestations	Grade 2	unrelated	Drug interrupted	Recovered/ resolved
Extension (on Week 70)	Latent tuberculosis*	Infections and infestations	Grade 1	unrelated	Drug interrupted	Not recovered/ not resolved
Extension (on Week 94)	Blood creatine phosphokinase increased*	Investigations	Grade 1	possible	Dose not changed	Recovered/ resolved

*TEAEs occurred after dose adjustment
Abbreviations: PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event

Assessment of the MAH's response

It is agreed that no new safety risk was observed from two elderly patients exposed to the dose of CT-P13 SC 240 mg. One of the two subjects aged >65 years experienced infections (respiratory track infection and latent tuberculosis) and one did not. For comparison, in the entire study population, the incidence of infections during treatment with the 240 mg SC dose was 21/54 (38.9%, 39.94/100 PY) in subjects who escalated from 120 mg SC, and 19/50 (38%, 29.18/100 PY) in subjects who escalated from placebo (table 8 of the response document, see assessment of Question 46). It is known from previous scientific data that the elderly are more at risk of serious infections during infliximab treatment; but there exists no definitive information if the risk is associated with the level of infliximab. Since the increased risk of infections is already covered in the SmPC Sections 4.4 and 4.8, it is agreed that no amendment is warranted in Section 4.2, which refers to Sections 4.4 and 4.8 regarding this risk in the elderly.

Conclusion

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

No need to update overall conclusion and impact on benefit-risk balance

14. 2nd request for supplementary information

14.1. Major objections

None

14.2. Other concerns

Clinical aspects

Efficacy

Please see Section 15 for 2nd round RSI questions and assessment.

15. Assessment of the responses to the 2nd request for supplementary information

15.1. Major objections

None.

15.2. Other concerns

Clinical aspects

Efficacy

UC - Study CT-P13 3.7

Question 1

The possibility to adjust the dose before W54/switch to active treatment is significantly intertwined in the primary endpoints as only patients who did not adjust the dose had a possibility to be responders at week 54. However, mentioning the possibility to increase the dose from the currently approved 120mg SC to 240mg in the SmPC would be promoting an off-label posology, which is not acceptable.

The MAH should discuss whether the results of the primary endpoint at 54 can be clinically interpreted and considered methodologically robust, enough to be included in the SmPC 5.1, without mentioning the possibility of dose escalation.

The following data are required, even though the possibility for dose escalation is no longer sought:

a. The MAH should provide a patient disposition flow chart where discontinuations and dose escalations are clearly outlined up to week 54 (corresponding to Figure 2 in Question 29 in the previous responses).

b. The MAH should provide tables outlining the number of patients who were: a) non-responder according to the clinical criteria b) dose was escalated/switch to active c) discontinuation before Week 54 d) missing data e) incomplete data f) any other reason and corresponding combination categories.

c. The intercurrent event of loss of response was handled differently for different patients and this flaw in the study design could skew the results of the primary outcome. Therefore, it is of interest how many patients had loss of response, how many of them received an escalated dose and how many patients regained response with and without dose escalation. The MAH should provide a table describing the primary and key secondary endpoints by treatment and subgroup: patients with dose adjustment meeting LoR (subgroup 1), patients with dose adjustment not meeting LoR (subgroup 2), patients without dose adjustment meeting LoR (subgroup 3), patients without dose adjustment not meeting LoR (subgroup 4) (corresponding to Table 16 in the response to the previous Q 35).

d. The MAH should also provide spaghetti plots of actual values of the modified Mayo score (overlay and individual) where the time point of dose escalation is standardized in the middle of the graph and 2 visits before and 3 visits after dose escalation are included.

The MAH could also make a proposal for how to include the W22 results in the SmPC and how to refer to the endpoints at W22 as these are not prespecified primary endpoints and not type I error controlled.

To enable assessment of the whole study the above requested tables should be provided even if the MAH might propose not to include any data from study 3.7 into the SPC or if only W22 data are included.

Summary of the MAH's response

Patients who participated in Study CT-P13 3.7 were eligible to receive adjusted dose from Week 22 if they met the loss of response (LoR) criteria according to Study CT-P13 3.7 Protocol Section 5.2 Treatments Administered. These were patients who experienced secondary loss of response (in other words, treatment failure) and were therefore expected to stop receiving the study drug and be withdrawn from the study to initiate new treatment. However, the option for dose adjustment was given for those patients who experienced LoR, in order to provide an alternative treatment option as rescue therapy in considering the ethical aspect of the study.

To demonstrate superiority of CT-P13 SC 120 mg treatment over Placebo, the primary and the key secondary endpoints were only compared between dosing of CT-P13 SC 120 mg and dosing of Placebo, excluding the effect of CT-P13 SC 240 mg treatment. Patients who received adjusted dose were considered as not achieving primary and key secondary endpoints based on pre-defined data analysis rules, as specified in the statistical analysis plan (SAP). Therefore, the treatment effect of CT-P13 SC 240 mg was not accounted for in the results of the primary and the key secondary endpoints. CELLTRION therefore wishes to maintain the W54 results from the UC study.

While the Agency's concern regarding the possibility of off-label treatment is acknowledged, the use of CT-P13 SC 240 mg in ulcerative colitis is not mentioned in the SPC. Therefore, with the current context there is no possibility to promote an off-label posology by mentioning dose adjustment to CT-P13 SC 240 mg.

In addition, Applicant presents pos-hoc analysis data requested by Agency as below.

a. Patient disposition flow chart where discontinuations and dose escalations are clearly outlined up to week 54.

Applicant provides the flow chart of patient disposition regarding discontinuation for all-randomized population as Figure 1.

