CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125544Orig1s000

MEDICAL REVIEW(S)

Medical Officer Review

Division of Gastroenterology & Inborn Errors Products

Application Type and Number: 351(k) BLA 125544

Applicant: Celltrion, Inc.

Date of Submission: October 5, 2015

PDUFA Goal Date: April 5, 2016

DGIEP Clinical Reviewer/Team Leader: Jessica J. Lee, MD, MMSc

DGIEP Division Director: Donna J. Griebel, MD

Review Completion Date: April 5, 2016

Proprietary Name (Proposed) / Nonproprietary Name: Inflectra / CT-P13

Therapeutic Class: TNF-α antagonist

Dosage Forms/Strength: Sterile lyophilized powder in a 20 mL capacity vial/ 100 mg per vial

Rote of Administration: Intravenous

Proposed Indication(s): Crohn's disease, pediatric Crohn's disease, ulcerative colitis, pediatric ulcerative colitis[1], rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis

1. Introduction

On October 5, 2015, Celltrion (the applicant) resubmitted a biologics license application (BLA) under section 351(k) of the Public Health Service Act (PHS Act) for Inflectra (CT-P13), a proposed biosimilar to US-licensed Remicade (infliximab). Remicade (BLA 103772), the reference product, received marketing approval in the U.S. on August 24, 1998 and its license is currently held by Janssen Biotech, Inc.

The Celltrion's BLA application (BLA 125544) was initially submitted on August 8, 2014, but received a Complete Response (CR) action on June 8, 2015 as the analytical data included in the BLA did not provide sufficient information to conclude that CT-P13 is highly similar to the reference product (i.e., US-licensed Remicade). Specific concerns raised in the CR letter included (1) lower levels of subvisible particulates in US-licensed Remicade compared to both CT-P13 and EU-approved Remicade, and (2) approximately 20% lower antibody-dependent

[1] It should be noted that Remicade's indication for pediatric ulcerative colitis is protected by orphan drug exclusivity expiring on September 23, 2018. Accordingly, FDA will not be able to license a proposed biosimilar product for this indication until the orphan exclusivity expires.

Reference ID: 3912326

cellular toxicity (ADCC) activity in some NK-based assays in CT-P13 compared to the reference product US-licensed Remicade, leading to residual uncertainty about whether CT-P13 is highly similar to US-licensed Remicade. To address both deficiencies, the applicant was advised to evaluate additional lots to determine whether the observed findings were due to small sample size. The CR letter also indicated that if the difference in ADCC persists following analysis of additional lots, the applicant should identify and demonstrate control of the product quality attributes that underlie ADCC activity in CT-P13 and provide an adequate justification, including an evaluation of the role of ADCC, particularly in the setting of inflammatory bowel disease (IBD), to support that the observed difference in ADCC is not relevant to clinical activity. Of note, Health Canada approved CT-P13 in 2014 for the same indications for which the applicant is seeking licensure in the U.S. except the Crohn's disease (CD) and ulcerative colitis (UC) indications, based on the conclusion that extrapolation of data from rheumatoid arthritis (RA) and ankylosing spondylitis (AS) to IBD indications was not justified due to questions regarding the possible difference in ADCC that might have relevance in IBD. Specifically, Health Canada's Summary Basis of Decision on Inflectra states, "since differences in ADCC have been observed between the two products and because ADCC may be an active mechanism of action for infliximab in the setting of IBD, but not in the setting of rheumatic disease (the studied populations), extrapolation from the settings of rheumatoid arthritis and ankylosing spondylitis to IBD cannot be recommended due to the absence of clinical studies in IBD."[2]

In the initial BLA application, the applicant included clinical trial data collected from patients with RA and AS. The clinical review team determined that, assuming the analytical deficiencies could be addressed to support a demonstration that CT-P13 is highly similar to US-licensed Remicade, the clinical data support a demonstration of no clinically meaningful differences between CT-P13 and US-licensed Remicade in the indications studied. However, because of residual uncertainty in the analytical characterization data in the initial BLA submission, specifically with respect to ADCC, it was not possible at that time to determine the potential clinical impact the differences in ADCC could have on other indications. The reader is referred to Dr. Juwaria Waheed's Clinical review, dated May 4, 2015, and Dr. Nikolay Nikolov's CDTL memorandum, dated June 8, 2015, for details.

The current resubmission includes additional information requested in the CR letter dated June 8, 2015. The reader is referred to the CMC review and Dr. Nikolay Nikolov's CDTL memorandum from the current review cycle for a detailed assessment of additional information submitted to support the conclusion that CT-P13 is highly similar to US-licensed Remicade.

As part of the collaborative review process of the application, this memorandum provides DGIEP's assessment on the appropriateness of extrapolating data from RA and AS to IBD indications (as used in this document "IBD" or "IBD indications" refers to Crohn's disease, pediatric Crohn's disease, ulcerative colitis, and pediatric ulcerative colitis[1]), as the applicant is seeking licensure of CT-P13 for the same indications for which US-Remicade is licensed. In addition, this document provides a review of the two uncontrolled clinical trials in IBD that were

[2] Summary Basis of Decision on Inflectra by Health Canada, available at http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/sbd_smd_2014_inflectra_159493-eng.php.

Reference ID: 3912326

included in the BLA submission, and the study design and interim immunogenicity data from an ongoing trial (Study CT-P13 3.4) in patients with CD.

2. Extrapolation of Existing Data to Support Biosimilarity to IBD Indications

The applicant seeks licensure for the same indications for which US-licensed Remicade is licensed (Crohn's disease, pediatric Crohn's disease, ulcerative colitis, pediatric ulcerative colitis[1], rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis). The Agency has explained that if a proposed product meets the statutory requirements for licensure as a biosimilar product under section 351(k) of the PHS Act based on, among other things, data derived from a clinical study or studies sufficient to demonstrate safety, purity, and potency in an appropriate condition of use, the applicant may seek licensure for one or more additional conditions of use for which the reference product is licensed.[3] However, the applicant would need to provide sufficient scientific justification for extrapolating clinical data to support a determination of biosimilarity for each condition of use for which licensure is sought. Hence, it is acceptable for the applicant to conduct clinical studies only in RA and AS patients to support licensure for additional indications for which the reference product is licensed, including IBD (Crohn's disease, pediatric Crohn's disease, ulcerative colitis, and pediatric ulcerative colitis[1]), if an adequate scientific justification is provided. The scientific justification for extrapolation should address the following issues that are described in the FDA guidance[3]:

- The mechanism(s) of action (MOA), if known or can reasonably be determined, in each condition of use for which licensure is sought;
- The pharmacokinetics (PK) and bio-distribution of the product in different patient populations;
- The immunogenicity of the product in different patient populations;
- Differences in expected toxicities in each condition of use and patient population; and
- Any other factor that may affect the safety or efficacy of the product in each condition of use and patient population for which licensure is sought.

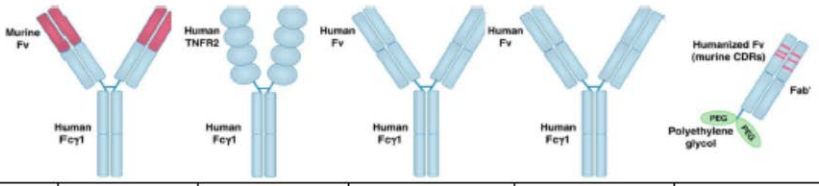
As described later in this review (see Table 1), the mechanisms of action of infliximab that are relevant to RA and AS (the studied populations) are also relevant to IBD, which supports extrapolation. Infliximab may also impact IBD through antibody-dependent cellular cytotoxicity (ADCC). ADCC is a mechanism of action that may not be relevant in RA or AS. During review of the applicant's initial submission, some concerns were raised by data that indicated that there were differences in ADCC activity between the two products; however, the applicant submitted additional analytical characterization data in this review cycle that demonstrated that the differences were not of the magnitude suggested by the earlier data. This updated ADCC activity information resolved residual uncertainty about the ability to extrapolate for the IBD indications.

[3] FDA Guidance for Industry, "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009" (April 2015), available at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm444661.pdf

Reference ID: 3912326

Furthermore, in considering the strength of evidence to support a conclusion that ADCC activity is critical to the efficacy of infliximab in IBD, it is important to note that the mechanism of action of TNF-α inhibitors in treating IBD is complex and, as summarized in Table 1, ADCC is only one of the several plausible mechanisms of action. Figure 1 below, which was presented during the Arthritis Advisory Committee Meeting held on February 9, 2016, compares ADCC activities of various TNF-α antagonists and their approved indications. While it is unknown whether ADCC has a role in imparting efficacy in TNF-α antagonists, it should be noted that certolizumab pegol, which does not have any ADCC activity, has been approved for the treatment of patients with CD. This product has not been studied in UC. Etanercept, which has low ADCC activity, is not approved in IBD. However, etanercept was not adequately studied in large randomized controlled trials using dose(s) identified for CD to assess whether it is effective in CD,[4] and it was not studied in UC.

Figure 1: The Role of Fc in the Anti-TNF-α Class Mechanism(s) of Action



	Infliximab	Etanercept	Adalimumab	Golimumab	Certolizumab (pegol)
ADCC	High	Low	High	High	None
CDC	High	Low	High	High	None
RA	Yes	Yes	Yes	Yes	Yes
CD/UC	Yes/Yes	No/NS	Yes/Yes	NS/Yes	Yes#/NS

NS=Not Studied
# approved indication in CD is based on reducing signs and symptoms and maintaining clinical response rather than achieving and maintaining /sustaining remission

Fc, fragment crystallizable region of the antibody; ADCC, antibody-dependent cellular cytotoxicity; CDC, complement-dependent cytotoxicity; RA, rheumatoid arthritis; CD, Crohn's disease; UC, ulcerative colitis.

Source: FDA Briefing Document for Arthritis Advisory Committee Meeting held on February 9, 2016; Figure 6.

Therefore, in light of the updated information on ADCC activity of Celltrion's product in the resubmission (summarized in the Mechanism of Action section below), the division has concluded that submitted data are adequate to support extrapolation to IBD indications.

The applicant's scientific justification to address each of the above principles to support extrapolation of clinical data from studies in RA and AS to IBD indications is described below.

[4] Sandborn WJ, et al. "Etanercept for active Crohn's disease: a randomized double-blind, placebo-controlled trial." *Gastroenterology* 2001;121:1088-94.

Reference ID: 3912326

1) Mechanism of Action

The primary mechanism of action of infliximab is to neutralize the biological activity of TNF-α by binding to the soluble and transmembrane forms of TNF-α and inhibit binding of TNF-α with its receptors.[5] Similar to the studied indications (RA and AS), TNF-α plays a central role in the pathogenesis of IBD, and TNF-α inhibition is important in treating the disease, as evidenced by the efficacy of the approved TNF-α monoclonal antibodies, but the detailed cellular and molecular mechanisms involved have not been fully elucidated.[6] However, the available scientific evidence suggests that for TNF-α inhibitors in IBD, in addition to binding and neutralization of soluble form of TNF-α (sTNF-α), other mechanisms of action, listed in Table 1, may play a role.[7] Binding to sTNF-α and transmembrane TNF-α (tmTNF-α) involves the fragment antigen-binding (Fab) region of the antibody, while the other plausible mechanisms of action involve the fragment crystallizable (Fc region) region of the antibody.

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[5] Prescribing Information for Remicade (last revised on October 2, 2015), accessed on March 5, 2016: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/103772s5373lbl.pdf

[6] Oikonomopoulos A, et al. "Anti-TNF Antibodies in Inflammatory Bowel Disease: Do We Finally Know How it Works?" *Current Drug Targets* 2013;14:1421-32.

[7] Tracey D, et al. "Tumor necrosis factor antagonist mechanisms of action: A comprehensive review." *Pharmacology & Therapeutics* 2008;117:244–79.

Reference ID: 3912326

Table 1: Known and Potential (Likely or Plausible) Mechanisms of Action of US-licensed Remicade in the Licensed Conditions of Use

Mechanism of Action of Remicade[6,7]	RA	AS	PsA	PsO	Adult and Pediatric CD	Adult and Pediatric UC
Mechanisms involving the Fab (antigen binding) region:						
Blocking TNFR1 and TNFR2 activity via binding and neutralization of s/tmTNF	Known	Known	Known	Known	Likely	Likely
Reverse (outside-to-inside) signaling via binding to tmTNF:	-	-	-	-	Likely	Likely
Apoptosis of lamina propria activated T cells	-	-	-	-	Likely	Likely
Suppression of cytokine secretion	-	-	-	-	Likely	Likely
Mechanisms involving the Fc (constant) region:						
Induction of CDC on tmTNF-expressing target cells (via C1q binding)	-	-	-	-	Plausible	Plausible
Induction of ADCC on tmTNF-expressing target cells (via FcγRIIIa binding expressed on effector cells)	-	-	-	-	Plausible	Plausible
Induction of regulatory macrophages in mucosal healing	-	-	-	-	Plausible	Plausible
ADCC: antibody-dependent cellular cytotoxicity; AS: ankylosing spondylitis; CD: Crohn's disease; CDC: complement-dependent cytotoxicity; MOA: mechanism of action; PsA: psoriatic arthritis; PsO: plaque psoriasis; RA: rheumatoid arthritis; UC: ulcerative colitis; sTNF: soluble TNF; tmTNF: transmembrane TNF						

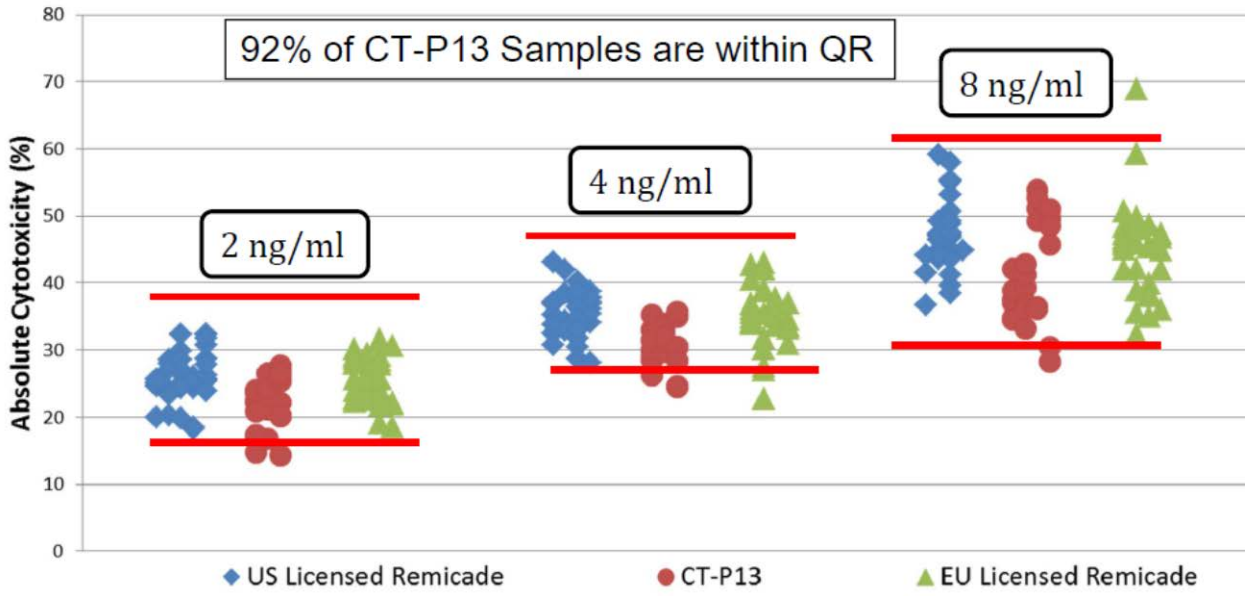
Source: FDA Briefing Document for Arthritis Advisory Committee Meeting held on February 9, 2016; Tables 1 and 21.

Based on review of the data included in the resubmission of the BLA, the product quality reviewers have concluded that the applicant provided adequate data to support a conclusion that CT-P13 and US-licensed Remicade are highly similar based on structural and functional analytical characterization. The product quality reviewers concluded that TNF-α binding and neutralization, believed to be the primary function of infliximab, are statistically equivalent

Reference ID: 3912326

between CT-P13 and US-licensed Remicade. Other mechanisms of action, such as reverse signaling and complement-dependent cytotoxicity (CDC), were within the quality range set by the applicant's data on the reference product, with no shift in activity evident between the test batches of CT-P13 and US-licensed Remicade. In the case of ADCC, the product quality reviewers noted a small downward shift in one of two assay formats (natural killer [NK] cells as effector cells) (see Figure 2); however, this shift does not indicate that the products are not highly similar, given that over 90% of the lots of CT-P13 were still within the quality range of the reference product (red bars in Figure 2). Furthermore, there was no similar downward shift in the other ADCC assay format (peripheral blood mononuclear cells [PBMC] as effector cells) (data not shown).

Figure 2: Antibody-dependent cellular toxicity of CT-P13, US-licensed Remicade and EU-approved Remicade using natural killer cells as effector cells



Source: FDA Briefing Document for Arthritis Advisory Committee Meeting held on February 9, 2016; Figure 9.

Based on the totality of data, the product quality reviewers concluded that the CT-P13 is highly similar to the reference product. As discussed in the Product Quality review and Dr. Nikolov's CDTL memorandum, the applicant has adequately addressed each of the known and potential mechanisms of action of US-licensed Remicade listed in Table 1 through the analytical similarity assessment.