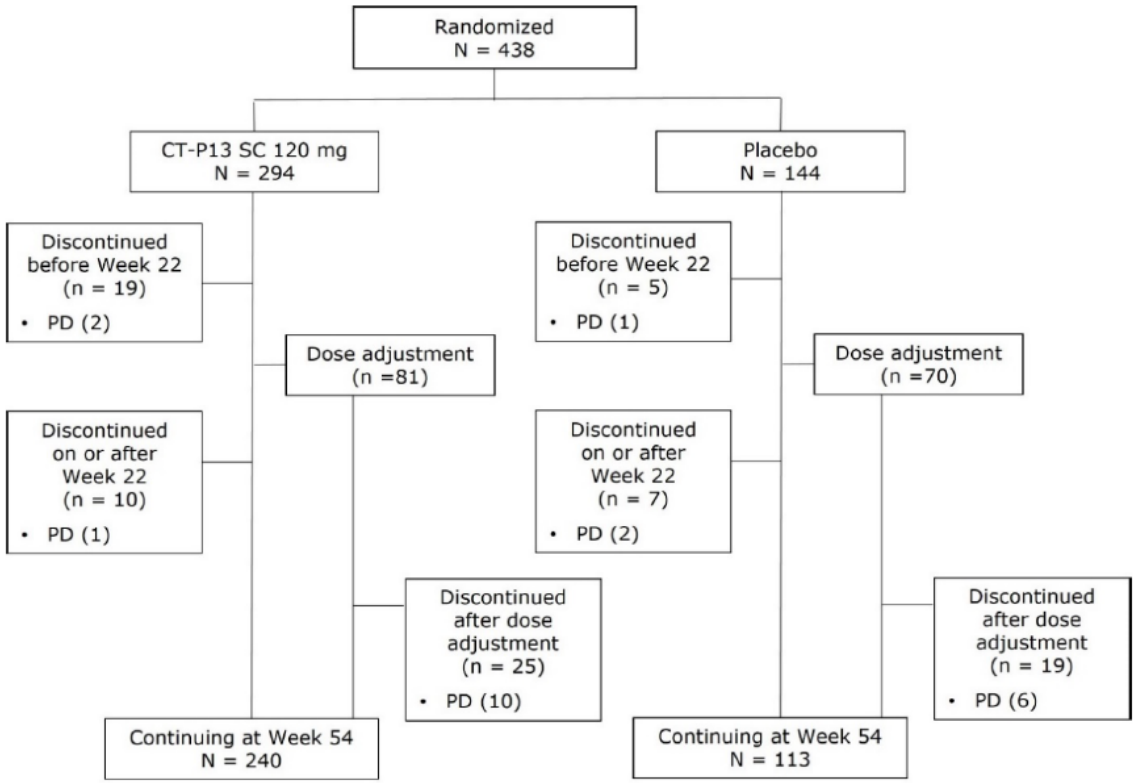


Figure 41: Flow chart of Patient Disposition of Study CT-P13 3.7: All-Randomized Population

In CT-P13 SC 120 mg group, 19 (6.5%) patients discontinued the study before Week 22. A total of 81 (27.6%) patients in CT-P13 SC 120 mg group received adjusted dose before Week 54 visit. Among patients who discontinued on or after Week 22, 25 (8.5%) patients discontinued after dose adjustment and 10 (3.4%) patients discontinued without dose adjustment.

In Placebo group, 5 (3.5%) patients discontinued the study before Week 22, and a total of 70 (48.6%) patients received adjusted dose before Week 54. Among patients who discontinued the study on or after Week 22, 19 (13.2%) patients discontinued after dose adjustment and 7 (4.9%) patients discontinued without dose adjustment.

b. Tables outlining the number of patients who were: a) non-responder according to the clinical criteria b) dose was escalated/switch to active c) discontinuation before Week 54 d) missing data e) incomplete data f) any other reason and corresponding combination categories.

As requested, the requested table including the number of patients that correspond to those criteria for the primary and the key secondary endpoints is presented below.

Table 100: Number of Patients who were Non-remitter/Non-responder for Primary and Key Secondary Endpoints at Week 54 in Study CT-P13 3.7: All-randomized Population

Endpoint Reason for non-remitter/non-responder	CT-P13 SC (N=294)	Placebo (N=144)	Total (N=438)
Clinical Remission[1]			
Discontinuation before Week 54	48 (16.3%)	24 (16.7%)	72 (16.4%)
Dose escalation or switch to CT-P13 SC from placebo	61 (20.7%)	58 (40.3%)	119 (27.2%)
Incomplete data	11 (3.7%)	9 (6.3%)	20 (4.6%)
Missing data	0	0	0
Non-remitter according to the clinical criteria	47 (16.0%)	23 (16.0%)	70 (16.0%)
Clinical Response[2]			
Discontinuation before Week 54	48 (16.3%)	24 (16.7%)	72 (16.4%)
Dose escalation or switch to CT-P13 SC from placebo	61 (20.7%)	58 (40.3%)	119 (27.2%)
Incomplete data	11 (3.7%)	9 (6.3%)	20 (4.6%)
Missing data	0	0	0
Non-responder according to the clinical criteria	16 (5.4%)	8 (5.6%)	24 (5.5%)
Endoscopic-histologic Mucosal Improvement[3]			
Discontinuation before Week 54	48 (16.3%)	24 (16.7%)	72 (16.4%)
Dose escalation or switch to CT-P13 SC from placebo	61 (20.7%)	58 (40.3%)	119 (27.2%)
Incomplete data	8 (2.7%)	2 (1.4%)	10 (2.3%)
Missing data	9 (3.1%)	7 (4.9%)	16 (3.7%)
Non-responder according to the clinical criteria	63 (21.4%)	29 (20.1%)	92 (21.0%)
Corticosteroid-free Remission[4]			
Discontinuation before Week 54	21/120 (17.5%)	13/61 (21.3%)	34/181 (18.8%)
Dose escalation or switch to CT-P13 SC from placebo	32/120 (26.7%)	29/61 (47.5%)	61/181 (33.7%)
Incomplete data	3/120 (2.5%)	2/61 (3.3%)	5/181 (2.8%)
Missing data	0/120	0/61	0/181
Non-remitter according to the clinical criteria	20/120 (16.7%)	6/61 (9.8%)	26/181 (14.4%)

Source: Section 5.3.5.3 Post-hoc Table 2.285

Note: A patient with two or more reasons for non-responder/non-remitter is included in one of the reasons in following order; c) discontinuation before Week 54 – b) dose escalation or switch to CT-P13 SC from placebo – e) incomplete data – d) missing data – a) non-remitter/non-responder according to the criteria – f) any other reason. There were no cases due to 'any other reason.'