In summary, the product quality reviewers found the small shift in the NK-cell assay format of ADCC to be acceptable given that over 90% of the lots of CT-P13 were within the quality range of the reference product, and the applicant has adequately addressed all other known and potential mechanisms of action. ADCC is one of the plausible mechanisms of action of US-licensed Remicade that may be relevant to its efficacy in IBD. This reviewer agrees with the

Reference ID: 3912326

product quality reviewers that the totality of data supports a conclusion that CT-P13 is highly similar to US-licensed Remicade.

2) Pharmacokinetics (PK)

With regard to the impact of PK on different patient populations, there were no notable differences between CD patients treated with US-licensed Remicade, as compared to patients treated with US-licensed Remicade for other indications, including RA and PsO.[5] Additionally, PK characteristics were similar between pediatric and adult patients with CD or UC following the administration of 5 mg/kg US-licensed Remicade.[5] The data included in the applicant's BLA submission demonstrated similar PK between CT-P13, US-licensed Remicade and EU-approved Remicade in healthy subjects. In addition, similar PK was demonstrated for CT-P13 and EU-approved Remicade in two different usage scenarios, i.e., in patients with RA receiving 3 mg/kg infliximab with concomitant use of methotrexate and in patients with AS receiving 5 mg/kg but without concomitant immunosuppressive therapy (see Clinical Pharmacology review for details). Based on these observations and submitted analytical data, which do not suggest that differences in PK should be expected between patient populations, a similar PK profile would be expected for pediatric and adult patients with IBD receiving CT-P13.

In addition, it should be noted that PK of infliximab is also influenced by immunogenicity. Specifically, the clearance of infliximab has been shown to be higher in patients who developed anti-drug-antibodies (ADA).[5] As described in the Immunogenicity section below, numerically similar rates of ADA development were observed between CD patients who received CT-P13 and those who received US-licensed Remicade in an ongoing study. Furthermore, as described previously, the applicant has adequately characterized the effect of concomitant immunosuppressive therapy to assure similar effect on PK in IBD patients, who may or may not be on concomitant immunosuppressive therapy. These data further support that PK profile would be expected to be similar between CD patients receiving CT-P13 and those receiving US-licensed Remicade.

3) Immunogenicity

In general, immunogenicity of US-licensed Remicade was affected primarily by the use of concomitant immunosuppressive therapy across different indications rather than by patient population, and the results were influenced by the type of immunoassay used.[5] In PsA, PsO, adult and pediatric CD, and adult and pediatric UC, the recommended dose is 5 mg/kg. Infliximab is used without methotrexate in PsO and may be used with or without concomitant immunosuppression in PsA, CD and UC. These usage scenarios were assessed in the applicant's RA study (concomitant use of methotrexate) and AS study (use of the higher dose of 5 mg/kg, but without concomitant immunosuppressive therapy). Based on review of the submitted data, the clinical pharmacology reviewers have concluded that there are sufficient data to support similar immunogenicity between CT-P13, EU-approved Remicade, and US-licensed Remicade, and that there are no clinically meaningful differences in immunogenicity among these products

Reference ID: 3912326

(see Clinical Pharmacology review for details). Based on these findings, similar immunogenicity would be expected for pediatric and adult patients with IBD receiving CT-P13, compared with those receiving US-licensed Remicade.

In addition, although an interim analysis of the ongoing post-marketing study in patients with CD is unnecessary to support a finding of no clinically meaningful differences between CT-P13 and US-licensed Remicade, including with respect to immunogenicity, it is notable that numerically similar rates of ADA formation were observed between patients who received the CT-P13 and US-licensed Remicade 5 mg/kg dosing regimen. After 14 weeks of treatment, 8 (15%) of 54 patients and 5 (12%) of 43 patients developed positive ADA in the CT-P13 treatment group and US-licensed Remicade group, respectively. These patients were allowed to be on concomitant immunosuppressive therapy. For additional detail on this study, the reader is referred to Section 4 (Summary of Preliminary Immunogenicity Data from Study CT-P13 3.4) of this document. Although the interim analysis did not include a separate analysis on the effect of concomitant immunosuppressive therapy, the applicant has adequately addressed this issue in two different usage conditions in RA and AS to assure similar effect on immunogenicity in IBD patients, who may or may not be on concomitant immunosuppressive therapy.

4) Toxicity

In controlled clinical trials that supported approval of the US-licensed Remicade, patients with IBD experienced similar adverse reactions as other indications, including RA. Similar common and serious adverse reactions have been reported across licensed indications and are described in the prescribing information. Since the safety profile of CT-P13 has been shown to be similar to that of US-licensed Remicade (see Dr. Juwaria Waheed's Clinical review and Dr. Nikolay Nikolov's CDTL memorandum) and submitted analytical data did not identify reasons to expect differential safety profiles between patient populations, a similar safety profile would be expected for pediatric and adult patients with IBD receiving CT-P13

Major toxicities of infliximab are serious infections, including tuberculosis and opportunistic infections, and malignancies, which are shared amongst disease populations. Given the similar product quality attributes, PK, and immunogenicity, there is no reason to expect that the safety evaluation in RA and AS would be different from the IBD population.

In summary, this reviewer considers the above described scientific justification adequate to extrapolate available clinical data on RA and AS to support licensure of CT-P13 in IBD indications.

3. Review of Two Uncontrolled Clinical Trials in Inflammatory Bowel Disease (IBD)

In this BLA submission, the applicant included data from two uncontrolled trials in IBD patients to further support licensure for IBD indications. However, since the additional analytical characterization data submitted by the applicant adequately addressed the residual uncertainty

Reference ID: 3912326

about whether CT-P13 is highly similar to US-licensed Remicade and there is adequate scientific justification to support extrapolating available clinical data in RA and AS to support licensure of CT-P13 in IBD indications (see Section 2 for details), additional clinical studies in IBD are not deemed necessary. Moreover, as described below, these two uncontrolled trials in IBD patients are not appropriately designed to support biosimilarity of CT-P13 to US-licensed Remicade for the IBD indications, should there have been remaining questions about whether the proposed product is biosimilar to the reference product in IBD.

1) Efficacy and safety of the biosimilar infliximab CT-P13 induction treatment in inflammatory bowel diseases: a prospective, multicenter, nationwide cohort[8]

Background and Study design

This clinical study report describes interim results from a prospective, open-label, single-arm, multicenter (12 sites in Hungary) trial, conducted between May 2014 and May 2015, intended to assess the efficacy, safety and immunogenicity of CT-P13 in the treatment of CD and UC. This trial was conducted to collect clinical data on CT-P13, as the authors state that, effective May 2014, the Hungarian National Health Fund only reimburses the "biosimilar" infliximab (Inflectra, Hospira, UK) approved for use in that jurisdiction for new induction treatment of IBD patients and transitioning from the innovator product to the "biosimilar" infliximab is not allowed. Of note, new induction is defined as no infliximab treatment in the previous 12 months.

Patients, ages older than 18 years, with a prior diagnosis of CD or UC based on clinical, biochemical, endoscopic and histological findings were eligible to enroll in the trial. The authors report that eligible CD patients included those with moderate to severe therapy-refractory or steroid-dependent luminal disease, or therapy-refractory simple fistulizing disease or complex fistulas; and, eligible UC patients included those with refractory, steroid-dependent or severe acute steroid-refractory colitis. While the diagnostic criteria for CD or UC appear appropriate, the eligibility criteria are poorly defined. For example, authors do not specify how moderate to severe disease (e.g., using the Crohn's Disease Activity Index [CDAI] or Mayo score), therapy-refractory disease (e.g., based on prior therapies tried at approved doses and duration), and steroid-dependent disease are defined. Since the authors did not use standardized, pre-specified eligibility criteria, it is not possible to conclude that the patients enrolled in this trial are comparable to those who were included in the clinical trials that supported marketing approval of US-licensed Remicade.

Eligible patients received 5 mg/kg of CT-P13 intravenously at Weeks 0, 2, and 6, and every 8 weeks, which is the same dosing regimen approved for US-licensed Remicade for both CD and UC. None of the patients received infliximab treatment with the originator compound within 12

[8] This reviewer reviewed the clinical study report submitted in the BLA, but it should be noted that the results of this study was published during the review cycle (Gecse KB, et al. *J Crohns Colitis* 2016;10(2):133-40).

Reference ID: 3912326

months prior to initiation of CT-P13. Patients only continued into the maintenance phase of the trial if clinical remission or response was achieved at Week 14.

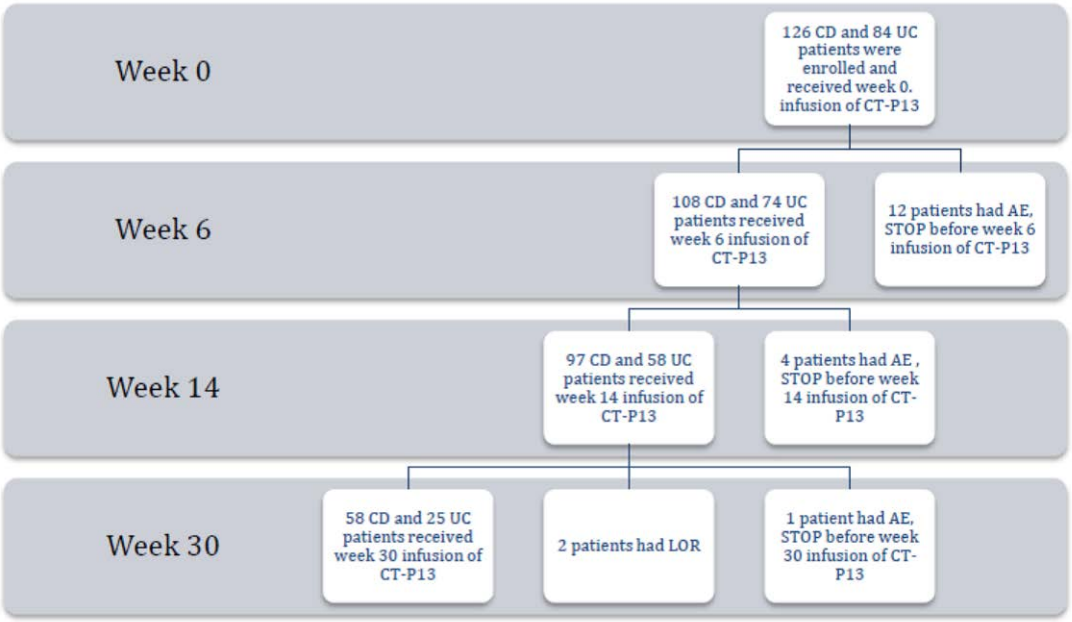
The authors state that a nationwide harmonized monitoring strategy was implemented during the conduct of this trial, as mandated by the National Health Fund. Demographic data were collected at baseline. The following data were collected at baseline and Weeks 14, 30 and 54: medication history, clinical activity, biochemical activity, therapeutic drug level monitoring, and adverse events. Endoscopic activity and imaging data were collected at baseline and Week 54.

Descriptive statistics were used to characterize demographics, clinical remission and response rates, and adverse events. Clinical response, remission rates and immunogenicity (i.e., antidrug antibody positivity rates) were compared between infliximab-exposed and infliximab-naïve patients by Chi square test or Fischer exact test.

Patient Disposition

Figure 3 illustrates patient disposition and follow-up information as of May 2015. Enrolled patients are continuing to be followed until Week 54. As of Week 30, CT-P13 treatment was discontinued in 19 patients due to adverse events (n=17) or loss of response (n=2). One patient was lost to follow up after Week 14 infusion.

Figure 3: Patient disposition/follow-up data as of May 2015



LOR: loss of response, AE: adverse event. 1 CD patient was lost to follow-up after week 14.

Source: "Efficacy and safety of the biosimilar infliximab CT-P13 induction treatment in inflammatory bowel diseases: a prospective, multicenter, nationwide cohort" in the applicant's BLA 125544 submission dated October 5, 2015; Module 5.3.6; Figure 1 (page 25 of 42).

Reference ID: 3912326

Because this is a report of an ongoing trial, the results are only available until 30 weeks. Therefore, longer term clinical data including the endoscopic data, due to be collected at 54 weeks, are not available at this time.

Demographics and Baseline Characteristics

A total of 210 consecutive patients with IBD (126 CD and 84 UC) were enrolled. The median age in years (IQR) for CD and UC were 24 (19-35) and 27 (22-37), respectively. The median disease duration in years (IQR) for CD and UC were 6 (3-11) and 4 (2-12), respectively. Thirty-three percent of CD patients had perianal disease at baseline. Of the 126 CD patients, 58% patients had non-stricturing, non-penetrating (or luminal) disease, 22% had stricturing disease, and 20% had penetrating (or fistulizing) disease at baseline.

Twenty-six percent of CD patients and 19% of UC patients had received anti-TNF treatment previously. At enrollment into the trial, 48% and 63% of CD patients were receiving concomitant corticosteroid and thiopurine therapy, respectively, and 64% and 57% of UC patients were receiving concomitant corticosteroid and thiopurine therapy, respectively. The study report does not specify the dose or duration of prior or concomitant therapies; therefore, it is not possible to comment on the potential impact of concomitant medications on the trial outcome. In general, use of concomitant immunomodulators, such as azathiopurine, 6-mercaptopurine, and methotrexate, has been associated with a decreased rate of anti-drug antibody development in patients treated with TNF-α antagonists.

Efficacy

Primary Endpoint:

The primary endpoint was clinical remission at Week 14. Clinical remission in CD was defined as a Crohn's Disease Activity Index or CDAI score of <150 for patients with luminal disease, and no fistula drainage as assessed by the Fistula Drainage Assessment for fistulizing disease. Clinical remission in UC was defined as a partial Mayo score of less than 3 points.

At Week 14, 52 (54%) of 97 CD patients and 34 (59%) of 58 UC patients achieved clinical remission (See Figure 2). The authors noted that clinical remission rates at Week 14 were higher in both CD and UC patients who were not previously exposed to infliximab compared to those who were previously exposed (61% vs. 36% in CD and 65% vs. 33% in UC, respectively). Although clinical remission rates appear favorable for CT-P13, these data must be interpreted with caution as there is no comparator group and the proportion of responders was calculated based on the number of patients remaining in the trial at the time of assessment. For example, if the primary analysis is repeated using the total number of patients who received at least one dose of CT-P13 as the denominator (n=126 for CD and n=84 for UC), clinical remission rates at 14 weeks for CD and UC patients decrease from 54% to 41% and 59% to 40%, respectively. It should be noted that the Prescribing Information for US-licensed Remicade, clinical trials that supported its marketing approval for CD and UC assessed clinical remission at Week 30 for CD

Reference ID: 3912326

(clinical remission rates was 39% in the 5 mg/kg dose group) and Weeks 8, 30 and 54 for UC (clinical remission rates ranged from 26 to 39% in the 5 mg/kg dose group).[5]

Secondary Endpoints:

The secondary endpoints included clinical response, biochemical response (total blood count, serum C-reactive protein [CRP], albumin), immunogenicity (using the ELISA method) and safety at Week 14; and, clinical response, remission, and steroid-free remission at Week 30.

Clinical response was defined as a decrease in CDAI > 70 points for luminal disease, and at least 50% reduction in the number of draining fistulas. Clinical response in UC was defined as a decrease in the partial Mayo score with more than 3 points. At Week 14, 81% of CD and 78% of UC patients achieved clinical response, and 54% of CD and 59% of UC patients were in clinical remission.

Table 2 summarizes the efficacy data resulting from the trial.

Table 2: Summary of Efficacy Data from the Hungarian Trial *

	Week 14		**Week 30**	
	CD n=97	**UC** n=58	**CD** n=58	**UC** n=25
Clinical response	79 (81%)	45 (78%)	39 (67%)	20 (80%)
Clinical remission	52 (54%)	34 (59%)	31 (53%)	17 (68%)
Steroid-free remission	NA	NA	29 (50%)	14 (56%)

CD, Crohn's disease; UC, ulcerative colitis; NA, not assessed

* The proportions of responders were calculated based on the number of patients remaining in the trial at the time of assessment instead of the total number of patients who received at least one dose of CT-P3 as the denominator (n=126 for CD and n=84 for UC).

Source: Reviewer's table from data included in "Efficacy and safety of the biosimilar infliximab CT-P13 induction treatment in inflammatory bowel diseases: a prospective, multicenter, nationwide cohort" in the applicant's BLA 125544 submission dated October 5, 2015.

The authors also reported "early clinical remission and response rates" at Week 6 although these assessments were not listed as primary or secondary endpoints. After 6 weeks of treatment with CT-P13, 84 (78%) and 53 (49%) of 108 CD patients achieved clinical response and clinical remission, respectively. Among 74 UC patients remaining in the trial at Week 6 assessment, 57 (77%) and 50 (68%) achieved clinical response and clinical remission, respectively.

Reference ID: 3912326

Similar to the primary efficacy analysis, the authors calculated the proportion of responders for the secondary endpoints based on the number of patients remaining in the trial at the time of assessment. For example, if the secondary analysis is repeated using the total number of patients who received at least one dose of CT-P13 as the denominator (n=126 for CD and n=84 for UC), clinical response rates at 14 weeks for CD and UC patients decrease from 81% to 63% and 78% to 54%, respectively. In the multi-dose trial (ACCENT I) that supported marketing approval of Remicade in the U.S., clinical response (decrease in CDAI ≥ 70) at Week 2 was used primarily to randomize the patients to treatment groups.[5] Week 14 data were not used to support the approval.