[1] Clinical remission is defined as modified Mayo score with a stool frequency subscore of 0 or 1, rectal bleeding subscore of 0, and endoscopic subscore of 0 or 1.

[2] Clinical response is defined as a decrease in modified Mayo score from baseline of at least 2 points and at least 30%, with an accompanying decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1 point.

[3] Endoscopic-histologic mucosal improvement is defined as an absolute endoscopic subscore of 0 or 1 point from modified Mayo score and an absolute Robarts Histopathology Index (RHI) score of 3 points or less with an accompanying laminal propria neutrophils and neutrophils in epithelium subscore of 0 point.

[4] Corticosteroid-free remission is defined as being in clinical remission by modified Mayo score in addition to not requiring any treatment with corticosteroid for at least 8 weeks at Week 54, among the patients who used oral corticosteroids at baseline.

c. Table describing the primary and key secondary endpoints by treatment and subgroup: patients with dose adjustment meeting LoR (subgroup 1), patients with dose adjustment not meeting LoR (subgroup 2), patients without dose adjustment meeting LoR (subgroup 3), patients without dose adjustment not meeting LoR (subgroup 4).

In Study CT P13 3.7, dose adjustment to CT P13 SC 240 mg was allowed from Week 22 when the patient met LoR criteria defined in the protocol. The LoR was defined as an increase in modified Mayo score (mMS) of ≥2 points and ≥30% from the Week 10 mMS with actual value of ≥5 points, and endoscopic subscore of ≥2 points.

Patients in Study CT-P13 3.7 were divided into four subgroups for CT-P13 SC 120 mg and placebo groups to evaluate the impact of meeting LoR criteria and dose adjustment.

Analysis results for the primary/key secondary endpoints for patients by dose adjustment status in all-randomised population are provided in Table 2. Primary endpoints include clinical remission at Week 54. Key-secondary endpoints include clinical response at Week 54, endoscopic-histologic mucosal improvement and corticosteroid-free remission at Week 54.

As shown in Table 2, as number of patients without dose adjustment meeting LoR criteria was very small and patients with dose adjustment were considered as non-remitter/non-responder, the Applicant believes that efficacy result of Week 54 is not impacted by the handling of the intercurrent event of Loss of Response.

Table 101: Number of Patients who achieved efficacy endpoints (Primary/Key-secondary) at Week 54 by dose adjustment status

	CT-P13 SC (N=294)				Placebo (N=144)			
	subgroup 1 (N' = 48)	subgroup 2 (N' = 29)	subgroup 3 (N' = 5)	subgroup 4 (N' = 187)	subgroup 1 (N' = 46)	subgroup 2 (N' = 21)	subgroup 3 (N' = 3)	subgroup 4 (N' = 64)
Primary endpoints								
Clinical Remission at Week 54	10 (20.8%)	10 (34.5%)	0	127 (67.9%)	13 (28.3%)	11 (52.4%)	0	30 (46.9%)
Key secondary endpoints								
Clinical response at Week 54	20 (41.7%)	20 (69.0%)	2 (40%)	156 (83.4%)	25 (54.3%)	16 (76.2%)	0	45 (70.3%)
Endoscopic-histologic mucosal improvement at Week 54	9 (18.8%)	9 (31.0%)	0	105 (56.1%)	12 (26.1%)	11 (52.4%)	0	23 (35.9%)
Corticosteroid-free remission at Week 54	7/21 (33.3%)	6/18 (33.3%)	0/0	44/70 (62.9%)	6/26 (23.1%)	4/11 (36.4%)	0/1	11/19 (57.9%)

Source: Section 5.3.5.3 Post-hoc Table 2.286
Note: LoR is defined as following: an increase in modified Mayo score ≥ 2 points and ≥ 30% from the Week 10 modified Mayo score with actual value of ≥ 5 points, and endoscopic subscore of ≥ 2 points. The patients who have at least one mMS result on or after Week 22 including Unscheduled and EOS visit are categorized according to LoR and dose adjustment from Week 22 prior to Week 54. Four subgroups; patients with dose adjustment meeting LoR (subgroup 1), patients with dose adjustment not meeting LoR (subgroup 2), patients without dose adjustment meeting LoR (subgroup 3), patients without dose adjustment not meeting LoR (subgroup 4). Except corticosteroid-free remission at Week 54, percentages are calculated using the number of patients in each subgroup as denominator. For corticosteroid-free remission at Week 54, percentages are calculated by using the number of patients who used oral corticosteroids at Baseline in each subgroup as the denominator.
[1] Clinical remission is defined as modified Mayo score with a stool frequency subscore of 0 or 1, rectal bleeding subscore of 0, and endoscopic subscore of 0 or 1.
[2] Clinical response is defined as a decrease in modified Mayo score from baseline of at least 2 points and at least 30%, with an accompanying decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1 point.
[3] Endoscopic-histologic mucosal improvement is defined as an absolute endoscopic subscore of 0 or 1 point from modified Mayo score and an absolute Robarts Histopathology Index (RHI) score of 3 points or less with an accompanying laminal propria neutrophils and neutrophils in epithelium subscore of 0 point.
[4] Corticosteroid-free remission is defined as being in clinical remission by modified Mayo score in addition to not requiring any treatment with corticosteroid for at least 8 weeks at Week 54, among the patients who used oral corticosteroids at baseline.
Abbreviations: LoR, loss of response; mMS, modified mayo score; N', number of patients in the subgroup; RHI, robarts histopathology index; SC, subcutaneous.

d. Spaghetti plots of actual values of the modified Mayo score (overlay and individual) where the time point of dose escalation is standardized in the middle of the graph and 2 visits before and 3 visits after dose escalation are included.