The authors also indicate that Week 30 data in this trial were based on patients who were Week 14 responders who were then able to maintain clinical response or achieve clinical remission at Week 30. However, instead of using the number of patients who were in clinical response at Week 14 as the denominator, the authors used the number of patients remaining in the trial at Week 30. Therefore, the reported data are biased and must be interpreted with caution.

The data on biochemical response will not discussed in this review as biochemical parameters have not been used to support product labeling in CD or UC, and there are inadequate data at this time to support a correlation between improvement in biochemical parameters and a clinically meaningful endpoint in IBD that has been shown to have a favorable effect on how a patient feels, functions, or survives. Results of immunogenicity and safety data are discussed below under the safety section.

Additional endpoints included sustained clinical remission and response, biochemical response, mucosal healing (Simple Endoscopic Score for Crohn's Disease [SES-CD] for CD and the Mayo score for UC), immunogenicity and safety at Week 54. However, these data are not included in the submitted report as the trial was ongoing at the time of BLA submission.

Safety

a) Immunogenicity

Anti-drug antibodies (ADA) were detected in 9 (9%) of 99 CD patients at baseline and 13 (21%) of 61 CD patients at Week 14. Compared to infliximab-naïve CD patients, those who were exposed to infliximab previously had higher baseline and Week 14 ADA positivity (4% vs. 24% and 17% vs. 39%, respectively).

ADA were detected in 6 (9%) of 68 UC patients at baseline and 10 (24%) of 42 UC patients at Week 14. Compared to infliximab-naïve UC patients, those who were exposed to infliximab previously had higher baseline and Week 14 ADA positivity (4% vs. 31% and 22% vs. 30%, respectively).

Because there is no comparator group in this trial, it is not possible to make conclusions on how the incidence of ADA development compares to that of US-licensed Remicade. In addition, immunogenicity is affected by the use of concomitant immunosuppressive therapy and the type of immunoassay used; thus, cross-study comparison (i.e., comparing

Reference ID: 3912326

immunogenicity data from this trial to data that supported US-licensed Remicade approval) is not appropriate.

b) Adverse Events

By Week 30, 36 (17%) of 210 enrolled patients experienced adverse events. Table 3 summarizes the adverse events observed during the trial. Infusion reactions and serious infections occurred in 7% and 6% of all patients, respectively. One patient developed invasive fungal sepsis, which resulted in death.

Table 3: Adverse events

Adverse event	Patient no. (%)
Infections	
Upper respiratory tract infection	6 (2.9%)
Pneumonia	1 (0.5%)
Tuberculosis	0 (0%)
Gastroenteritis	2 (1%)
Vaginitis	1 (0.5%)
Urinary tract infection	1 (0.5%)
Viral infections (influenza, herpes, varicella)	0 (0%)
Invasive fungal infection	1 (0.5%)
Acute infusion reactions	
Anaphylaxis	1 (0.5%)
Other	13 (6.2%)
Possible delayed hypersensitivity	1 (0.5%)
Arthralgia	9 (4.3%)
Malignancy	0 (0%)

Source: "Efficacy and safety of the biosimilar infliximab CT-P13 induction treatment in inflammatory bowel diseases: a prospective, multicenter, nationwide cohort" in the applicant's BLA 125544 submission dated October 5, 2015; Module 5.3.6; Table 3 (page 24 of 42).

The safety analysis is also limited by lack of a comparator group. However, it is reassuring that adverse events observed in this trial are similar to those described in the Prescribing Information

Reference ID: 3912326

for US-licensed Remicade, and no new concerning adverse events were observed during this trial.

Summary

While this open-label, multicenter trial provides clinical data on patients treated with CT-P13 in Hungary, it is not possible to make conclusions regarding the efficacy, immunogenicity or safety of CT-P13 due to its open-label study design and lack of a comparator group (e.g., US-licensed Remicade and/or EU-approved Remicade). In addition, there are a number of concerns with comparing the data from this trial to clinical trial data that supported approval of US-licensed Remicade including, but not limited to, lack of objective criteria to define eligible patient population and differences in timing of efficacy assessments. Furthermore, the authors used flawed percentage calculations for efficacy analysis based on the number of patients remaining at the time of analysis instead of the total number of patients who received at least one dose of CT-P13. Therefore, this reviewer does not consider data resulting from the Hungarian trial to be appropriate to support that CT-P13 is biosimilar to US-licensed Remicade. However, as stated previously, data from this trial are not needed to support licensure of CT-P13 in IBD indications, since the additional analytical characterization data submitted in this review cycle and scientific justification described in Section 2 provide sufficient evidence to support extrapolation.

2) Interim Report: Post-marketing real-world clinical experience with CT-P13 (infliximab) (monoclonal antibody, recombinant) in patients with inflammatory bowel disease at Akershus University Hospital, Norway

Date of report: September 7, 2015

Background and Study Design

This interim study report describes prospectively collected, uncontrolled "real-world" experience in 78 patients with CD and UC treated with CT-P13 in a single center in Norway. This post-marketing experience was collected under routine care without a formal protocol.

The dose regimen used was the same as that approved by the European Medicines Agency (EMA), but the time intervals between doses were controlled flexibly based on the investigator's decision under routine care. Concomitant medications were permitted as clinically indicated, and included paracetamol, azathiopurine, oral or rectal 5-aminosalicylic acid, systemic or rectal corticosteroids, methotrexate, 6-mercaptopurine, and antibiotics for treatment of IBD (e.g., quinolone, metronidazole). The study report does not specify the dose or duration of prior or concomitant therapies.

The interim report states that patients with "moderate to severe active" CD and UC were enrolled, but there were no pre-specified criteria that were used to assess the severity of disease at baseline. The following efficacy endpoints were assessed:

Reference ID: 3912326

Patients with moderate to severe active CD

- Proportion of patents achieving clinical response, which is defined by a decrease in Harvey-Bradshaw index (HBI) ≥ 4 at Week 14 and Week 30 in patients with HBI > 4 points at baseline
- Proportion of patents achieving clinical remission, which is defined as Harvey-Bradshaw index ≤ 4 at Week 14 and Week 30
- Effect of disease markers of calprotectin and CRP at Week 14 and Week 30
- Trough levels of CT-P13 at Week 14 and Week 30

Patients with moderate to severe active UC

- Proportion of patients achieving clinical response defined by a decrease in partial Mayo scores from baseline of at least 3 points at Week 14 and Week 30
- Proportion of patients achieving clinical remission defined as a partial Mayo score of 2 points or lower, with no individual subscore exceeding 1 point at Week 14 and Week 30
- Simple Clinical Colitis Activity index at Week 14 and Week 30
- Effect of disease markers of calprotectin and CRP at Week 14 and Week 30
- Trough levels of CT-P13 at Week 14 and Week 30

It should be noted that none of the clinical outcome measures that were used to collect efficacy data in this study (Harvey-Bradshaw index, partial Mayo (excluding endoscopy), and Simple Clinical Colitis Activity index) has been used by this Review Division to support marketing approval of IBD products. In addition, this study does not include a control group to support comparative efficacy claims based on resulting data. Additional efficacy endpoints, including calprotectin, CRP and trough levels of CT-P13, have been collected as exploratory endpoints in IBD trials and have not been used to support labeling claims.

In light of the study design, the applicant used descriptive statistics to summarize the results.

Demographics and Baseline Characteristics

A total of 78 patients with IBD were enrolled, including 46 CD (33 TNF-naïve and 13 with prior exposure to one or more TNF-α antagonists) and 32 UC (27 TNF-naïve and 5 with prior exposure to one or more TNF-α antagonists) patients. Fifty-nine percent of CD patients had stricturing or penetrating disease, and 37% of CD patients had undergone bowel resection in the past. Approximately 60% of UC patients had extensive colitis. Table 4 summarizes the demographics and baseline clinical characteristics of enrolled patients.

Reference ID: 3912326

Table 4: Demographics and baseline clinical characteristics of IBD patients

	Moderate to severe active CD (N=46)	Moderate to severe UC (N=32)
Age at diagnosis (years)		
Mean	30	33
Median (range)	25 (9-66)	31 (13-65)
Age at start if treatment (years)		
Mean	39	40
Median (range)	37.5 (16-80)	43 (18-70)
Sex, no (%)		
Male	22 (47.8)	17 (53.1)
Female	24 (52.2)	15 (46.9)
Disease duration (years)		
Mean	8	6.5
Median (range)	3.5 (0-38)	3 (0-44)
Prior anti-TNF agent		
Remicade®, n(%)	4 (8.7)	2 (6.3)
Humira®, n(%)	10 (21.7)	4 (12.5)
Cimzia®, n(%)	1 (2.3)	0
Simponi®, n(%)	0	2 (6.3)
≥2 anti-TNF agent	1 (2.2)	2 (6.3)
Anti-TNF naive	33 (71.7)	27 (84.4)
Concomitant medications		
AZA/6-MP, n(%)	25 (54.3)	18 (56.3)
MTX, n(%)	6 (13.0)	1 (3.1)
Steroids, n(%)	5 (10.9)	18 (56.3)

Source: "Interim Report: Post-marketing real-world clinical experience with CT-P13 (infliximab) in patients with inflammatory bowel disease at Akershus University Hospital, Norway" in the applicant's BLA 125544 submission dated October 5, 2015; Module 5.3.6; Table 7-2 (page 13 of 34).

Although the interim report states that baseline disease characteristics in all subgroups were in line with moderate to severe active status of the disease, this reviewer notes that there were no specific criteria that were used (using an accepted clinical activity score and/or endoscopic evaluation) to determine disease activity status at baseline. While disease location and behavior (e.g., stricturing, penetrating) are commonly used to characterize the overall disease state, they do not reflect current disease activity. In addition, there are no control groups to compare the baseline demographic and disease characteristics between patients who received CT-P13 and another product.

Reference ID: 3912326

Efficacy

As shown in Table 5, 34 (79%) patients achieved clinical remission based on a HBI score of ≤ 4 at Week 14, and 22 (56%) patients achieved clinical response.

Table 5: Clinical remission and response rates at Week 14 based on Harvey-Bradshaw index (HBI) in CD patients receiving CT-P13

	Naïve of anti-TNF agent (N=33)	Prior anti-TNF agent (N=13)	Total (N=46)
Clinical Remission	23/30 (76.7%)	10/13 (76.9%)	34/43 (79.1%)
Clinical Response	15/30 (50.0%)	7/9 (77.8%)	22/39 (56.4%)

Source: "Interim Report: Post-marketing real-world clinical experience with CT-P13 (infliximab) in patients with inflammatory bowel disease at Akershus University Hospital, Norway" in the applicant's BLA 125544 submission dated October 5, 2015; Module 5.3.6; Table 7-6 (page 18 of 34).

Enrolled CD patients had a baseline mean ± SD HBI score of 7.7 ± 5.2, which decreased to 2.4 ± 2.2 (data not shown). However, the baseline HBI scores of enrolled patients ranged from 0 to 20, which indicate that patients with inactive disease at baseline were also included in this analysis of patients with "moderate to severely active disease." There is also no control group in this analysis to be able to make any efficacy conclusions, and as stated previously, HBI scores have not been used by this Review Division to support product labeling for IBD products.

As shown in Table 6, 18 (56%) and 24 (75%) of UC patients achieved clinical remission and clinical response based on partial Mayo score, respectively.

Table 6: Clinical remission and response rates at Week 14 based on partial Mayo score in UC patients receiving CT-P13

	Naïve of anti-TNF agent (N=27)	Prior anti-TNF agent (N=5)	Total (N=32)
Clinical Remission	16/27 (59.3%)	2/5 (40.0%)	18/32 (56.3%)
Clinical Response	22/27 (81.5%)	2/5 (40.0%)	24/32 (75.0%)

Source: "Interim Report: Post-marketing real-world clinical experience with CT-P13 (infliximab) in patients with inflammatory bowel disease at Akershus University Hospital, Norway" in the applicant's BLA 125544 submission dated October 5, 2015; Module 5.3.6; Table 7-11 (page 23 of 34).

Reference ID: 3912326

Enrolled UC patients had a baseline mean ± SD partial Mayo score of 7.2 ± 2, which decreased to 2.1 ± 2 (data not shown). However, the baseline partial Mayo scores of enrolled patients ranged from 1 to 9, which indicate that patients with inactive and/or mild disease at baseline were also included in this analysis of patients with "moderate to severely active disease." It should also be noted that partial Mayo score includes the Physician Global Assessment (PGA) subscore but excludes the endoscopy subscore. The utility of the PGA is questionable because the concept it purports to measure that is distinct from the other components of the Mayo score (stool frequency and rectal bleeding) is not clear; therefore, its use or inclusion in the Mayo score has been discouraged in recent IBD clinical development programs. Since endoscopic assessment can determine whether the treatment has a favorable effect on the underlying intestinal inflammation, it is an important component of outcome assessment in UC. Therefore, partial Mayo score has not been used to support product labeling for IBD products. Similar to the CD analysis, there is no control group in this analysis to be able to support any efficacy conclusions.

Safety

There were no deaths. A total of 15 adverse events were reported in 15 patients (10 CD patients and 5 UC patients). Four patients discontinued CT-P13 treatment due to adverse events, all of which appear to reflect hypersensitivity reactions (severe infusion reaction, muscle and joint pain, arthralgia, and rash/itching). Infection was reported in 6 (8%) patients (2 cases of herpes, 1 case of Campylobacter enterocolitis, 1 case of erysipelas of right knee, 1 case of recurrent upper respiratory infection, and 1 case of suspected pneumonia). Other adverse events reported include fatigue, pustular psoriasis, increased transaminases, palpitations and rash.

Eight (10%) patients (4 CD patients and 4 UC patients) developed anti-infliximab antibodies after treatment with CT-P13. One CD patient experienced severe infusion-related reaction (no description provided) and one UC patient had mild infusion-related reaction (rash and itching).

Adverse reactions and immunogenicity data reported in this interim report are similar to those described in the Prescribing Information for US-licensed Remicade, and it does not appear that the post-marketing experience in one Norwegian center thus far has uncovered any new concerning safety signals associated with the use of CT-P13.

Summary

While this trial provides post-marketing experience on IBD patients treated with CT-P13 in one center in Norway, it is not possible to make conclusions regarding the efficacy, immunogenicity or safety of CT-P13 in IBD patients based on how the study was conducted (i.e., without a formal protocol and flexible changes in dose intervals at the discretion of the investigator), its open-label study design and lack of a comparator group (e.g., US-licensed Remicade and/or EU-approved Remicade). In addition, there are a number of concerns with comparing the data from this trial to clinical trial data that supported approval of US-licensed Remicade, including but not limited to, lack of objective criteria to define eligible patient population and differences in

Reference ID: 3912326

primary efficacy endpoint and timing of efficacy assessments. Furthermore, clinical outcome measures based on the HBI or partial Mayo score are not sensitive enough to assess the relevance of small differences in the analytical data. Therefore, this reviewer does not consider data resulting from the Norwegian post-marketing trial to be appropriate to support that CT-P13 is biosimilar to US-licensed Remicade. However, as stated previously, data from this trial are not needed to support licensure of CT-P13 in IBD indications, since the additional analytical data and scientific justification described in Section 2 provide sufficient evidence to support extrapolation.

4. Review of the Ongoing Trial in Crohn's Disease (Study CT-P13 3.4)

A randomized, double-blind, parallel-group, phase 3 study to demonstrate noninferiority in efficacy and to assess safety of CT-P13 compared to Remicade in patients with active Crohn's disease (Study CT-P13 3.4)

Following the first approval of CT-P13 in South Korea on July 20, 2012 and in the EU on September 10, 2013, Study CT-P13 3.4 was initiated in the countries where CT-P13 was approved as well as in the U.S. under IND 118135.

On December 10, 2015, the applicant submitted an interim immunogenicity data report from this ongoing clinical trial to support similar immunogenicity between CT-P13, EU-approved Remicade and US-licensed Remicade in IBD patients. No efficacy or safety data were submitted for review. It should also be noted that, during an Arthritis Advisory Committee meeting that was convened on February 9, 2016 to discuss BLA 125544, a few committee members stated that results of this ongoing trial should be reviewed either prior to approval or when it becomes available to make decisions about the IBD indication. Accordingly, this section reviews whether the design of the study would be adequate to be able to further support a determination that there are no clinically meaningful differences between CT-P13 and US-licensed Remicade for use in IBD patients. This section also reviews the interim report of immunogenicity data to support similarity in immunogenicity. However, as stated previously, data from this trial are not needed to support licensure of CT-P13 in IBD indications, since the additional analytical characterization data submitted in this review cycle and scientific justification described in Section 2 provide sufficient evidence to support extrapolation.

1) Review of the Study Design for Study CT-P13 3.4

Study CT-P13 3.4 is a phase 3, randomized, double-blind, controlled clinical trial intended to demonstrate that CT-P13 (b) (4)

Other objectives include evaluation of efficacy, PK, and safety (including immunogenicity) (b) (4)

Reference ID: 3912326

It should be noted that the applicant has not discussed the trial design with the Division or provided adequate scientific justification (b) (4)

(b) (4)

Eligible patients are randomized in a 1:1:1:1 ratio to 1 of 4 treatment groups:

- Group 1: CT-P13 followed by CT-P13 at Week 30
- Group 2: US-licensed Remicade or EU-approved Remicade followed by CT-P13 at Week 30
- Group 3: US-licensed Remicade or EU-approved Remicade followed by US-licensed Remicade or EU-approved Remicade at Week 30
- Group 4: CT-P13 followed by US-licensed Remicade or EU-approved Remicade at Week 30

Figure 4 illustrates the schema of the study design.

(b) (4)

Reference ID: 3912326

Figure 4: Schema of Study CT-P13 3.4 from BLA submission

(b) (4)

(b) (4)

Source: "Interim immunogenicity data from Study CT-P13 3.4: A randomized, double-blind, parallel-group, phase 3 study (b) (4) *submitted as Information Amendment on December 10, 2015 under the applicant's BLA 125544 submission dated October 5, 2015; Figure 1 (page 8 of 23).*

(b) (4)

Patients received CT-P13 or either US-licensed Remicade or EU-approved Remicade 5 mg/kg at Weeks (b) (4). (b) (4) The applicant indicated in the interim report that the enrollment completed on November 26, 2015 and a total of 220 patients have been randomized into the four treatment groups.

(b) (4) The overall study

remains blinded, but unblinding of treatment assignments was performed for the first 109 randomized patients with adequate immunogenicity data.

(b) (4)

The approved dosing regimen for US-licensed Remicade for Crohn's disease is 5 mg/kg at Weeks 0, 2, and 6, followed by a maintenance regimen of 5 mg/kg every 8 weeks. (b) (4)

[10] FDA Guidance for Industry: Scientific considerations in demonstrating biosimilarity to a reference product (April 2015), available at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf

(b) (4)

Reference ID: 3912326

(b) (4)

Lastly, as described earlier in this section, the applicant has not previously requested Agency's feedback on the trial design (b) (4)

(b) (4)

In addition, as stated previously, data from this trial are not needed to support licensure of CT-P13 in IBD indications, since the additional analytical characterization data submitted in this review cycle and scientific justification described in Section 2 provide sufficient evidence to support extrapolation.

2) *Summary of Preliminary Immunogenicity Data from Study CT-P13 3.4*

The interim report contained immunogenicity data from the first 109 randomized patients who received at least one dose of study drug and had immunogenicity results both at Week 0 (Dose 1) and Week 14 (Dose 4). Other PK, efficacy and safety data have not been analyzed and, therefore, were not included in the interim report.

The applicant indicated that the Enzyme-Linked Immuno-Sorbent Assay (ELISA) method has been validated in accordance with the FDA guidance; however, the full validation report will be provided as part of the final clinical study report of Study CT-P13 3.4. The reader is referred to the Clinical Pharmacology review for the acceptability of the ELISA method used to assess the immunogenicity data.

The applicant indicated that immunoassays to detect ADA followed a 3-tiered approach, consisting of (1) a screening assay, (2) confirmatory assay, and (3) titration.

(b) (4)

Reference ID: 3912326

Of the 109 patients included in the preliminary analysis of the immunogenicity data, 54 had received CT-P13, 43 had received US-licensed Remicade, and 12 had received EU-approved Remicade. Table 7 summarizes the incidence of ADA in these patients.

Table 7: Summary of anti-drug antibody (ADA) incidence of Crohn's disease patients treated with CT-P13, US-licensed Remicade, or EU-approved Remicade in Study CT-P13 3.4

	CT-P13 (N=54)	US-licensed Remicade® (N=43)	EU-approved Remicade® (N=12)	Total (N=109)
	Number of patients (%)			
Baseline (Week 0)				
Positive	1 (1.9)	0	0	1 (0.9)
Negative	53 (98.1)	43 (100.0)	12 (100.0)	108 (99.1)
		55 (100.0)[1]		
Week 14 (all patients)				
Positive	8 (14.8)	5 (11.6)	4 (33.3)	17 (15.6)
		9 (16.4)[1]		
Negative	46 (85.2)	38 (88.4)	8 (66.7)	92 (84.4)
		46 (83.6)[1]		
Week 14 (excluding patients with pre-dose ADA positive result)				
Positive	7 (13.0)	5 (11.6)	4 (33.3)	17 (15.6)
		9 (16.4)[1]		
Negative	46 (85.2)	38 (88.4)	8 (66.7)	92 (84.4)
		46 (83.6)[1]		

[1]US-licensed Remicade and EU-approved Remicade were combined.

Source: "Interim immunogenicity data from Study CT-P13 3.4: A randomized, double-blind, parallel-group, phase 3 study to demonstrate noninferiority in efficacy and to assess safety of CT-P13 compared to Remicade in patients with active Crohn's disease," submitted as Information Amendment on December 10, 2015 under the applicant's BLA 125544 submission dated October 5, 2015; Table 7 (page 19 of 23).

Except for one patient in the CT-P13 treatment group, all remaining patients had negative ADA at baseline (Week 0). At Week 14, 8 (15%) of 54 patients, 5 (12%) of 43 patients, and 4 (33%) of 12 patients had positive ADA in the CT-P13 treatment group, US-licensed Remicade group, and EU-approved Remicade group, respectively. The proportion of patients with positive ADA results in the CT-P13 treatment group at Week 14 was numerically similar to that observed in the US-licensed Remicade group. The proportion of patients with positive ADA results in the EU-approved Remicade group was numerically higher. However, these data must be interpreted with caution since the sample size is small and the study was not powered to demonstrate similarity in immunogenicity. The applicant indicated that neutralizing antibody data are currently not available and, therefore, will be reported at a later time.

Reference ID: 3912326

Table 8 summarizes the ADA titer results of the 109 patients included in the interim analysis.

Table 8: Summary of anti-drug antibody (ADA) titer results of Crohn's disease patients treated with CT-P13, US-licensed Remicade, or EU-approved Remicade in Study CT-P13 3.4

	CT-P13 (N=54)	US-licensed Remicade® (N=43)	EU-approved Remicade® (N=12)	Total (N=109)
Week 0 (Baseline)				
Number of patient with ADA positive (%)	1(1.9)[2]	0	0	-
Mean ADA Titer (± SD)	-[2]	-	-	-
Median ADA Titer (Min, Max)	-[2]	-	-	-
Week 14				
Number of patient with ADA positive (%)	8 (14.8%)	5 (11.6%)	4 (33.3%)	17 (15.6%)
		9[1]		
Mean ADA Titer (± SD)	2.3 (±1.49)	2.4 (±0.89)	3.5 (±2.08)	2.6 (± 1.50)
		2.9 (±1.54)[1]		
Median ADA Titer (Min, Max)	2.0 (1,5)	3.0 (1,3)	3.5 (1,6)	2.0 (1,6)
		3.0 (1,6)[1]		

[1]US-licensed Remicade and EU-approved Remicade were combined.

[2]One patient had a positive baseline ADA result but could not be further analyzed for titration due to insufficient sample volume.

Note: The ADA titer values were transformed using a [log2(x)] + 1 transformation (where x is the reported titer result)

Source: "Interim immunogenicity data from Study CT-P13 3.4: A randomized, double-blind, parallel-group, phase 3 study to demonstrate noninferiority in efficacy and to assess safety of CT-P13 compared to Remicade in patients with active Crohn's disease," submitted as Information Amendment on December 10, 2015 under the applicant's BLA 125544 submission dated October 5, 2015; Table 8 (page 20 of 23).

The antibody titer results at Week 14 were numerically similar between treatment groups. Although the results are reassuring, these data should be interpreted with caution given the small sample size.

In summary, the interim analysis of immunogenicity data suggests that ADA development is similar between Crohn's disease patients who received CT-P13 and US-licensed Remicade. Although these results are based on an interim analysis, they provide reassurance that immunogenicity to CT-P13 is unlikely to be different in IBD patients compared to other populations studied.

Reference ID: 3912326

5. Summary and Conclusions

The BLA 125544 application for Inflectra (CT-P13), a proposed biosimilar to US-licensed Remicade, was resubmitted on October 5, 2015 to seek licensure for the same indications for which US-Remicade is licensed, including the IBD indications (CD, pediatric CD, UC, and pediatric UC[1]). At the time of a Complete Response (CR) action on June 8, 2015 based on review of the initial BLA submission, the applicant was informed that the submitted analytical data did not provide sufficient information to conclude that CT-P13 is highly similar to the reference product (i.e., US-licensed Remicade). One of the main concerns raised was the approximately 20% lower antibody-dependent cellular toxicity (ADCC) activity in CT-P13 compared to the reference product, leading to residual uncertainty about whether CT-P13 is highly similar to US-licensed Remicade.

In the current resubmission, the applicant provided sufficient analytical similarity data to support a conclusion that CT-P13 and US-licensed Remicade are highly similar (see Product Quality review from this review cycle for details). The applicant has also submitted adequate scientific justification (based on the mechanism of action, PK, immunogenicity, and toxicity) to support extrapolation of clinical data from other studied populations (i.e., RA and AS) to IBD indications. Most importantly, the applicant has adequately addressed each of the known and potential mechanisms of action of US-licensed Remicade through comparative analytical testing. Secondly, available PK and bio-distribution data support similarities in these parameters between CD and RA. The applicant provided data that demonstrate similar PK between CT-P13 and US-licensed Remicade (see Clinical Pharmacology review for details), and submitted analytical data did not identify reasons to expect differences in PK between the studied populations and IBD patients exposed to CT-P13. Thirdly, immunogenicity is affected primarily by the use of concomitant immunosuppressive therapy rather than by patient population, and the applicant has addressed these usage scenarios in the RA and AS trials. To strengthen the scientific justification to support similar immunogenicity in IBD patients, the applicant also submitted an interim report of immunogenicity data to demonstrate that anti-drug antibody (ADA) development is similar between CD patients who received CT-P13 and US-licensed Remicade. Lastly, available safety data support similarities in adverse reactions across licensed indications. The applicant provided data that demonstrate similar safety profiles between CT-P13 and US-licensed Remicade in RA and AS patients (see Clinical review for details), and submitted analytical data did not identify reasons to expect differential safety profiles between the studied populations and IBD patients exposed to CT-P13. Given the similar product quality attributes, PK, and immunogenicity, there is no reason to expect that the safety evaluation in RA and AS would be different from the IBD population.

In conclusion, the applicant's submitted data provide adequate scientific justification to support extrapolation and licensure of CT-P13 in IBD indications.

Reference ID: 3912326

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/s/

JESSICA J LEE
04/05/2016

DONNA J GRIEBEL
04/05/2016

Medical Officer's Review of BLA 125544
Division of Dermatology and Dental Products

Type: Biosimilar 351(k)
Serial Amendment: 000
Supporting Document Number: 001

Correspondence date: 8-AUG-2015
CDER Stamp date: 8-AUG-2015
Review Date: 4-APR-2016

Applicant: Celltrion, Inc.
23 Academy-road
Yeonsu-gu, Incheon
Republic of Korea 406-840

Drug: INFLECTRA (CT-P13) a proposed biosimilar to infliximab
Route of Administration: Intravenous
Dosage Form: Powder for reconstitution
Pharmacologic Category: Anti-human tumor necrosis factor alpha (TNFα) human-murine immunoglobulin G1 (IgG1) monoclonal antibody
Proposed Indication:

1) Crohn's Disease (CD):
    - reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.
    - reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing disease.
2) Pediatric Crohn's Disease:
    - reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely active disease who have had an inadequate response to conventional therapy.
3) Ulcerative Colitis (UC):
    - reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.
4) Pediatric Ulcerative Colitis:
    - reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely active disease who have had an inadequate response to conventional therapy.[1]
5) Rheumatoid Arthritis (RA) in combination with methotrexate:
    - reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active disease.

[1] This reflects information for Inflectra that Celltrion submitted on August 8, 2014. We note that Remicade's indication for pediatric ulcerative colitis is protected by orphan drug exclusivity expiring on September 23, 2018. See the Orphan Drug Designations and Approvals database at http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm. Accordingly, FDA will not be able to license a proposed biosimilar product for this indication until the orphan exclusivity expires.

Reference ID: 3911978

6) Ankylosing Spondylitis (AS):
    - reducing signs and symptoms in patients with active disease
7) Psoriatic Arthritis (PsA):
    - reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function.
8) Plaque Psoriasis (PsO):
    - treatment of adult patients with chronic severe (i.e., extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate.

Project Manager: Paul Phillips
Team Leader: David Kettl, MD
Medical Officer: Gary Chiang, MD, MPH.

Executive Summary:

The Division of Dermatology and Dental Products has concluded that the proposed drug product INFLECTRA (CT-P13), a proposed biosimilar to US-licensed Remicade (infliximab), has provided sufficient scientific evidence under section 351(k) of the Public Health Service Act (PHS Act) to demonstrate that the proposed biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between the proposed biosimilar product and the reference product in terms of the safety, purity and potency of the product.

No clinical data was available for indications sought under the dermatology review purview. For additional information on the indications evaluated in this application, please refer to the clinical review from DPARP, the review memo from the Division of Gastrointestinal and Inborn Errors Products (DGIEP), or the Cross-Discipline Team Leader (CDTL) review for details of the submitted application.

It is the Division's conclusion that sufficient scientific evidence is presented for use of CT-P13 in "the treatment of adult patients with chronic severe (i.e., extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate."

Introduction:

CELLTRION is developing CT-P13 as a proposed biosimilar to US-licensed Remicade (infliximab). Remicade was licensed in the United States (US) in 1998. Remicade is also licensed in many countries worldwide, including the European Union (EU) via the Centralized Procedure.

CT-P13 is a chimeric human-murine immunoglobulin G1 (IgG1) monoclonal antibody that binds with high affinity to human tumor necrosis factor alpha (TNFα). The active

Reference ID: 3911978

substance is a glycoprotein with 1 N-linked glycosylation site in the CH2 domain of each heavy chain. Each heavy chain consists of 450 amino acids with 11 cysteine residues, and each light chain consists of 214 amino acids with 5 cysteine residues. All cysteines in the heavy and light chains are involved in either intra- or inter- disulfide bonding.

As part of the totality of the evidence for a demonstration of biosimilarity, the clinical development program for CT-P13 is to support a demonstration that no clinically meaningful differences exist between CT-P13 and the reference product, US-licensed Remicade in terms of its pharmacokinetics, efficacy, safety, and immunogenicity. The following three controlled studies provide the primary evidence to support the determination of no clinically meaningful differences between CT-P13 and the reference product, US-licensed Remicade:

- Study 1.4 is a single-dose, 3-way pharmacokinetics (PK) study which establishes similar pharmacokinetics between CT-P13 and US-licensed Remicade, as well as supporting the PK element of the scientific bridge between CT-P13, US-licensed Remicade and EU-approved Remicade. This scientific bridge between the products is necessary to justify the relevance of comparative data generated using EU-approved Remicade to support demonstration of biosimilarity of CT-P13 to US-licensed Remicade.
- Study 3.1 is the comparative clinical study that provides the efficacy data for CT-P13 in rheumatoid arthritis (RA) to support a demonstration of no clinically meaningful differences. It was designed as a randomized, double-blind, parallel-group study between CT-P13 and EU-approved Remicade.
- Study 1.1, although designed as a primary PK study between CT-P13 and EU-approved Remicade in ankylosing spondylitis (AS) patients, the study also captures safety and efficacy in AS as secondary endpoints. This was also a randomized, double-blind, parallel-group study.

Additional long-term safety and immunogenicity data for patients who had a single transition at week 54 from EU-approved Remicade to CT-P13 or continued to receive CT-P13 came from studies 3.2, and 1.3, open-label, long-term extension studies in RA and AS, respectively.

Extrapolation to Plaque Psoriasis:

Celltrion is seeking licensure for the indications studied in the clinical program, i.e., RA and AS, as well as for psoriatic arthritis, plaque psoriasis, adult and pediatric Crohn's disease, and adult and pediatric ulcerative colitis[1] for which they have not submitted clinical data. To support the use of CT-P13 for the non-studied indications, Celltrion has provided adequate scientific justification for the extrapolation of biosimilarity to those indications.

The justification addresses the issues for the testing and extrapolation to conditions of use outlined in Guidance for Industry: “Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009.”

Reference ID: 3911978

If a biological product meets the statutory requirements for licensure as a biosimilar biological product under section 351(k) of the PHS Act based on, among other things, data derived from a clinical study or studies sufficient to demonstrate safety, purity and potency in an appropriate condition of use, the applicant may seek licensure for one or more additional conditions of use for which the reference product (i.e., US-licensed Remicade) is licensed.[2] However, the applicant would need to provide sufficient scientific justification for extrapolating clinical data to support a determination of biosimilarity for each condition of use for which licensure is sought.

Such scientific justification for extrapolation should address, for example, the following issues for the tested and extrapolated conditions of use:

- The mechanism(s) of action (MOA) in each condition of use for which licensure is sought
- The pharmacokinetics (PK) and bio-distribution of the product in different patient populations
- The immunogenicity of the product in different patient populations
- Differences in expected toxicities in each condition of use and patient population
- Any other factor that may affect the safety or efficacy of the product in each condition of use and patient population for which licensure is sought

The Agency has determined that differences between conditions of use with respect to the factors described above do not necessarily preclude extrapolation. A scientific justification should address these differences in the context of the totality of the evidence supporting a demonstration of biosimilarity.

Consistent with the principles outlined in the above FDA guidance, Celltrion has provided sufficient justification to extrapolate data from the comparative clinical studies of CT-P13 in RA and AS to support a determination of biosimilarity for the additional indications for which US-licensed Remicade is licensed. Considerations specific to plaque psoriasis include:

- The primary mechanism of action (MOA) of infliximab is direct binding and blocking of TNF receptor-mediated biological activities. Infliximab binds to both soluble (s) and transmembrane (tm) TNF, thus blocking TNF binding to its receptors TNFR1 and TNFR2 and the resulting downstream pro-inflammatory cascade of events. The scientific literature indicates that this MOA is the primary MOA in RA, AS, PsA, PsO. The data provided by Celltrion showed similar TNF binding and potency to neutralize TNFα, supporting the determination of analytical similarity pertinent to this MOA. Therefore, the demonstration of biosimilarity of CT-P13, which included clinical studies in RA and AS, can

[2] Guidance for Industry "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009", April 2015 http://www fda.gov/downloads/Drugs/Guidances/UCM273001.pdf

Reference ID: 3911978

reasonably be extrapolated to plaque psoriasis based on common mechanism of action.