Applicant provides overlay and individual spaghetti plots of partial Mayo score at 2 visits before (including the time of dose adjustment) and 3 visits after dose adjustment for patients with dose adjustment meeting Lose of response (subgroup 1) and patients with dose adjustment not meeting loss of response (subgroup 2) for CT-P13 SC group (Figure 2). While the modified Mayo score is assessed only at three time points (Weeks 10, 22, and 54), the partial Mayo score is assessed at seven time points (Weeks 10, 14, 22, 30, 38, 46, and 54) in the maintenance phase per protocol and a spaghetti plot was generated based on the partial Mayo score. Dose adjustments were allowed based on loss of response criteria starting at week 22, the condition of "2 visits before and 3 visits after dose escalation" could not be satisfied if calculated with modified Mayo score due to not enough visits, partial Mayo score was substituted to create a spaghetti plot.

Overall, partial Mayo scores in 1st after dose adjustment visit were decreased after dose adjustment compared to dose adjustment visit. In the long term (2nd and 3rd after dose adjustment), the decreased partial Mayo scores were further reduced or maintained compared to the dose adjustment visit, with a few outliers in both subgroups 1 and 2 in the CT-P13 SC group.

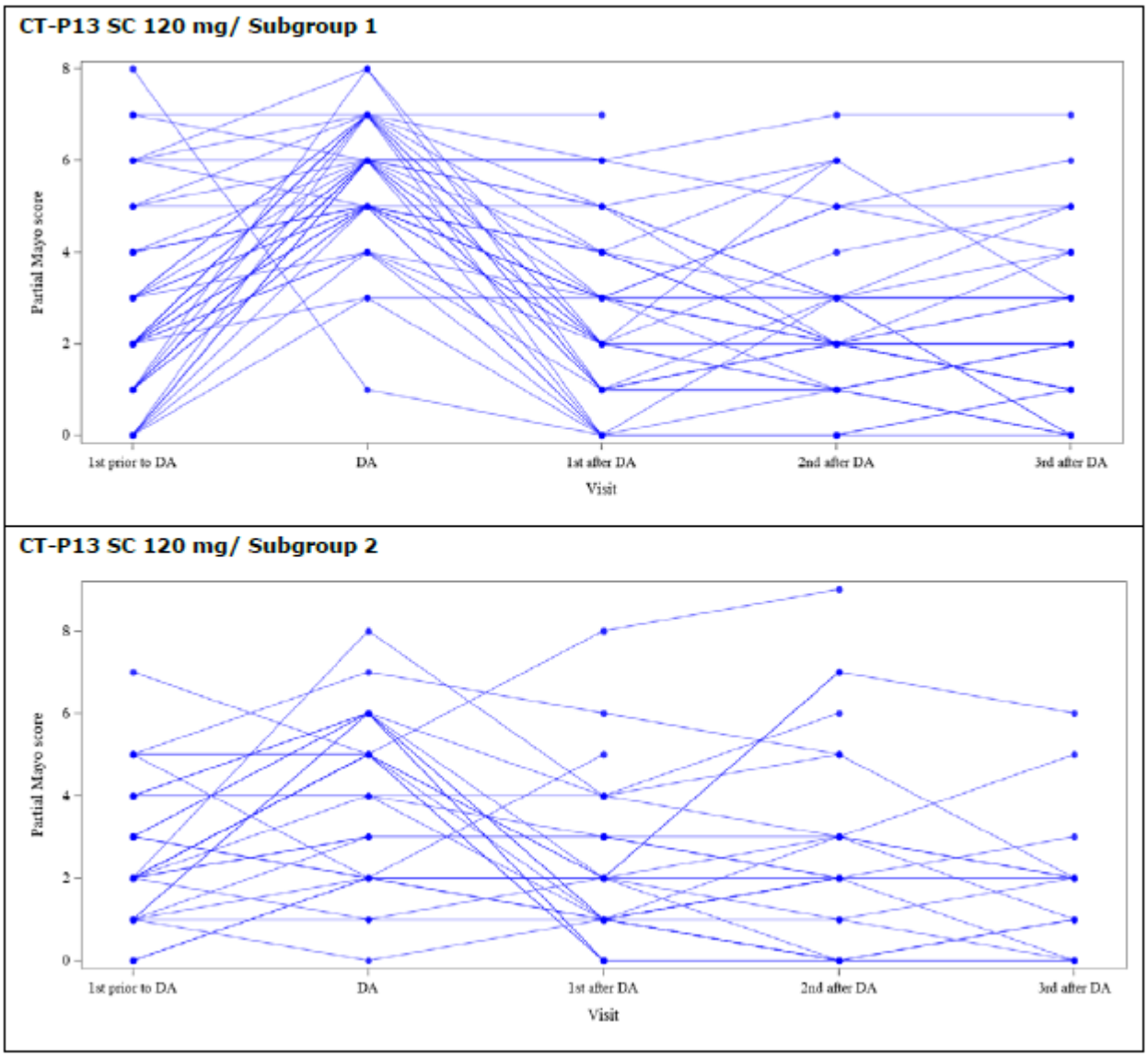


Figure 42: Partial Mayo Score versus Time by Dose Adjustment Status

Assessment of the MAH's response

The Applicant has provided the requested tables and figures

The numbers in the flow chart and in table 1 and 2 do not add up. According to the Flow chart 81 and 70 patients in SC 120 and placebo groups, respectively received a dose escalation. According to Table 2 the numbers seem to be 77 and 67 and in Table 1 the numbers are 61 and 58. This discrepancy might be due to missing efficacy data or different classification of patients who increased the dose on W54. However, as these discrepancies do not affect the final conclusions or the SPC, the issue will not be pursued further.

The efficacy results in table 2 and the spaghetti plots illustrate that there is no apparent benefit to be gained from a dose escalation from 120mg to 240mg Remsima in UC patients. Although a decrease on Partial Mayo score is seen immediately after the dose escalation, the improvement does not last rendering it clinically insignificant. The initial improvement also needs to be interpreted with caution as subjective symptom assessment after an open label dose adjustment is prone to bias due to expectations and the results are also prone to regression to the mean. Therefore, the decision to withdraw the application for dose escalation

is endorsed.