- Because similar PK was demonstrated between CT-P13 and US-licensed Remicade, a similar PK profile would be expected for CT-P13 in patients with plaque psoriasis.

  In general, immunogenicity of the US-licensed Remicade was affected primarily by the use of concomitant immunosuppressive therapy across different indications rather than by patient population, and the results were influenced by the type of immunoassay used. In plaque psoriasis the recommended dose is 5 mg/kg. US-licensed Remicade is used without methotrexate in plaque psoriasis. This usage scenario was assessed in Celltrion's AS study (use of 5 mg/kg dose without concomitant immunosuppressive therapy). Celltrion provided adequate bridging data to justify the relevance of comparative data with EU-approved Remicade in Celltrion's AS study to support a demonstration of biosimilarity of CT-P13 to US-licensed Remicade.
- No differences in expected toxicities that are relevant to the plaque psoriasis population were noted between the CT-P13 product and the EU-approved Remicade arms in the clinical trials. See the clinical review by Dr. Waheed.
- Based on the above considerations, the Division concluded that it is reasonable to extrapolate clinical data of CT-P13 from RA and AS to support a demonstration of biosimilarity of CT-P13 in plaque psoriasis.

The Agency presented the application for CT-P13 to the Arthritis Advisory Committee (AAC) on 9-FEB-2016. The Agency asked the AAC to evaluate the scientific justification provided to extrapolate data from the comparative clinical studies of CT-P13 in RA and AS to support a determination of biosimilarity for the following additional indications for which US-licensed Remicade is indicated (PsA, PsO, adult and pediatric CD, and adult UC). The Committee agreed that there is sufficient scientific justification to extrapolate clinical data to the other conditions of use for which the reference product is licensed.

Overall Conclusion:

The biosimilar licensure pathway under section 351(k) of the Public Health Service Act (PHS Act) requires a demonstration that the proposed biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between the proposed biosimilar product and the reference product in terms of the safety, purity and potency of the product. This statutory requirement has been met to demonstrate that CT-P13 is biosimilar to US-licensed Remicade.

The Division has also determined that the applicant has provided proper justification to support extrapolation of clinical data from RA and AS to support the proposed use of CT-P13 in the treatment of adult patients with chronic severe (i.e., extensive and/or disabling)

Reference ID: 3911978

plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate.

Gary Chiang, M.D., M.P.H.
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Division of Dermatology and Dental Products
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Reference ID: 3911978

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/s/

GARY T CHIANG
04/04/2016

DAVID L KETTL
04/04/2016

KENDALL A MARCUS
04/04/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES **Public Health Service**

Food and Drug Administration
Center for Drug Evaluation and Research
ODE II / DPARP / HFD-570
10903 New Hampshire Ave.
Silver Spring, MD 20993

Memo to File

Addendum to Primary Clinical Review

BLA#: 125,544

Reviewer: Juwaria Waheed, MD, CDER/OND/DPARP

Submission: August 8, 2014 (Original NDA)

Complete Response June 8, 2015

BLA Resubmission October 5, 2015

Reviewed: March 10, 2016

Product: CT-P13, proposed biosimilar to US-licensed Remicade

Proposed use: Treatment of Rheumatoid Arthritis (RA) Rheumatoid Arthritis in combination with methotrexate, Ankylosing Spondylitis (AS), Psoriatic Arthritis (PsA), Plaque Psoriasis (PsO), Crohn's Disease (CD), Pediatric Crohn's Disease, Ulcerative Colitis (UC), and Pediatric Ulcerative Colitis[1]

Sponsor: Celltrion

Recommendation on Regulatory Action

Recommend approval of BLA 125,544 for CT-P13 as a biosimilar to US-licensed Remicade.

This biologic licensing application (BLA) 125544 seeks approval of the product CT-P13 (proposed trade name: Inflectra) which is a proposed biosimilar to US-licensed Remicade (active ingredient infliximab, a TNFα-inhibitor). The biosimilar licensure pathway under section 351(k) of the Public Health Service Act (PHS Act) requires that the proposed biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between the proposed biosimilar and reference products in terms of safety, purity and potency. Both parts of the statutory definition need to be met to demonstrate biosimilarity, but the foundation of the data demonstrating biosimilarity is extensive structural and functional characterization to support a demonstration that the products are highly similar.

The product quality review by OBP (Office of Biotechnology Products) team, of structural and functional characterization, concluded that CT-P13 is highly similar to US-licensed Remicade notwithstanding minor differences in clinically inactive components. The submitted clinical pharmacology, efficacy, safety, and immunogenicity data from the clinical development program of CT-P13, support a demonstration of no clinically meaningful differences between CT-P13 and US-licensed Remicade.

[1] Remicade's indication for pediatric ulcerative colitis is protected by orphan drug exclusivity expiring on September 23, 2018

Therefore, CT-P13 meets both parts of the statutory definition to demonstrate biosimilarity to the reference product in that CT-P13 is highly similar to the reference product notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between CT-P13 and the reference product in terms of safety, purity and potency. The applicant has also provided adequate scientific justification to allow for extrapolation of data to support biosimilarity in all indications that US-licensed Remicade is licensed for (PsA, PsO, adult and pediatric CD, and adult and pediatric UC).

Background

Celltrion submitted BLA 125544 seeking approval for CT-P13, a proposed biosimilar to US-licensed infliximab (Remicade) in August 2014. At the time, the Applicant did not provide sufficient data to support the conclusion that CT-P13, is analytically highly similar to US-licensed Remicade. Consequently, the Agency took a complete response (CR) action for the application in June 2015. The applicant resubmitted the BLA in October 2015 adequately addressing the specific deficiencies in the CR letter.

In terms of clinical data, all data were reviewed in the original cycle and captured in the clinical review from the first review cycle. Please refer to the original primary clinical review, dated May 04, 2015.

This re-submission included clinical data from ongoing open-label post-marketing studies and registries, and interim immunogenicity data from an ongoing randomized, controlled study 3.4 in patients with Crohn's disease. This document updates the primary clinical review from the first cycle with the new safety and immunogenicity information of CT-P13. Detailed discussion of the clinical data from patients with inflammatory bowel disease (IBD), including the design and data from study 3.4, is also provided in the review by the Division of Gastroenterology, and Inborn Errors Products (DGIEP), as part of the collaborative review of this application (refer to Dr. Jessica Lee's review).

Summary of Safety

The bulk of the safety data for CT-P13 is derived from clinical studies using EU-approved Remicade as a comparator. The Applicant has established a scientific bridge to justify the relevance of the safety data generated using EU-Remicade in the CT-P13 program. The safety population in the clinical program comprised of over 800 individuals, including healthy subjects and patients using two different dosing regimens. Safety data were derived from the comparative clinical study in RA (study 3.1), PK study in AS (study 1.1) and healthy subjects (study 1.4); three supportive studies in patients with RA (conducted in the Philippines, Russia and Japan); and long-term extension studies (LTE study 3.2 in RA, LTE study 1.3 in AS). Patients with RA received 3 mg/kg CT-P13 or EU-approved Remicade in combination with methotrexate and folic acid and patients with AS received 5 mg/kg CT-P13 or EU-approved Remicade, for over one year. Healthy subjects received a single dose of 5 mg/kg CT-P13, EU-approved Remicade or US-licensed Remicade. Overall, the safety database was adequate to provide a reasonable comparative safety and immunogenicity assessment, using two approved dosing regimens of Remicade in two distinct patient populations. The safety analysis did not identify any new safety signals compared to the known safety profile of US-licensed Remicade. In each study, the overall incidences of treatment-emergent adverse events, serious adverse events (SAEs), AEs leading to discontinuation, infections, infusion-related reactions and anaphylaxis, were similar between CT-P13 and the comparator products. The incidence of deaths, anaphylaxis and immunogenicity were similar between treatment groups. Refer to original clinical review for a detailed discussion.

Summary of Updated Safety Information

The primary clinical review from the original application included review of safety data with a data cut-off date of 19 July 2014.

At the time of this BLA resubmission in October 2015, Celltrion provided a safety update summarizing the clinical safety information of CT-P13 based on data available as of 31 May 2015 (data cut-off) date, as summarized in **Table 1** below. All of these studies are open-label and uncontrolled limiting their utility to draw definitive conclusions on safety or efficacy. The applicant also submitted data from two observational, cohort studies in patients with inflammatory bowel disease (IBD), from Hungary and Norway. Refer to Dr. Jessica Lee's review for discussion of safety and efficacy in the post marketing IBD program.

Table 1. CT-P13 Post-Marketing Studies and Registries outside US

Protocol Duration (Current status)	**Design**	**Number of Patients**
CT-P13 4.2 RA registry in EU and Korea Ongoing	Phase 4, observational, cohort study in patients with RA	N=179
CT-P13 4.3 IBD registry in EU and Korea Ongoing	Phase 4, observational, cohort study in patients with IBD	N=54
CT-P13 4.4 AS registry in EU and Korea Ongoing	Phase 4, observational, cohort study in patients with AS	N=164
Korean Post-Marketing Surveillance (PMS) study in Korea Ongoing	Observational study	N=845
Hungary IBD study	Prospective, observational, cohort study in patients with IBD	N=210
Norway IBD study	Observational, cohort study in patients with IBD	N=78

Source: Table adapted from the Celltrion 351(k) BLA submission RA: Rheumatoid Arthritis, EU: European Union, IBD: Inflammatory Bowel Disease, AS: Ankylosing Spondylitis

The post-marketing experience with CT-P13 includes 3 registry studies, one each in RA, AS and IBD, studies 4.2 (n=179), 4.3 (n=54), and 4.4 (n=164), respectively; and one Korean post-marketing surveillance (PMS) study (n=845). Among these 1,242 patients enrolled in the CT-P13 observational post-marketing studies & registries, 983 patients were confirmed to receive CT-P13 treatment.

The safety database for the post marketing studies captured serious adverse events (SAEs); the database has not yet been established to evaluate all adverse events (AEs) yet since these studies are currently ongoing. Overall, the SAE's including adverse events of special interest within the SAEs in the CT-P13 post-marketing studies are comparable to the known safety profile of US-licensed Remicade. No new safety signals have been identified.

Study 4.2 (RA Registry)

In the ongoing RA Registry study, CT-P13 4.2, 179 patients have been enrolled as of 31 May 2015 (CT-P13 group: 98; other TNF blocker group: 62; Biologic naïve group: 19). A total of 10 SAE's have been reported thus far. These include musculoskeletal pain, myalgias, polyarthritis, pneumonia, anaphylactic reaction, infusion related reaction, lobar pneumonia, overdose, asthma and acute pyelonephritis. Treatment was discontinued in 3 patients because of SAEs which include pneumonia, anaphylactic reaction and polyarthritis. No deaths occurred in this registry cohort during the reporting period.

Study 4.3 (IBD Registry)

In the ongoing IBD registry, 54 patients have been exposed to CT-P13 as of 31 May 2015. The first annual report of this study includes safety data from 24 patients with CD or UC enrolled in this study up to 31 Dec 2014; 1 patient who switched from Remicade® to CT-P13 and 23 patients who received CT-P13 only. Overall, 7 patients (29.2%) experienced 15 treatment-emergent AEs. The majority of adverse events were of mild or moderate intensity.

Two SAE's have been reported in this registry thus far. One patient with ulcerative colitis had an SAE of intervertebral disc protrusion requiring surgery. The second SAE was of ileus in one patient with Crohn's disease. The patient, a 50 year old male with a prior history of right sided hemicolectomy, developed ileus and required an acute operation for derotation of small intestinal loops via enterotomy. No sign of acute inflammation was found. The patient recovered from the event with sequelae of intestinal obstruction. No action was taken for CT-P13.

Events of special interest were reported in two patients with moderate to severe active CD. A decrease in platelet count has been observed in one patient, rated as mild and unrelated to treatment with CT-P13. For the second patient an increase in ALT and AST were reported; these hepatobiliary events were of moderate intensity and rated as related to treatment. Both patients recovered and continued treatment with CT-P13.

No TEAEs lead to permanent discontinuation of the drug. There were no deaths during the course of this study.

Study 4.4 (AS Registry)

In the ongoing AS Registry study, CT-P13 4.4, 164 patients have been enrolled up to 31 May 2015 (CT-P13 group: 80; other TNF blocker group: 84). One SAE was reported. The SAE was captured as hepatitis toxic, the patient presented with jaundice, elevated AST (660), ALT (759), and total bilirubin (8.8). At one month, AST and ALT normalized while the total bilirubin remained mildly elevated at 2.8. Concomitant medications included isoniazid. Both CT-P13 and isoniazid were discontinued. No further information is available for this registry at this time.

Korean Post-Marketing Surveillance (PMS) Study

In the Korean PMS study of Remsima® (CT-P13), 845 patients have been enrolled up to 31 May 2015 (377 AS patients; 246 RA patients; 118 CD patients; 99 UC patients; 2 PsA patients; 3 PsO patients).

Fourteen additional SAEs were reported in 14 patients since the submission of 4-Month Safety Update (first BLA cycle review). A total of 33 SAEs were reported including three cases of pneumonia and five cases of tuberculosis (TB). Two deaths were reported, one due to pneumonia in a 74 year old female and the other due to cardiac arrest and interstitial lung disease in a 71-year old male.

Conclusions from CT-P13 Post-Marketing Data

The post-marketing experience with CT-P13 includes 3 registry studies, one each in RA, AS and IBD, studies 4.2 (n=179), 4.3 (n=54), and 4.4 (n=164), respectively; and one Korean post-marketing surveillance (PMS) study (n=845). Among these 1,242 patients enrolled in the CT-P13 observational post-marketing studies & registries, 983 patients were confirmed to receive CT-P13 treatment.

Overall, the SAE's including adverse events of special interest within the SAEs in the CT-P13 post-marketing studies are comparable to the known safety profile of US-licensed Remicade. No new safety signals have been identified. However, given the open-label and uncontrolled nature of these observational studies and registries these conclusions should be interpreted with caution.

Interim Immunogenicity Results from Study 3.4

Immunogenicity assessment of a proposed biosimilar product is generally a required component of 351(k) licensing applications. In the CT-P13 development program, immunogenicity of CT-P13 was prospectively assessed in the RA and AS controlled studies (studies 3.1 and 1.1 respectively), their respective extension studies (LTE study 3.2 in RA and 1.3 in AS) and in healthy subjects (study 1.4).

To further support similarity in immunogenicity between CT-P13 and US-licensed Remicade, the Applicant submitted an interim analysis of immunogenicity in patients with CD from on-going, Study 3.4, summarized in Table 2.

Table 2. Interim Analysis of Immunogenicity Data in Study 3.4

	CT-P13 (N=54)	US-licensed Remicade® (N=43)	EU-approved Remicade® (N=12)	Total (N=109)
	Number of patients (%)			
Baseline (Week 0)				
Positive	1 (1.9)	0	0	1 (0.9)
Negative	53 (98.1)	43 (100.0)	12 (100.0)	108 (99.1)
		55 (100.0)[1]		
Week 14 (all patients)				
Positive	8 (14.8)	5 (11.6)	4 (33.3)	17 (15.6)
		9 (16.4)[1]		
Negative	46 (85.2)	38 (88.4)	8 (66.7)	92 (84.4)
		46 (83.6)[1]		
Week 14 (excluding patients with pre-dose ADA positive result)				
Positive	7 (13.0)	5 (11.6)	4 (33.3)	17 (15.6)
		9 (16.4)[1]		
Negative	46 (85.2)	38 (88.4)	8 (66.7)	92 (84.4)
		46 (83.6)[1]		

Source: Table excerpted from the Celltrion 351(k) BLA submission
[1] US-licensed Remicade and EU-approved Remicade were combined

Study 3.4 is an ongoing randomized, double-blind, controlled, post-marketing study in patients with active Crohn's Disease (CD), comparing efficacy, safety, and immunogenicity of CT-P13 with US-licensed Remicade and EU-approved Remicade after multiple doses of 5 mg/kg. This study was not a part of the clinical program originally submitted to support the BLA and thus is not discussed in detail. However, Celltrion submitted an interim analysis of immunogenicity with repeat doses of CT-P13 with US-licensed Remicade and EU-approved Remicade from the study to supplement the immunogenicity information from study 1.4 (single dose of the same products in healthy volunteers). The immunogenicity assessment was planned at Weeks 0, 14, 30, 54, and end-of-study visit.

Eligible patients were randomized in a 1:1:1:1 ratio to 1 of 4 treatment groups receiving a 2-hour IV infusion of 5 mg/kg of either CT-P13, US-licensed Remicade, or EU-approved Remicade at Weeks 0, 2, 6, and 14 and then every 8-weeks through Week 54.

- Group 1: CT-P13 only
- Group 2: Remicade followed by CT-P13 at Week 30
- Group 3: Remicade only
- Group 4: CT-P13 followed by Remicade at Week 30

As of September 14, 2015, a total of 109 patients were randomized and received at least 1 dose of study drug and had immunogenicity results both at Week 0 (Dose 1) and Week 14 (Dose 4), of which 54 patients received CT-P13, 43 patients received US-licensed Remicade, and 12 patients received EU-approved Remicade. The previously developed ELISA method, which was further optimized and fully validated, has been used for the immunogenicity sample analysis.