The Applicant proposes to maintain the W54 results of the UC study 3.7 in the SPC section 5.1 but it is apparent that the Applicant did not grasp the problem concerning the study design leading to biased outcome.

According to study protocol, patients were offered a dose escalation if they met LoR criteria after week 22. However, based on the provided results, 29/294 patients in the infliximab group and 21/144 in the placebo group were switched to 240 mg Remsima despite not meeting LoR criteria. Hence, a total of 35% (50/144) of all patients who received a dose adjustment did not meet LoR criteria. No special criteria for these dose escalation decisions were prespecified or explained post hoc. Some patients with LoR were immediately established as being treatment failures, while others, were considered non-responders only if they remained non-responders also at week 54. The criteria for continuing on randomized treatment despite LoR were never defined in the protocol.

The Applicant believes that efficacy results of Week 54 are not impacted by the handling of the intercurrent event of Loss of Response. Patients without dose adjustment despite meeting LoR criteria were few (5 and 3 in SC 120 and placebo groups, respectively). Therefore, it is agreed that these particular patients are not expected to have a meaningful impact on the final outcome even though they were included as potential responders at week 54. (None of these patients were remitters/responders at W 54.)

However, handling of the LoR event was different for different patients. The different handling was not according to protocol, not randomised and not free from bias. Ultimately, 10% of all patients in the SC 120mg group and 15% in the placebo group were classified as non-remitter/non-responder only due to dose escalation, not due to per protocol LoR. As 35% of all patients who received a dose adjustment did not meet LoR criteria, classifying patients with dose escalation as non-responders as if they were all patients who lost response after W22 is simply not reflecting reality.

Out of all non-responders at W54, only 5.5% were classified as non-responders based on clinical criteria, with no difference between treatment groups, while the rest of the non-responders were due to intercurrent events, mainly dose adjustment, which did not equal LoR.

As all patients randomised are included in the primary endpoint, all the aforementioned issues have a direct impact on the results of the primary endpoint.

As understood by the assessor, the intention of the study protocol was to reflect a treatment policy situation where a patient in case of loss of response could either be taken off the randomised treatment (incl. placebo) and switched to alternative/rescue therapy or continue in hope of better days to come. This approach likely reflects the real-world situation and could have been an acceptable approach. The decision to continue with a double dose was in effect handled as a switch to rescue therapy. Handling a switch to rescue therapy as a treatment failure is in line with the EMA guideline on the development of new medicinal products for the treatment of Crohn's Disease. However, in this particular study where the investigators knew that patients could be assigned to placebo although the efficacy of the active treatment as maintenance therapy is already established, the psychological incentive to start rescue therapy may have been higher than usual.

Some patients were apparently not considered to benefit from the treatment by the treating physician despite not meeting clinical LoR criteria. These patients were also "put on rescue therapy". In study 3.7 such physician decisions were abundant (35% of all dose escalations) and done off protocol, without prespecified criteria or any post hoc explanation. Therefore, the outcome does not reflect the prespecified primary endpoint, as the protocol defined all dose escalations to be consequences of LoR and dose

escalations by physicians' decision (other than LoR) were not specified in the protocol as appropriate reason to start "rescue therapy" nor an intercurrent event. In the protocol, "Patient develops signs of disease progression in the investigator's judgement" was a reason for withdrawal, but these patients were not recorded as withdrawals.

The reason for the high number of this type of protocol violations may be related to the definition of LoR. In the protocol, the LoR criteria were based on modified Mayo score (including the endoscopic subscore): *"an increase in modified Mayo score of ⩾2 points and ⩾30% from the Week 10 modified Mayo score with actual value of ⩾5 points, and endoscopic subscore of ⩾2 points."* However, the modified Mayo score was only recorded at weeks 10, 22 and 54. Hence, according to protocol it was not even possible to detect a LoR between W22 and 54. Therefore, if not done on W22, the decisions to escalate the dose were probably based on partial Mayo score (excluding the endoscopic subscore), which was recorded at every visit. The problem is that a patient who meets the hitherto undefined criteria for LoR by partial Mayo, would not necessarily be a non-responder according to the modified Mayo, which defines the primary endpoint.

To conclude, the off-label dose escalation after W22 meaningfully affects the interpretation of the results at W54 and the true impact of Remsima SC maintenance regiment cannot be estimated based on the results of this study. 35% of the dose escalations were not according to protocol, which introduces a major bias and puts the whole planning and conduct of the study into question. Therefore, the W54 results from study 3.7 are invalid for inclusion in the SPC.

While there is no doubt that Remsima SC is in fact more effective than placebo in the treatment of UC, the magnitude of the difference cannot be accurately estimated based on the results of this trial. The UC indication is already granted and is not put into question but no new useful information for the prescriber has been presented with this application.

Of note, the same flaw in study design was present in study 3.8 in CD patients, including suboptimal definition of non-remitter/non-responder and unclear criteria and some non-compliance with the protocol regarding dose escalation. However, the number of patients receiving dose escalation despite not meeting LoR criteria was small and the overall data were more robust. Hence, inclusion of study 3.8 results in SPC 5.1 is considered acceptable.

Conclusion

Issue not resolved.

The results from study 3.7 are invalid for inclusion in the SPC. The follow-up question is upgraded to a MO.

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

No need to update overall conclusion and impact on benefit-risk balance

CD - Study CT-P13 3.8

Question 2

The flow chart provided in response to Q28 shows that 44 patients received dose adjustment, while the flow chart provided in response to Q29 shows 39 patients receiving dose adjustment. The difference should be clarified.

Summary of the MAH's response

Response to Question 28 provided flow chart providing how many patients had received adjusted dose in all randomized population throughout the whole study duration including Maintenance (from Week 10 to Week 54) and Extension phase (from Week 56 to Week 102). The number of patients received dose adjustment during Maintenance phase on or after Week 22 until Week 54 was 44 in CT-P13 SC 120 mg group and 49 in Placebo group.