The summary of immunogenicity data is shown in Table 2. At baseline, all patients were ADA negative except 1 patients in CT-P13 group. At Week 14, the number of patients with positive ADA was 8/54 (14.8 %), 5/43 (11.6 %) and 4/12 (33.3 %) at Week 14 in the CT-P13 treatment group, US-licensed Remicade group, and EU-approved Remicade group, respectively. This interim analysis shows the incidence of ADA formation was similar between CT-P13 and US-licensed Remicade in patients with IBD treated with 5 mg/kg dosing regimen. In this interim analysis, the ADA incidence was numerically higher in patients treated with the EU-approved Remicade, likely due to the small sample size of this subgroup.

Summary of Safety and Immunogenicity

In summary, safety outcomes, including immunogenicity, were similar between patients treated with CT-P13 or comparator products. No new safety signals were identified in the CT-P13 clinical program compared to the known safety profile of Remicade. Further, the accumulated clinical safety data from ongoing registries and observational studies in RA, AS, and IBD, appear consistent with the safety seen in CT-P13 clinical development program. The safety and immunogenicity results add to the totality of evidence to support the conclusion that there are no clinically meaningful differences between CT-P13 and the US-licensed Remicade.

Advisory Committee

An Arthritis Advisory Committee (AAC) meeting was convened on February 9, 2016 to discuss BLA 125544. The advisory committee panel, in addition to arthritis committee members, included a diverse panel of experts from relevant disciplines including gastroenterology, dermatology, pediatrics, immunology, chemical and biomedical engineering and statistics, for a total of 24 members.

The Agency posed to the committee three questions for discussion and one question to vote upon. The discussion questions asked whether CT-P13 is highly similar to the reference product, that there are no clinically meaningful differences between CT-P13 and US-licensed Remicade, and lastly, if there is sufficient scientific justification to extrapolate data from the studied indications of RA and AS to support a determination of biosimilarity of CT-P13 for the additional indications for which US-licensed Remicade is licensed, namely psoriatic arthritis (PsA), plaque psoriasis (PsO), adult and pediatric Crohn's disease (CD), and adult and pediatric ulcerative colitis (UC)[1]). The voting question asked the committee to vote if they agree that based on the totality of the evidence, CT-P13 should receive licensure as a biosimilar product to US-licensed Remicade for each of the indications for which US-licensed Remicade is currently licensed and CT-P13 is eligible for licensure (RA, AS, PsA, PsO, adult CD, pediatric CD, adult UC). 21 members voted in favor and 3 members voted against.

A synopsis of the AC panel discussion is provided below under each question. Refer to the official advisory committee transcript for a comprehensive discussion.

1. **DISCUSSION:** Does the Committee agree that CT-P13 is highly similar to the reference product, US-licensed Remicade, notwithstanding minor differences in clinically inactive components?

[1] Remicade's indication for pediatric ulcerative colitis is protected by orphan drug exclusivity expiring on September 23, 2018. Although FDA is interested in the Committee's views regarding the scientific justification for extrapolating clinical data to support a determination of biosimilarity for CT-P13 for this indication, FDA is not asking the Committee to vote on licensure of CT-P13 for pediatric ulcerative colitis because FDA will not be able to license a proposed biosimilar product for this indication until the orphan exclusivity expires.

Summary of AC Panel Discussion: Some discussion occurred on the relevance of the small analytical differences between CT-P13 and Remicade, including the observed 20% difference in some of the NK-based ADCC assays. The Agency clarified that this degree of difference does not preclude the conclusion of high similarity because 90% of the CT-P13 lots tested were within the quality range +/- 3 standard deviation of the reference product and that a control strategy of the manufacturing process can ensure that quality and mitigate concerns about a potential drift. To address a request for a clarification on the meaning of clinically inactive ingredients, the FDA explained that the law does not require that the two products are the same thus minor differences are expected in components such as C-terminal lysine, an example of a clinically inactive component. Glycosylation and Fcgamma receptor binding are other areas of product development where differences may arise due to inherent variability. The committee opined that overall the totality of the evidence supported the conclusion that CT-P13 is highly similar to the reference product, US-licensed Remicade, notwithstanding minor differences in clinically inactive components.

2. **DISCUSSION:** Does the Committee agree that there are no clinically meaningful differences between CT-P13 and US-licensed Remicade in the studied conditions of use (rheumatoid arthritis (RA) and ankylosing spondylitis (AS))?

   Summary of AC Panel Discussion: Discussion occurred on the selection of 12% similarity margin and missing data. The statistician experts on the committee acknowledged the rigor which FDA has applied to ensure the interpretability of the clinical efficacy data to rule out clinically meaningful differences. The committee expressed an opinion that preserving 50% of the treatment effect balanced by feasibility considerations is a reasonable approach to the selection of similarity margin. Some members pointed out it is important not to ignore the value of point estimate. The Agency further clarified the determination of similarity margin as well as other analyses undertaken such as tipping point analysis to comprehensively evaluate the efficacy data and the potential impact of missing data on the efficacy conclusions.

   The discussion then moved on to the practical implications of having an approved biosimilar product on the market such as assessing post-marketing safety, naming and identification of the biosimilar, switching between the reference product and the proposed biosimilar, physician & patient preference for a specific biologic vs. formulary decisions. The committee opined that overall the totality of the evidence supported the conclusion that no clinically meaningful differences exist between CT-P13 and US-licensed Remicade in the studied indications of RA and AS.

3. **DISCUSSION:** Does the Committee agree that there is sufficient scientific justification to extrapolate data from the comparative clinical studies of CT-P13 in RA and AS to support a determination of biosimilarity of CT-P13 for the following additional indications for which US-licensed Remicade is licensed (psoriatic arthritis (PsA), plaque psoriasis (PsO), adult and pediatric Crohn's disease (CD), and adult and pediatric ulcerative colitis (UC)[1])? If not, please state the specific concerns and what additional information would be needed to support extrapolation. Please discuss by indication if relevant.

   Summary of AC Panel Discussion: The overall sentiment was that Celltrion has provided sufficient analytical and clinical data to support the justification for extrapolation to all indications including the IBD indications. Specifically, many expressed that if CT-P13 meets the statutory requirements of being

biosimilar to US-Remicade in terms of analytical similarity, safety, purity and potency, and there are no clinically meaningful differences between the two, then the biosimilar should be expected to work across all indications similar to the reference product. A few committee members expressed concern about the risk of potential safety and efficacy differences based on the limited clinical information in the IBD population. Therefore some of them expressed interest in having the additional data including safety, efficacy and immunogenicity results from the ongoing clinical study in IBD initiated by Celltrion to provide further comfort in prescribers. However, other members acknowledged the limitation of that study to address the observed analytical differences.

The potential benefits of having biosimilars such as CT-P13 in the marketplace were also discussed.

4. **VOTE:** Does the Committee agree that based on the totality of the evidence, CT-P13 should receive licensure as a biosimilar product to US-licensed Remicade for each of the indications for which US-licensed Remicade is currently licensed and CT-P13 is eligible for licensure (RA, AS, PsA, PsO, adult CD, pediatric CD, adult UC)?

    a. **DISCUSSION:** Please explain the reason for your vote. If you voted no, explain whether this was applicable to all or some of the indications and why.

The voting result was: 21 = yes, 3 = no, and 0 = abstain. The committee as a whole stated that the total package showed a large number of analytical techniques proving that the threshold for overall biosimilarity had been met. The three committee members who voted “No” were primarily concerned with the extrapolation to the Crohn’s Disease, Ulcerative Colitis and pediatric Ulcerative Colitis indications due to the limited clinical data in these indications and the ongoing study in IBD. Concerns were also expressed by the consumer representative that the introduction of biosimilars would need more education to the community and to patients to provide more confidence in these products..

Labeling

I recommend labeling for CT-P13 should resemble the current label of US-licensed Remicade as closely as possible consistent with the conclusion that CT-P13 is biosimilar to US-licensed Remicade. Labeling discussions are ongoing at the time of this review.

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/s/

JUWARIA F WAHEED
03/11/2016

NIKOLAY P NIKOLOV
03/11/2016

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sarah Yim, M.D. Supervisory Associate Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) Badrul Chowdhury, M.D, Ph.D. Director, DPARP
Subject	Division Director Summary Review
BLA #	351(k) BLA 125544
Applicant Name	Celltrion, Inc.
Date of Submission	August 08, 2014
PDUFA Goal Date	June 08, 2015
Proprietary Name (proposed) / Nonproprietary Name	Inflectra / CT-P13[1]
Dosage Forms / Strength	Sterile lyophilized powder, 100 mg/20mL vial for reconstitution and intravenous injection
Proposed Indication(s)	All the approved indications previously approved for the reference product[2]: 1. Crohn's Disease (Adult and Pediatric) 2. Ulcerative Colitis (Adult and Pediatric[3]) 3. Rheumatoid Arthritis 4. Ankylosing Spondylitis 5. Psoriatic Arthritis 6. Plaque Psoriasis
Action:	*Complete Response*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
CDTL Review	Nikolay Nikolov, MD
Medical Officer Review	Juwaria Waheed, MD
Biostatistical Review	Primary: Gregory Levin, PhD; Secondary: Ruthanna Davi, PhD; Tertiary: Thomas Permutt, PhD.
Pharmacology Toxicology Review	Primary: Matthew Whittaker, PhD; Secondary: Timothy Robison, PhD
Product Quality Review	Primary: Peter Adams, PhD, Secondary: Kurt Brorson,

[1] In this document, I generally refer to Celltrion's proposed product by the Celltrion descriptor "CT-P13" because the Agency is continuing to consider its approach to nonproprietary naming of biosimilar products.
[2] See US-licensed Remicade prescribing information
[3] This reflects information for Inflectra that Celltrion submitted on August 8, 2014. We note that the indication for pediatric ulcerative colitis is protected by orphan drug exclusivity expiring on September 23, 2018. See the Orphan Drug Designations and Approvals database at http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm

Reference ID: 3775988

	PhD; Tertiary: David Frucht, PhD
Product-Immunogenicity	Primary: Will Hallett, PhD; Secondary: Harold Dickensheets, PhD
CMC-Statistical Review	Primary: Meiyu Shen, PhD; Secondary: Yi Tsong, PhD
CMC-Facility and Microbiology	DP: Bo Chi, PhD; DS: Maria Candau-Chacon PhD; Secondary: Patricia Hughes, PhD
Clinical Pharmacology Review	Primary: Lei He, PhD; Secondary: Ping Ji, PhD
OSI	Primary: Anthony Orencia, M.D.; Secondary: Janice Pohlman, MD MPH; Tertiary: Kassa Ayalew MD MPH
OSE/DMEPA	Primary: Teresa McMillan, PharmD; Secondary: Lubna Merchant, MS PharmD

OND=Office of New Drugs
CDTL=Cross-Discipline Team Leader
CMC=Chemistry, Manufacturing, and Controls
OSI=Office of Scientific Investigation
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

1. Introduction

This is a 351(k) biologic license application (BLA) submitted by Celltrion, Inc. for CT-P13, a proposed biosimilar to Remicade (infliximab). Celltrion is seeking licensure of CT-P13 for the same indications previously approved for the reference product, US-licensed Remicade, on the basis of the following:

- Analytical data intended to support the following purposes:
  - A demonstration that CT-P13 can be manufactured in a well-controlled and consistent manner, leading to a product that is sufficient to meet required quality standards
  - A demonstration that CT-P13 and US-licensed Remicade are highly similar
  - A justification of the scientific relevance of comparative data that were generated using EU[4]-approved Remicade to a demonstration of biosimilarity.
    - Because the comparative clinical studies in the application utilized EU-approved Remicade, 3-way analytical characterization data from a comparison of CT-P13, US-licensed Remicade, and EU-approved Remicade were utilized to provide a scientific basis (along with pharmacokinetic data) for justifying the relevance of the comparative clinical data between CT-P13 and EU-approved Remicade as applicable to the demonstration of biosimilarity between CT-P13 and US-licensed Remicade.
- Study CT-P13 1.4, a single-dose pharmacokinetic (PK) study providing a 3-way comparison of CT-P13, US-licensed Remicade, and EU-approved Remicade. This study is the only clinical study that included US-licensed Remicade as a comparator, and serves as the primary basis for:
  - Evaluating the PK similarity of CT-P13 and US-licensed Remicade, and

[4] EU=European Union

Reference ID: 3775988

  - Providing a scientific basis (along with analytical data) for justifying the relevance of comparative clinical data between CT-P13 and EU-approved Remicade as applicable to the demonstration of biosimilarity between CT-P13 and US-licensed Remicade.
- Study CT-P13 3.1, a comparative clinical study intended to demonstrate the similarity in efficacy and safety between CT-P13 and EU-approved Remicade. This is a 54-week, randomized, double-blind, parallel group study conducted outside the US in approximately 600 patients with moderate to severely active rheumatoid arthritis (RA) on background methotrexate (MTX), who were randomized 1:1 to CT-P13 or EU-approved Remicade at a dose of 3 mg/kg.
  - The applicant also provided results from Study CT-P13 1.1, which is a 54-week randomized, double-blind, parallel-group study conducted outside the US in 250 patients with moderate to severe Ankylosing Spondylitis (AS) who were randomized 1:1 to CT-P13 or EU-approved Remicade at a dose of 5 mg/kg. This study was intended to support PK similarity in a patient population not taking concomitant immunosuppressives, and also included descriptive assessments of efficacy and safety.
- Open-label extensions (OLE) of Study 1.1 and Study 3.1 were utilized to evaluate the safety of patients transitioning from treatment with EU-approved Remicade to treatment with CT-P13. Patients in the OLE who were on EU-approved Remicade were transitioned to CT-P13, and patients who were on CT-P13 remained on CT-P13.

2. Background

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) was passed as part of health reform (Affordable Care Act) that was signed into law on March 23, 2010. The BPCI Act created an abbreviated licensure pathway for biological products shown to be "biosimilar" to or "interchangeable" with an FDA-licensed biological product (the "reference product"). This abbreviated licensure pathway under section 351(k) of the PHS Act permits reliance on certain existing scientific knowledge about the safety and effectiveness of the reference product, and enables a biosimilar biological product to be licensed based on less than a full complement of product-specific preclinical and clinical data.

Section 351(i) of the PHS Act defines the terms "biosimilar" or "biosimilarity" to mean that "the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product" (see section 351(i)(2) of the PHS Act). A 351(k) application must contain, among other things, information demonstrating that the proposed product is biosimilar to a reference product based upon data derived from analytical studies, animal studies, and a clinical study or studies, unless FDA determines, in its discretion, that certain studies are unnecessary in a 351(k) application (see section 351(k)(2) of the PHS Act).

It is under this relatively new paradigm that Celltrion seeks licensure of CT-P13. The development of CT-P13 was conducted exclusively outside of the US and was geared towards

Reference ID: 3775988

meeting the requirements of non-US regulatory agencies. Much of the clinical development program was ongoing or completed at the time of Celltrion's first meeting with FDA in July 2013. FDA input in the pre-submission period addressed the purpose and design of the 3-way PK bridging study between CT-P13, EU-approved Remicade and US-licensed Remicade, expectations for safety and immunogenicity data, and expectations regarding the information needed to support proposed extrapolation of existing clinical data to support a demonstration of biosimilarity for other conditions of use not studied, particularly in light of possible differences observed in the functional data pertaining to antibody-dependent cellular cytotoxicity (ADCC).

At the time of this review, CT-P13 is approved in several regions outside the US, marketed under the trade names Inflectra and Remsima. CT-P13 has been approved in the European Union (EU), South Korea, Japan, and India for all of the indications currently listed in the approved US-licensed Remicade label. In 2014, Health Canada approved CT-P13 for all indications except ulcerative colitis and Crohn's disease. Health Canada's Summary Basis of Decision explained that extrapolation to the inflammatory bowel disease (IBD) indications was not recommended because differences in the ability of the two products to induce ADCC could not be ruled out, ADCC could not be ruled out as a mechanism of action in IBD, and clinical data in IBD indications that might help address those concerns were not available.

3. Chemistry, Manufacturing, and Controls (CMC)

CT-P13 drug substance (DS) is a chimeric human-murine IgG1κ monoclonal antibody that binds with high affinity to human TNFα. It is a glycoprotein with 1 N-linked glycosylation site in the CH2 domain of each heavy chain. Each heavy chain consists of 450 amino acids with 11 cysteine residues, and each light chain consists of 214 amino acids with 5 cysteine residues. All cysteines in the heavy and light chains are involved in either intra- or inter- disulfide bonding. CT-P13 drug substance is a colorless to light yellow and slightly opalescent to opalescent solution and free of foreign particles, with a pH of approximately 7.2. The DS is manufactured at the Celltrion Incheon site in Korea using bioreactor mammalian Sp2/0 transfectoma cell culture and a conventional purification scheme.

The CT-P13 drug product (DP) is formulated as a sterile, white, lyophilized powder in a 20 mL type I borosilicate glass vial with a 20 mm (b) (4) butyl rubber stopper and a 20 mm flip-off seal. Each CT-P13 drug product vial contains 100 mg CT-P13 drug substance as the active ingredient, and sodium dihydrogen phosphate monohydrate, di-sodium hydrogen phosphate dihydrate, sucrose and polysorbate 80 as excipients.

As mentioned above, the analytical/product quality data were necessary for three purposes: 1) demonstrating the product could be manufactured in a well-controlled and consistent manner, to meet FDA requirements for product approval, 2) demonstrating that CT-P13 and US-licensed Remicade are "highly similar", and 3) providing a scientific bridge between CT-P13, US-licensed Remicade, and EU-approved Remicade, to justify data generated using EU-approved Remicade as the comparator as relevant to the demonstration of biosimilarity between CT-P13 and US-licensed Remicade. A total of 13 batches of US-licensed Remicade,

Reference ID: 3775988

11 batches of EU-approved Remicade, and 13 batches of CT-P13 were used in the 3-way analytical similarity assessment originally submitted in the BLA, with an additional 3 to 5 batches of each product tested during the review cycle for certain assays, to boost the statistical power of the analytical similarity exercise.

Multiple analytical assessments were used to evaluate seven categories of product quality characteristics: primary structure, higher order structure, content, purity, charged isoforms, glycosylation, and biological activity. Assessments ranged from those that are done routinely for lot release, to extended characterization tests, to tests that would ordinarily be used primarily in research into, and establishment of, product mechanisms of action. A detailed discussion of the tests and test results may be found in the product quality reviews, and will not be recapitulated here.

The CMC/product quality review team concluded that the manufacture of CT-P13 was adequate to meet the product quality standards that would ordinarily be expected for approval. Results from most assessments, including those assessing the primary mechanism of TNF binding activity, were considered to be supportive of analytical similarity between CT-P13 and US-licensed Remicade. However, residual uncertainty regarding whether CT-P13 meets the statutory criteria of "highly similar" remain, as follows:

- Differences in FcγRIII binding and antibody-dependent cellular cytotoxicity (ADCC) activity
    - Both FcγRIII binding and ADCC were 20 to 25% lower with CT-P13 compared to US-licensed Remicade and EU-approved Remicade in certain, but not all, assays assessing FcγRIII binding or ADCC. As ADCC is a cell-killing activity mediated through FcγR receptors, and NK cells primarily use FcγRIII to bridge to target cells, in the setting of decreased FcγRIII binding, a corresponding decrease in ADCC activity in NK cell assays would not be unexpected. However, based on the currently available data it is not clear whether the apparent difference in FcγRIII binding and ADCC activity is a true difference in biological activity or whether this is a statistical anomaly due to the analysis of a limited number of lots.
    - The existence of FcγRIII and ADCC differences, if confirmed, would raise the question of whether these differences are due to structural differences between CT-P13 and US-licensed Remicade. An obvious etiology would be glycosylation differences, which are known to impact on Fc-mediated effector function. Based on the original 2-way analysis comparing CT-P13 and EU-approved Remicade, CT-P13 appeared to have a lower percentage of afucosylated glycoforms (5.9% compared to 9.7%). This tied the findings together neatly, because the degree of fucosylation affects binding to FcγRIIIa, and would be expected to therefore impact on ADCC activity, particularly in NK cell-dependent assays. However, in the 3-way analysis of CT-P13, EU-approved Remicade and US-licensed Remicade, the percentage of afucosylated glycoforms was much closer between the three products (5.2%, 6%, and 5.8%, respectively).
    - Furthermore, there appears to be a higher level of H2L1 (~5%, a non-intact form of the antibody missing a light chain) variant in CT-P13 compared to US-

Reference ID: 3775988

licensed Remicade, and this could also potentially play a role in decreasing NK-dependent ADCC activity. While this level is not more than would ordinarily be allowed with biotherapeutics, the product quality team could not rule out a role for this variant in contributing to differences in ADCC activity or immunogenicity.

- The product quality team also raised concerns that the differences observed in the immunogenicity results of the 3-way PK study (see Section 8 below) could be due to real differences (as opposed to sampling artifact or other chance findings) in the analytical characteristics of CT-P13 and US-licensed Remicade, such as:
    - Differences in the H2L1 variant, described above, and
    - Differences in subvisible (1 to 5 microns) particles
        - Data from a limited number of lots showed higher levels of subvisible particulates in the 1 to 5 micron range with CT-P13 and EU-approved Remicade compared to US-licensed Remicade. While this might not be a concern if observed in isolation, the pattern of subvisible particles was consistent with the immunogenicity results in the 3-way PK study, which also suggested less immunogenicity with US-licensed Remicade. If analytical differences exist between US-licensed Remicade and EU-approved Remicade, this raises questions regarding the relevance of data generated using EU-approved Remicade as a comparator in the development program.

Therefore, based on the data provided to date, the product quality review team was unable to conclude that CT-P13 is highly similar to US-licensed Remicade.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology team that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

Study CT-P13 1.4 is the pivotal clinical pharmacokinetic (PK) study that allows for an evaluation of the comparative PK of CT-P13 and US-licensed Remicade and also serves as part of the scientific justification (along with 3-way analytical data) for the relevance of comparative clinical data acquired with EU-approved Remicade to a demonstration of biosimilarity to US-licensed Remicade. Study 1.4 is a randomized, double-blind, single-dose study of 5 mg/kg of CT-P13, US-licensed Remicade, or EU-approved Remicade in healthy volunteers (n=71/arm). In this study, the pairwise comparisons of CT-P13, US-licensed Remicade and EU-approved Remicade met the pre-specified acceptance criteria for PK similarity (90% Confidence Intervals [CI] for the ratios of geometric mean of AUCinf, AUClast, and Cmax, within the interval of 80% to 125%). Therefore this study met the intended objectives of demonstrating PK similarity of CT-P13 and US-licensed Remicade and

Reference ID: 3775988

supporting a scientific bridge to justify the relevance of the comparative clinical data acquired with EU-approved Remicade.

Additional PK data were acquired in two different patient populations representing two usage scenarios. Study 1.1 is a 54-week randomized, double-blind study of CT-P13 vs. EU-approved Remicade in 250 patients with ankylosing spondylitis (AS). Patients received the dosing regimen described in the Remicade label, which is 5 mg/kg at 0, 2, and 6 weeks, then every 6 weeks. These patients were not on concomitant immunosuppressive therapy. The 90% CI for the geometric mean ratios (GMR) of Cmax and AUC at steady state (AUCss) were within the range of 80% to 125%, which is supportive of PK similarity.

PK data were also obtained in Study 3.1, which is the 54-week comparative clinical study of CT-P13 vs. EU-approved Remicade in approximately 600 patients with rheumatoid arthritis (RA) who were on background methotrexate (MTX). Consistent with the Remicade label, patients in Study 3.1 received 3 mg/kg at 0, 2, and 6 weeks, then every 8 weeks. PK results were comparable in both groups and were therefore consistent with the results of Study 1.4 and Study 1.1.

Immunogenicity

See Section 8 below.

6. Clinical Microbiology

I concur with the conclusions reached by the microbiology review team that there are no outstanding clinical microbiology or sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

The primary comparative clinical study in the development program was Study 3.1, a 54-week, randomized, double-blind, parallel group study conducted outside the US in approximately 600 patients with moderate to severely active rheumatoid arthritis (RA) on background methotrexate (MTX), who were randomized 1:1 to CT-P13 or EU-approved Remicade at a dose of 3 mg/kg. Study 3.1 met its pre-specified primary endpoint, which was a similarity margin of ±15% in the proportion of patients achieving an ACR20 response.[5] The study was completed prior to interactions with FDA, and the FDA did not agree with the chosen margin beforehand. However, based on FDA's analysis of the data provided, the smaller margin considered optimal by the review team (±12%) would also have been met by the results of Study 3.1. Approximately 60.9% of patients randomized to CT-P13 and 58.9%

[5]An ACR20 Response is defined as a ≥20% improvement in tender joint count, swollen joint count and at least 3 of the 5 remaining core set variables of patient global assessment (on visual analog scale [VAS]), physician global assessment on a VAS, patient assessment of pain on a VAS, Health Assessment Questionnaire-Disability Index score, and acute phase reactant (erythrocyte sedimentation rate or c-reactive protein).

Reference ID: 3775988

of patients randomized to EU-approved Remicade remained in the study and achieved an ACR20 response at Week 30, for an estimated absolute difference between treatments of 2.0% (90% CI: -4.6%, +8.7%; 95% CI: -5.8%, +9.9%).

Study 1.1 in ankylosing spondylitis (AS) patients was designed primarily as a PK study, but also assessed efficacy. This study represented a different usage scenario, not only due to the indication of AS, but due to the different dose (5 mg/kg) and lack of concomitant immunosuppressives in this study. The primary efficacy endpoint was the proportion of patients achieving an ASAS20 response.[6] In the pre-specified efficacy analysis of patients remaining in the study at Week 30, 70.5% of patients randomized to CT-P13 and 72.4% of patients randomized to EU-Remicade achieved an ASAS20 response, for an estimated odds ratio of 0.91 (95% CI: 0.51, 1.62). In an FDA analysis of all randomized patients, 63.2% of patients on CT-P13 and 67.2% on EU-Remicade remained in the study and achieved an ASAS20 response at Week 30, for an estimated difference of -4.0% (95% CI: -15.9%, 8.0%), which supports similar efficacy of CT-P13 and EU-approved Remicade in this usage scenario.

Therefore, Study 3.1 and supportive Study 1.1 are consistent in supporting a conclusion of no clinically meaningful differences between CT-P13 and EU-approved Remicade in patients with RA and AS. For a discussion of extrapolation of data to support biosimilarity in other conditions of use that have not been studied, see Section 13 below.

8. Safety

Safety Overview

The safety of CT-P13, along with a descriptive comparative assessment of safety compared to EU-approved Remicade, was provided primarily by Study 3.1 (in 602 RA patients), and Study 1.1 (in 250 AS patients), which were both 54-week studies. The one-year extension studies Study 3.2 (in 302 RA patients rolling over from Study 3.1) and Study 1.3 (in 174 AS patients rolling over from Study 1.1) provided controlled data on patients who transitioned from EU-approved Remicade to CT-P13, compared to patients who remained on CT-P13 throughout. The only data that allowed for a descriptive comparative assessment of the safety of CT-P13 and US-licensed Remicade was the single-dose PK study in healthy volunteers, Study 1.4.

There were 4 deaths in the clinical development program; 2 in patients receiving CT-P13 and 2 in patients receiving EU-approved Remicade. There was a roughly similar incidence of treatment-emergent adverse events (approximately 70%), infections (close to 40%), serious infections (2 to 4%), infusion reactions (approximately 3%), and anaphylaxis (1 to 2%) in the CT-P13 and EU-approved Remicade groups. Thus the overall safety of CT-P13 and EU-approved Remicade appeared descriptively similar in the longer term, repeat-dose studies.

[6] ASAS20 response is defined as an improvement of at least 20% and an absolute improvement from baseline of at least 1 unit on a 0 to 10 scale in at least 3 of 4 domains: patient global assessment of disease status, patient assessment of spinal pain, function according to the Bath Ankylosing Spondylitis Functional Index (BASFI), morning stiffness as assessed by the last 2 questions of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).

Reference ID: 3775988

In Study 1.4, after a single-dose of 5 mg/kg in healthy volunteers, the incidence of treatment emergent adverse events was 42% for CT-P13, 30% for EU-approved Remicade, and 46% for US-licensed Remicade. The incidence of infections followed a similar pattern: 25% in the CT-P13 group, 17% in the EU-approved Remicade group, and 34% in the US-licensed Remicade group. There were no deaths or serious infections. Although no concerning or unexpected safety concerns were identified in Study 1.4, and CT-P13 appeared to have similar single-dose safety compared to US-licensed Remicade, because of the limited exposure, sample size (n=71 per group), and population (healthy volunteers) in this study, limited conclusions can be drawn.

As described in the FDA guidance for industry, Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, a sponsor may need to evaluate a subset of patients to provide a substantive descriptive assessment of whether a single cross-over from the reference product to the proposed biosimilar would result in a major risk in terms of hypersensitivity, immunogenicity, or other reactions. Extension studies 3.2 and 1.3 included patients who were transitioned from EU-approved Remicade (total n=227) and patients who remained on CT-P13 throughout (total n=249). There were no cases of anaphylaxis in patients transitioning from EU-approved Remicade to CT-P13 and two cases in patients who remained on CT-P13 throughout. The incidence of infusion reactions did not increase in the group who transitioned compared to the group who remained on the same treatment. Therefore significant safety concerns with transitioning patients from the reference product to CT-P13 would not be anticipated, provided that the bridge between EU-approved Remicade and US-licensed Remicade is confirmed.

Immunogenicity

As per the US-licensed Remicade label, the development of antibodies to infliximab has been associated with increased clearance and decreased exposure, and patients with anti-drug antibodies (ADA) were more likely to have reduced efficacy. Patients who were ADA positive were 2 to 3-fold more likely to have an infusion reaction than those who were negative. Concomitant MTX use may decrease the incidence of ADA production and increase infliximab concentrations. The ADA rate for Remicade (using an Enzyme-Linked Immunosorbent Assay [ELISA]) has ranged from 15 to 51% across disease populations and studies.

The only immunogenicity data allowing for a direct comparison of CT-P13 and US-licensed Remicade were the data following single-dose administration in healthy subjects in PK study 1.4. Immunogenicity samples in the rest of the CT-P13 development program were analyzed using an electrochemiluminescent assay (ECLA), but the ECLA appeared to be more susceptible to interference by circulating drug, so the sponsor developed an ELISA assay with better tolerance to circulating drug and both ECLA and ELISA assays were used for Study 1.4. Using ECLA, at Day 57 following a single dose of 5 mg/kg in healthy volunteers, the ADA rate in Study 1.4 was approximately 14%, 7%, and 3% for CT-P13, EU-approved Remicade, and US-licensed Remicade, respectively. Using ELISA, the incidence of ADA for CT-P13, EU-approved Remicade, and US-licensed Remicade was approximately 27%, 25%, and 11%

Reference ID: 3775988

respectively. All subjects testing positive in the ELISA screening assay in Study 1.4 also tested positive in the neutralizing antibody (NAb) assay and neutralizing antibody titers trended higher in CT-P13 patients compared to patients treated with US-licensed Remicade or EU-approved Remicade. While there are limited publically available data on the comparative immunogenicity of EU-approved Remicade and US-licensed Remicade, the 14% difference observed Study 1.4 appeared to be larger than observed with other publically available data; i.e., in a single-dose 3-way PK study of another product described as a "potential biosimilar to infliximab," the ADA rates for EU-approved Remicade and US-licensed Remicade were 32.6% and 28.2%, respectively, at Day 85.[7]

With chronic dosing in Study 1.1 (in AS patients, 5 mg/kg dose) and Study 3.1 (in RA patients on MTX, 3 mg/kg dose), ADA rates identified by ECLA (at Week 54) were approximately 20% in Study 1.1 and approximately 40%, in Study 3.1, but occurred at similar rates in the CT-P13 and EU-approved Remicade arms in each study. Systemic exposures of CT-P13 or EU-approved Remicade were lower in ADA positive patients compared to those who were ADA negative, but the magnitude of the impact of ADAs on PK parameters was similar between the treatments. This was corroborated by analyses of the impact of ADA on efficacy parameters in Study 3.1, which suggested lower response rates in ADA positive patients, but a similar pattern between treatments. On a related note, the incidence of infusion-related reactions and anaphylaxis trended higher among ADA positive patients compared to ADA negative patients, but the incidence of these events was similar or lower with CT-P13 compared to EU-approved Remicade.

Notably, in Study 1.4, despite lower apparent immunogenicity with US-licensed Remicade, and a trend toward higher neutralizing antibody titers with CT-P13, the magnitude of the differences observed did not translate into significant differences in PK, as PK similarity criteria were met in Study 1.4 for all 3 pairwise comparisons (CT-P13 vs. US-licensed Remicade, CT-P13 vs. EU-approved Remicade, and US-licensed Remicade vs. EU-approved Remicade).

In summary, the clinical and clinical pharmacology review teams concluded that the data in the clinical development program for CT-P13 suggest there were no clinically meaningful differences as a result of immunogenicity to CT-P13, EU-approved Remicade or US-licensed Remicade and that the differences in immunogenicity rates do not rise to the level of a deficiency that would preclude approval. After further internal discussion, the CMC/CMC immunogenicity review teams were aligned with the clinical and clinical pharmacology teams' position, and agreed to relay the comment on immunogenicity rates and titers as an additional comment (additional comment #1 below). However, there remains a concern that the differences in subvisible particles, which were identified as a potential cause of differences in immunogenicity, could be due to analytical differences between the products, and therefore a deficiency comment remains regarding this concern (deficiency comment #1 below).

[7] ACR Abstract 1501, 2014. Udata C et al., "Immunogenicity Assessment of PF-06438179, a Potential Biosimilar to Infliximab, in Healthy Volunteers."

Reference ID: 3775988

9. Advisory Committee Meeting

Due to questions regarding the adequacy of the analytical characterization data to determine whether CT-P13 is highly similar to US-licensed Remicade, an advisory committee meeting was not held during this review cycle.

10. Pediatrics

As a proposed biosimilar, this application for CT-P13 triggers the requirements of the Pediatric Research Equity Act (PREA) for every indication for which licensure is sought. The CT-P13 pediatric plan was discussed at the Pediatric Review Committee (PeRC) meeting of April 29, 2015. PeRC agreed with the applicant's current request for waivers and deferrals.