However, in Response to Question 29, 39 patients in CT-P13 SC 120 mg group and 45 patients in Placebo group who had received adjusted dose before Week 54 visit were reported. As mentioned in Response to Question 50, the number of patients who started the adjusted dose at Week 54 was 9. These patients (5 patients in CT-P13 SC 120 mg group and 4 patients in Placebo group) were excluded in Response to Question 29.

Assessment of the MAH's response

The discrepancy in numbers has been explained.

Conclusion

Issue resolved.

☐Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

SPC

Question 3

In section 5.1 the following paragraph is included for both CD and UC:

… the impact of use of immunosuppressant (azathioprine, 6-mercaptopurine and methotrexate) on efficacy was evaluated. There was no significant difference between patients with and without immunosuppressants in the primary and the key secondary efficacy endpoints.

No data were provided to justify the statements. The statements should be removed or appropriately justified for both indications.

Summary of the MAH's response

Per the comment from CHMP, an additional post-hoc analysis was performed to evaluate the impact of the use of immunosuppressant (azathioprine, 6-mercatopurine and methotrexate) on efficacy as presented in Table 1, Table 2.

As shown in Table 1, Table 2 there was no significant difference between patients with and without immunosuppressants in the (co-)primary and the key secondary efficacy endpoints for both studies (Studies CT-P13 3.7 [UC] and CT-P13 3.8 [CD]).

The difference in the proportion of patients achieving corticosteroid-free remission at week 54 in the CT-P13 SC arm appears to be relatively greater than other endpoints for both Studies CT-P13

3.7 and CT-P13 3.8. However, the proportion of patients achieving corticosteroid-free remission was calculated using the number of patients who received corticosteroid at baseline as a denominator, the results should therefore be interpreted with caution considering the small number of patients actually included in the calculation.

Therefore, based on the results of the post-hoc analysis presented in Table 1, Table 2 CELLTRION wishes to maintain the statement in section 5.1 of the SmPC.

Table 102: Summary of the impact of use of immunosuppressant (azathioprine, 6-mercaptopurine and methotrexate) on the primary and key secondary endpoints in study CT-P13 3.7

	CT-P13 SC 120 mg (N=294)				Placebo (N=144)			
	Patients with AZA/6MP/ MTX (N'=65)	Patients without AZA/6MP/ MTX (N'=229)	Difference (95% CI)[1]	P-value[2]	Patients with AZA/6MP/ MTX (N'=32)	Patients without AZA/6MP/ MTX (N'=112)	Difference (95% CI)[1]	P-value[2]
Proportion of Patients Achieving Clinical Remission at Week 54	32 (49.2%)	95 (41.5%)	5.3 (-8.3, 18.9)	0.4119	7 (21.9%)	23 (20.5%)	1.5 (-12.6, 19.8)	0.8535
Proportion of Patients Achieving Clinical Response at Week 54	34 (52.3%)	124 (54.1%)	-3.6 (-17.3, 9.9)	0.5760	10 (31.3%)	35 (31.3%)	1.5 (-15.3, 20.8)	0.8682
Proportion of Patients Achieving Endoscopic-histologic Mucosal Improvement at Week 54	27 (41.5%)	78 (34.1%)	4.6 (-8.4, 18.2)	0.4763	8 (25%)	16 (14.3%)	9.8 (-4.7, 27.8)	0.2106
Proportion of Patients Achieving Corticosteroid-free Remission at Week 54[3]	12/26 (46.2%)	32/94 (34.0%)	13.0 (-7.3, 33.4)	0.1966	3/16 (18.8%)	8/45 (17.8%)	1.6 (-17.5, 27.4)	0.8906

Source: Section 5.3.5.3 Post-hoc Tables 2.275-2.278
Note: Analysis is stratified by Previous exposure to biologic agent and/or JAK inhibitors (used or not used), Use of treatment with oral corticosteroids at Week 0 (used or not used) and Clinical remission at Week 10 (remitter or non-remitter by modified Mayo score [Study 3.7]). Patients with dose adjustment to CT-P13 SC 240 mg prior to Week 54 are considered as non-remitter/non-responder.
N' = number of patients with/without AZA/6MP/MTX at Baseline
[1] The difference of proportions between patients with/without AZA/6MP/MTX estimated using CMH weights, and the 95% stratified Newcombe CI with CMH weights are presented.
[2] The nominal p-value from stratified CMH test is presented in descriptive purpose.
[3] The proportion of patients achieving corticosteroid-free remission was calculated using the number of patients who received corticosteroid at baseline as a denominator, the results should therefore be interpreted with caution considering the small number of patients actually included in the calculation.

Table 103: Summary of the impact of use of immusuppressant (azathioprine, 6-mercaptopurine and methotrexate) on the co-primary and key secondary endpoints in study CT-P13 3.8

	CT-P13 SC 120 mg (N=231)				Placebo (N=112)			
	Patients with AZA/6MP/ MTX (N'=71)	Patients without AZA/6MP/ MTX (N'=160)	Difference (95% CI)[1]	P-value[2]	Patients with AZA/6MP/ MTX (N'=40)	Patients without AZA/6MP/ MTX (N'=72)	Difference (95% CI)[1]	P-value[2]
Proportion of Patients Achieving Clinical Remission (based on CDAI) at Week 54	47 (66.2%)	97 (60.6%)	-2.5 (-16.4, 10.8)	0.7194	16 (40%)	20 (27.8%)	11.1 (-7.0, 29.3)	0.2380
Proportion of Patients Achieving Endoscopic Response (Based on SES-CD [Central]) at Week 54	37 (52.1%)	81 (50.6%)	-0.5 (-14.7, 13.6)	0.9492	10 (25%)	10 (13.9%)	9.8 (-5.3, 26.8)	0.2082
Proportion of Patients Achieving CDAI-100 Response at Week 54	49 (69.0%)	103 (64.4%)	-2.0 (-15.8, 10.9)	0.7686	18 (45%)	25 (34.7%)	9.0 (-9.7, 27.5)	0.3592
Proportion of Patients Achieving Clinical Remission (Based on AP and SF) at Week 54	42 (59.2%)	89 (55.6%)	-4.1 (-18.2, 9.7)	0.5647	16 (40%)	19 (26.4%)	12.3 (-5.9, 30.4)	0.1872
Proportion of Patients Achieving Endoscopic Remission (Based on SES-CD [Central]) at Week 54	25 (35.2%)	55 (34.4%)	-1.4 (-14.7, 12.7)	0.8439	7 (17.5%)	5 (6.9%)	9.6 (-3.6, 25.3)	0.1318
Proportion of Patients Achieving Corticosteroid-free Remission (Based on CDAI) at Week 54[3]	13/23 (56.5%)	27/76 (35.5%)	8.2 (-14.7, 30.9)	0.4875	4/12 (33.3%)	5/32 (15.6%)	18.3 (-7.5, 45.1)	0.1820

Source: Section 5.3.5.3 Post-hoc Tables 2.279-2.284
Note: Analysis is stratified by Previous exposure to biologic agent and/or JAK inhibitors (used or not used), Use of treatment with oral corticosteroids at Week 0 (used or not used) and Clinical remission at Week 10 (remitter or non-remitter by CDAI score [Study 3.8]). Patients with dose adjustment to CT-P13 SC 240 mg prior to Week 54 are considered as non-remitter/non-responder.

Assessment of the MAH's response

No significant difference in primary and key secondary outcome was seen between patients with or without immunosuppressant treatment (azathioprine, 6-mercatopurine and methotrexate). The SPC paragraph may remain in the section about Crohn's but not in the UC section as the whole UC section should be deleted (see MO).

Conclusion

Issue resolved.

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

No need to update overall conclusion and impact on benefit-risk balance

Question 4

In section 5.1 for CD the MAH should add an explanation that patients with dose escalation were considered non-responders. This could be in the form of a suffix to the results table.

Summary of the MAH's response

Per EMA's comment, suffix has been added in the results table of Section 5.1 to explain that patients with dose escalation were considered non-responders.

Assessment of the MAH's response

The following sentence was added as a suffix to the results table: *"Patients with dose adjustment prior to Week 54 were considered non-responders/non-remitters."* *An alternative wording is still requested to add more clarity.*

Conclusion

Issue partly resolved.

☐Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

Question 5

In section 4.8 the MAH should propose a revision of the paragraph on immunogenicity. ADA status and especially high ADA titres had a clear association with drug concentrations and loss of response in study 3.8. This should be reflected in the SPC as the current text is misleading. To properly justify the amended text, which is also referring to UC patients, the correlation between loss of response and ADA status, median ADA titres and drug concentrations should be presented for both indications in tables where subgroups 1 and 3 are pooled and compared to subgroups 2 and 4, as defined in responses to Q 34.

Summary of the MAH's response

Per the comment from CHMP, an additional post-hoc analysis was performed to explore the correlation between loss of response and ADA status, median ADA titres and drug concentrations for both indications in Studies CT-P13 3.7 and CT-P13 3.8.

As shown in Table 3, in study CT-P13 3.7, and in Table 4 in study CT-P13 3.8, the proportion of ADA positive patients was slightly higher in the patients with loss of response (subgroup 1+3 pooled) compared to the patients without dose adjustment and not meeting loss of response (subgroup 4). The proportion of ADA positive patients was higher in the patients with dose adjustment and not meeting loss of response (subgroup 2), but since the number of patients included in subgroup 2 is limited, the result of subgroup 2 was not considered when interpretating the overall trend. However, the association between ADA titre and loss of response was seen in the CT-P13 SC treatment arm as the median ADA titre was higher in patients with loss of response (subgroup 1+3 pooled) compared to patients without loss of response. Lastly, the correlation between drug concentrations and loss of response was evaluated, and relatively lower drug concentration was observed in patients with loss of response (subgroup 1+3 pooled) compared to patients without loss of response (subgroup 2 and subgroup 4).

In addition, further analyses conducted with integrated safety data from studies CT-P13 3.7 and CT-P13 3.8 in the CT-P13 SC treatment arm in a post-hoc manner to assess potential impact of ADA on safety suggests that the incidence of infection, malignancy and immune-mediated AEs, TEAE and TESAE by ADA titre quartile showed no apparent correlation between ADA titre and AE incidences. The data is presented in Table 5 and Table 6.

Therefore, the paragraph on immunogenicity in section 4.8 is revised to indicate the impact of ADA on efficacy, while the text on safety profile remains unamended.

Assessment of the MAH's response

The proposed wording is acceptable with a small editorial amendment. The word "slight" should be deleted as it is too vague.

Conclusion

Issue resolved.

☐Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

16. 3rd request for supplementary information

16.1. Major objections

Clinical aspects/SPC

1. Study 3.7 in UC patients does not provide methodologically robust and clinically significant information for the prescriber. The study was not conducted according to protocol. The number and nature of the protocol violations are such that the W54 results do not provide a meaningful interpretation. Further, it would not be possible to describe the study appropriately without mentioning the possibility to increase the dose from the currently approved 120mg SC to 240mg, which would be promoting an off-label posology. Hence the description of the study should be removed from SPC 5.1.

16.2. Other concerns

Clinical aspects/SPC

2. Including p-values in the table describing efficacy results from study 3.8 in CD patients is not acceptable. The results are merely descriptive as the interpretation of the outcome is hampered by the study design.
3. Please see attached product information for additional minor amendments.

17. Assessment of the responses to the 3rd request for supplementary information

17.1. Major obections

Question 1

Study 3.7 in UC patients does not provide methodologically robust and clinically significant information for the prescriber. The study was not conducted according to protocol. The number and nature of the protocol

violations are such that the W54 results do not provide a meaningful interpretation. Further, it would not be possible to describe the study appropriately without mentioning the possibility to increase the dose from the currently approved 120mg SC to 240mg, which would be promoting an off-label posology. Hence the description of the study should be removed from SPC 5.1.

Summary of the MAH's response

The Applicant acknowledges that in Study CT-P13 3.7, some patients who did not meet the loss of response (LoR) criteria underwent a dose adjustment. Thus, the applicant proposes to show key efficacy results at Week 22, as per the recommendation received from the CHMP in the 2nd RSI, which weren't influenced by dose adjustment design. The key efficacy results at Week 22 are presented in Table 1, demonstrating significant findings with all p-values still below 0.05.

Table 104 Proportion of patients achieving primary and key secondary endpoints at Week 22: all-randomized population

	CT-P13 SC 120 mg (N=294)	Placebo SC (N=144)	Difference (95% CI)[1]	P-value[2]
Clinical Remission at Week 22	128 (43.5%)	41 (28.5%)	13.8 (4.1, 22.7)	0.0025
Clinical Response at Week 22	187 (63.6%)	64 (44.4%)	18.3 (8.4, 27.9)	0.0002
Endoscopic-histologic Mucosal Improvement at Week 22	105 (35.7%)	36 (25%)	9.5 (0.2, 18.0)	0.0343

Source: CSR CT-P13 3.7 Post-text Tables 14.2.3.1, 14.2.3.4 and 14.2.3.5.
Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; SC, subcutaneous.
Clinical remission is defined as modified Mayo score with a stool frequency subscore of 0 or 1, rectal bleeding subscore of 0, and endoscopic subscore of 0 or 1.
Clinical response is defined as a decrease in modified Mayo score from baseline of at least 2 points and at least 30%, with an accompanying decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1 point.
Endoscopic-histologic mucosal improvement is defined as an absolute endoscopic subscore of 0 or 1 point from modified Mayo score and an absolute Robarts Histopathology Index (RHI) score of 3 points or less with an accompanying laminal propria neutrophils and neutrophils in epithelium subscore of 0 point.

The Applicant has updated Section 5.1 of the SmPC with the Week 22 results presented above.

As an alternative, considering the CHMP's opinion, a post-hoc analysis excluding patients who did not meet the LoR criteria but received a dose adjustment was conducted.

Assessment of the MAH's response

The Week 22 endpoints were not pre-specified in the protocol and SAP. Generally, post-hoc analyses are included in SmPC 5.1. only in exceptional situations. Furthermore, as previously discussed, it has become apparent during the assessment that the overall study conduct and the concordance of the protocol and planned statistical analyses are not considered to produce reliable and robust results. For all the aforementioned reasons, the Week 22 results are not considered adequate for inclusion in the SmPC.

The alternative approach proposed by the MAH to exclude patients who did not meet the LoR criteria but received a dose adjustment, and to present W54 data from this subpopulation is not acceptable. This

approach would also be presenting post-hoc data. Moreover, W54 data could not be presented without mentioning the possibility to dose adjust, which would be promoting off-label dosing.

Conclusion

Issue not resolved. A major objection remains.

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance

17.2. Other concerns

Question 2

Including p-values in the table describing efficacy results from study 3.8 in CD patients is not acceptable. The results are merely descriptive as the interpretation of the outcome is hampered by the study design.

Summary of the MAH's response

Agency's comment to exclude the p-values in the table is acceptable. The p-value is therefore deleted from the table.

Assessment of the MAH's response

P-values were removed from the table.

Conclusion

Issue resolved.

☐Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

Question 3

Please see attached product information for additional minor amendments.

Summary of the MAH's response

The minor amendments suggested by the Agency are acceptable. Please see the product information for applicant's response to Agency's suggestions for minor amendments.

Assessment of the MAH's response

Suggested amendments have been implemented.

Conclusion

Issue resolved.

☐Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

18. 4th request for supplementary information

18.1. Major objections

Clinical aspects/SPC

1. Study 3.7 in UC patients does not provide methodologically robust and clinically significant information for the prescriber. The study was not conducted according to protocol. The number and nature of the protocol violations are such that the W54 results do not provide a meaningful interpretation. Further, it would not be possible to describe the study appropriately without mentioning the possibility to increase the dose from the currently approved 120mg SC to 240mg, which would be promoting an off-label posology.

   The Week 22 endpoints were not pre-specified in the protocol and SAP. Generally, post-hoc analyses are included in SmPC 5.1. only in exceptional situations. In this case, there is no clinical necessity to include the data.

   Furthermore, it has become apparent during the assessment that the overall study conduct and the concordance of the protocol and planned statistical analyses are not considered to produce reliable and robust results. For all the aforementioned reasons, the Week 22 results are not considered adequate for inclusion in the SmPC. Hence the description of the study should be removed from SPC 5.1.

19. Assessment of the early responses to the 4th request for supplementary information

19.1. Major Objections

Question 1

Study 3.7 in UC patients does not provide methodologically robust and clinically significant information for the prescriber. The study was not conducted according to protocol. The number and nature of the protocol violations are such that the W54 results do not provide a meaningful interpretation. Further, it would not be possible to describe the study appropriately without mentioning the possibility to increase the dose from the currently approved 120mg SC to 240mg, which would be promoting an off-label posology.

The Week 22 endpoints were not pre-specified in the protocol and SAP. Generally, post-hoc analyses are included in SmPC 5.1. only in exceptional situations. In this case, there is no clinical necessity to include the data.

Furthermore, it has become apparent during the assessment that the overall study conduct and the concordance of the protocol and planned statistical analyses are not considered to produce reliable and robust results. For all the aforementioned reasons, the Week 22 results are not considered adequate for inclusion in the SmPC. Hence the description of the study should be removed from SPC 5.1.

Summary of the MAH's response

The MAH agreed to delete the proposed text.

Assessment of the MAH's response

Study 3.7 is no longer described in the SPC section 5.1.

Conclusion

Issue resolved.

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance

20. Attachments

1. Product Information (changes highlighted) as adopted by the CHMP on 30 May 2024