11. Other Relevant Regulatory Issues

- **Inspections:** No issues precluding approval were found on inspection of the manufacturing facilities or of selected clinical sites.
- **Financial Disclosure:** No issues.
- **Exclusivity or Patent Issues:** Celltrion requested licensure for pediatric ulcerative colitis. However, this indication is protected by orphan drug exclusivity expiring on September 23, 2018 (see the Orphan Drug Designations and Approvals database at http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm).

12. Labeling

Labeling negotiations were not initiated during this review cycle due to the CMC-related concerns that were determined to preclude approval.

13. Decision/Action/Risk Benefit Assessment

- **Regulatory Action**

The action on this application will be Complete Response.

- **Assessment of Biosimilarity**

Section 351(i) of the PHS Act defines the terms "biosimilar" or "biosimilarity" to mean that "the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety,

Reference ID: 3775988

purity, and potency of the product" (see section 351(i)(2) of the PHS Act). Because of the issues surrounding the FcγRIII binding/ADCC activity and differences in subvisible particulates, the product quality review team was unable to conclude that CT-P13 is highly similar to US-licensed Remicade. Differences in subvisible particulates raised additional concerns regarding the analytical bridge between EU-approved Remicade and US-licensed Remicade that would (along with the 3-way PK data) provide a scientific justification for the relevance of comparative data with EU-approved Remicade to a demonstration of biosimilarity to US-licensed Remicade. Without an adequate bridge, it would be difficult to conclude there are no clinically meaningful differences between CT-P13 and the reference product, which is US-licensed Remicade. Therefore, based on the data available in this application, it cannot be determined whether the statutory standards for biosimilarity have been met, and the application cannot be approved at this time.

The applicant sought licensure for all the indications for which US-licensed Remicade is licensed. To support extrapolation of data acquired in RA and AS to support biosimilarity in the other conditions of use, the applicant provided a scientific justification. Infliximab binds to both soluble and transmembrane TNF, and its primary mechanism of action (MOA) is direct binding of TNF and blocking of TNF receptor-mediated biological activities. The scientific literature indicates that this MOA is the primary MOA in RA, AS, psoriatic arthritis, and psoriasis. The data on MOA are not as straightforward in inflammatory bowel disease (IBD), which appears to involve a more complicated, multifactorial process. At this time, final determination regarding the adequacy of the scientific justification for extrapolation will not be made, pending resolution of the uncertainties that have precluded the determination of biosimilarity.

- **Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies**
  Not applicable.

- **Recommendation for other Postmarketing Requirements and Commitments**
  Not applicable.

- **Comments for Action Letter**

<u>Deficiency Comments:</u>

1) You provided data from a limited number of lots showing lower levels of subvisible particulates in the range of 1 to 5 microns in US-licensed Remicade compared to both CT-P13 and EU-approved Remicade. The observed differences may be due to the limited number of lots of CT-P13, US-licensed Remicade and EU-approved Remicade used to perform the analysis. However, these results suggest that analytical differences may exist between US-licensed Remicade and EU-approved Remicade, which, if confirmed, could impact the assessment of the adequacy of the analytical bridge between the three products. To address this concern, provide results of subvisible particulate analysis from an adequate number of additional CT-P13, US-licensed Remicade and EU-approved Remicade lots.

Reference ID: 3775988

2) You evaluated the analytical similarity of CT-P13 and US-licensed Remicade using a variety of functional assays. Your data generated using a standard NK-cell based killing ADCC assay suggest that CT-P13 has ~20% lower ADCC activity compared to the reference product US-licensed Remicade, which correlates with differences in FcγRIIIa binding. The difference in ADCC leads to residual uncertainty about whether CT-P13 is highly similar to US-licensed Remicade, as the role of ADCC remains uncertain in the clinical activity of the reference product (e.g., in the setting of inflammatory bowel disease). Furthermore, you did not adequately justify the impact of the difference in ADCC on the analytical similarity assessment and did not identify the structural basis underlying this difference. For example, you should determine whether the H2L1 variant that is present at relatively high levels in CT-P13 compared to US-licensed Remicade plays a role in decreasing NK-dependent ADCC activity. On the other hand, the Agency has not excluded the possibility that analysis of additional lots of CT-P13, US-licensed Remicade and EU-approved Remicade lots could overcome a statistical anomaly due to the analysis of a limited number of lots. To this point, we note that prior differences in glycan patterns were reduced when additional lots of CT-P13, US-licensed Remicade and EU-approved Remicade were analyzed. To address the current deficiency with respect to differences in ADCC activity, we recommend that you repeat the evaluation of ADCC using additional lots to determine whether the ADCC difference you have reported was due to small sample size and decreases when additional lots are evaluated. If the difference in ADCC persists following analysis of additional lots, you should identify and demonstrate control of the product quality attributes that underlie ADCC activity in CT-P13 (e.g., glycan pattern, contribution of H2L1 variant, etc.) and provide an adequate justification, including an evaluation of the role of ADCC particularly in the setting of inflammatory bowel disease, that the observed difference in ADCC is not relevant to clinical activity.

Additional Comments:

1) You conducted comparative clinical study CT-P13 1.4 to assess the immunogenicity of CT-P13 and US-licensed Remicade, and differences were observed in immunogenicity incidence rates between these products. This single dose, healthy volunteer study suggests a potential trend towards increased neutralizing immunogenic responses in CT-P13-treated subjects compared to the pooled group of subjects receiving either U.S.-licensed Remicade or EU-approved Remicade [27% vs. 19%, respectively (90% confidence Interval: -2.5%, +20%)]. Differences are also observed in binding antibody titers (mean transformed titers 4.74 vs 3.63 in CT-P13 and US-Remicade samples, respectively) and neutralizing antibody titers (mean transformed titers 3.42 vs 2.63, respectively). To address these observations, provide a rationale for why the results from study CT-P13 1.4 are in alignment with the conclusion that the immunogenicity profiles of CT-P13 and US-licensed Remicade are similar.

2) The current drug product stability data using Process B batches of CT-P13 support an expiry date of 42, not (b) (4) months. To address this concern, adjust your proposed expiry dating to reflect existing data and provide a stability protocol to support post-approval expiry extension.

Reference ID: 3775988

3) We acknowledge the plan outlined in your 10 Apr 2015 letter to develop and validate a revised version of the visible particle test for reconstituted drug product. The revised test will use (b) (4) and visual inspection of 20 reconstituted vials. Data supporting the assay revision have not been provided to the BLA. To address this concern, submit the assay SOP, validation report and revised specification to the Agency for review.

Reference ID: 3775988

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/s/

SARAH K YIM
06/08/2015

BADRUL A CHOWDHURY
06/08/2015

Cross-Discipline Team Leader Review

Date	June 08, 2015
From	Nikolay P. Nikolov, M.D.
Subject	Cross-Discipline Team Leader Review
BLA #	351(k) BLA 125,544
Applicant	Celltrion
Date of Submission	August 08, 2014
PDUFA Goal Date	June 08, 2015
Proprietary Name (Proposed) / Nonproprietary names	Inflectra/ CT-P13[1]
Dosage Forms / Strength	Sterile lyophilized powder in a 20 mL capacity vial/ 100 mg per vial
Route of Administration	Intravenous
Proposed Indication(s)	• Crohn's Disease (Adult and Pediatric) • Ulcerative colitis (Adult and Pediatric[2]) • Rheumatoid arthritis • Ankylosing spondylitis • Psoriatic arthritis • Plaque psoriasis
Recommended:	*Complete Response Action*

1. Introduction

Celltrion has submitted a biologics license application (BLA) under section 351(k) of the Public Health Service Act (PHS Act) for CT-P13, a proposed biosimilar to Remicade (infliximab). BLA # 103772 for Remicade was initially licensed by FDA on August 24, 1998, and the BLA is currently held by Janssen Biotech, Inc. US-licensed Remicade is the reference product for Celltrion's 351(k) BLA. Celltrion is seeking licensure of CT-P13 for the same indications as US-licensed Remicade:[3]

1) Crohn's Disease:
    - reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.

[1] In this document, I generally refer to Celltrion's proposed product by the Celltrion descriptor "CT-P13" because the Agency is continuing to consider its approach to nonproprietary naming of biosimilar products.
[2] This reflects information for Inflectra that Celltrion submitted on August 8, 2014. We note that the indication for pediatric ulcerative colitis is protected by orphan drug exclusivity expiring on September 23, 2018. See the Orphan Drug Designations and Approvals database at http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm
[3] Remicade USPI

Reference ID: 3775998

- reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing Crohn's disease.

2) Pediatric Crohn's Disease:
   - reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy.
3) Ulcerative Colitis:
   - reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.
4) Pediatric Ulcerative Colitis:
   - reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.[4]
5) Rheumatoid Arthritis (RA) in combination with methotrexate:
   - reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis.
6) Ankylosing Spondylitis:
   - reducing signs and symptoms in patients with active ankylosing spondylitis.
7) Psoriatic Arthritis:
   - reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in patients with psoriatic arthritis.
8) Plaque Psoriasis:
   - treatment of adult patients with chronic severe (i.e., extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate.

Although the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) is the lead division for this application and provided the written clinical review, clinical input pertaining to their respective indications was obtained from the Division of Gastroenterology and Inborn Errors Products (DGIEP), and the Division of Dermatology and Dental Products (DDDP) during the course of the review.

[4] This indication is protected by orphan drug exclusivity expiring on September 23, 2018. See the Orphan Drug Designations and Approvals database at http://www.accessdata fda.gov/scripts/opdlisting/oopd/index.cfm.

Reference ID: 3775998

2. Background

The BPCI Act

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) was passed as part of health reform (Affordable Care Act) that President Obama signed into law on March 23, 2010. The BPCI Act created an abbreviated licensure pathway for biological products shown to be "biosimilar" to or "interchangeable" with an FDA-licensed biological product (the "reference product"). This abbreviated licensure pathway under section 351(k) of the PHS Act permits reliance on certain existing scientific knowledge about the safety and effectiveness of the reference product, and enables a biosimilar biological product to be licensed based on less than a full complement of product-specific preclinical and clinical data.

Section 351(i) of the PHS Act defines the terms "biosimilar" or "biosimilarity" to mean that "the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product" (see section 351(i)(2) of the PHS Act). A 351(k) application must contain, among other things, information demonstrating that the proposed product is biosimilar to a reference product based upon data derived from analytical studies, animal studies, and a clinical study or studies, unless FDA determines, in its discretion, that certain studies are unnecessary in a 351(k) application (see section 351(k)(2) of the PHS Act).

Development of a biosimilar product differs from development of a biological product intended for submission under section 351(a) of the PHS Act (i.e., a "stand-alone" marketing application). The goal of a "stand-alone" development program is to demonstrate the safety, purity and potency of the proposed product based on data derived from a full complement of clinical and nonclinical studies. The goal of a biosimilar development program is to demonstrate that the proposed product is biosimilar to the reference product. While both stand-alone and biosimilar product development programs generate analytical, nonclinical, and clinical data, the number and types of studies conducted will differ based on differing goals and the different statutory standards for licensure.

To support a demonstration of biosimilarity, FDA recommends that applicants use a stepwise approach to developing the data and information needed. At each step, the applicant should evaluate the extent to which there is residual uncertainty about the biosimilarity of the proposed product to the reference product and identify next steps to try to address that uncertainty. The underlying presumption of an abbreviated development program is that a molecule that is shown to be analytically and functionally highly similar to a reference product is anticipated to behave like the reference product in the relevant clinical setting(s). The stepwise approach should start with extensive structural and functional characterization of both the proposed biosimilar product and the reference product, as this analytical characterization serves as the foundation of a biosimilar development program. Based on these results, an

Reference ID: 3775998

assessment can be made regarding the analytical similarity of the proposed biosimilar product to the reference product and the amount of residual uncertainty remaining with respect to both the structural/functional evaluation and the potential for clinically meaningful differences.

The level of residual uncertainty after the comparative analytical characterization drives the type and amount of data needed to resolve remaining questions about whether the proposed product is biosimilar to the reference product. The results of nonclinical and/or clinical studies to resolve remaining questions should further reduce residual uncertainty and support a demonstration of biosimilarity. Additional data may resolve certain questions or may identify other differences (e.g., pharmacokinetic (PK) differences) that would raise concerns as well as residual uncertainty such that additional studies/data would be necessary. While the differences may raise questions about whether the proposed biosimilar product is biosimilar to the reference product, identified differences should not be considered in isolation and do not necessarily preclude continued development to support a demonstration of biosimilarity. However, the applicant would need to evaluate the observed differences and explain why the differences between the proposed biosimilar product and the reference product should not preclude FDA from finding the proposed product meets the standard for biosimilarity.

The 'totality of the evidence' submitted by the applicant should be considered when evaluating whether an applicant has adequately demonstrated that a proposed product meets the statutory standard for biosimilarity to the reference product. Such evidence generally includes structural and functional characterization, animal study data, human PK and pharmacodynamics (PD) data, if applicable, clinical immunogenicity data, and other clinical safety and effectiveness data.

Reference Product

In general, an applicant needs to provide information to demonstrate biosimilarity based on data directly comparing the proposed product with the US-licensed reference product. When an applicant's proposed biosimilar development program includes data generated using a non-US-licensed comparator to support a demonstration of biosimilarity to the US-licensed reference product, the applicant must provide adequate data or information to scientifically justify the relevance of these comparative data to an assessment of biosimilarity and establish an acceptable bridge to the US-licensed reference product. As a scientific matter, the type of bridging data needed will always include data from analytical studies (e.g., structural and functional data) that directly compares all three products [i.e., the proposed biosimilar product (CT-P13), the US-licensed reference product (US-licensed Remicade), and the non-US-licensed comparator product (EU-approved Remicade)] and is likely to also include bridging clinical PK and/or PD study data for all three products.

Relevant Regulatory History

The development of CT-P13 was conducted exclusively outside of the US and was geared towards meeting the biosimilar product approval requirements of non-US regulatory agencies. During the development of CT-P13, the applicant initially sought scientific and procedural advice from European National Competent Authorities and from the European Medicines

Reference ID: 3775998

Agency's Committee for Medicinal Products for Human Use (CHMP) covering the quality, nonclinical and clinical programs. The advice received was implemented and the clinical development program was refined and amended accordingly.

The first interaction with the FDA occurred at a Biosimilar Biological Product Development (BPD) Type 3 meeting held on 10 July 2013 and further discussed at a BPD Type 4 meeting held on 28 April 2014. Additional interactions occurred to discuss the initial Pediatric Study Plan (iPSP).

At the BPD Type 3 meeting, in addition to product quality and non-clinical comments, FDA recommendations to the applicant regarding clinical development included:

- Establish PK similarity between CT-P13, US-licensed Remicade and EU-approved Remicade using all three PK variables (AUCinf, Cmax and AUClast).
- Provide a detailed description of the methodology and plans for qualification of the assays that will be used for the detection of anti-drug antibodies.
- Assess safety and immunogenicity in the setting of patients who undergo a single transition from EU-approved Remicade to CT-P13 to provide a descriptive comparison with patients who continue on EU-approved Remicade.

At the BPD Type 4 meeting, general agreement was reached on the proposed format and content of the BLA, including the Agency's expectation of the information needed to support a demonstration of biosimilarity and extrapolation of clinical data to support the demonstration of biosimilarity for each indication for which licensure is sought.

Of note, CT-P13 is approved in several regions outside the U.S. and is marketed under the trade names Inflectra® and Remsima®. CT-P13 has been approved outside the U.S. for the same indications previously approved for US-licensed Remicade in several regions including the EU, The Republic of Korea, Japan, and India. In 2014, Health Canada approved CT-P13 for all indications except ulcerative colitis and Crohn's disease, with the conclusion that extrapolation of data from the settings of rheumatoid arthritis and ankylosing spondylitis to IBD indications was not justified due to questions regarding the possible difference in antibody-dependent cellular cytotoxicity (ADCC) that might have relevance in IBD.

3. CMC

CMC Reviewer: Peter Adams, Ph.D.; CMC Team Leader: Kurt Brorson, Ph.D.; CMC Supervisory: David Frucht, M.D., Ph.D.
CMC Statistical Reviewer: Meiyu Shen, Ph.D.; CMC Statistical Supervisor: Yi Tsong, Ph.D.
OBP Director: Steven Kozlowski, M.D., Ph.D.

- **General product quality considerations**

CT-P13 drug substance (DS) is a chimeric human-murine IgG1κ monoclonal antibody that binds with high affinity to human TNFα. It is a glycoprotein with 1 N-linked glycosylation site

Reference ID: 3775998

in the CH2 domain of each heavy chain. Each heavy chain consists of 450 amino acids with 11 cysteine residues, and each light chain consists of 214 amino acids with 5 cysteine residues. All cysteines in the heavy and light chains are involved in either intra- or inter- disulfide bonding. CT-P13 drug substance is a colorless to light yellow and slightly opalescent to opalescent solution and free of foreign particles, with a pH of approximately 7.2. The DS is largely manufactured at the Celltrion Incheon site in The Republic of Korea using bioreactor mammalian Sp2/0 transfectoma cell culture and conventional purification scheme. Large scale CT-P13 DS manufacturing process evolved over two major phases, identified as Process A (used in early development) and Process B (used in clinical development). The CMC review team determined that the applicant provided sufficient evidence of comparability of CT-P13 DS materials produced with processes A and B to support extrapolation between the clinical data sets. Additional manufacturing process refinements were made after comparability studies of process A and process B, but before validation of process B. The CMC review team determined that the refinements were unlikely to affect comparability and the product remains subject to the same release criteria.

The CT-P13 drug product (DP) is formulated as a sterile, white, lyophilized powder in a 20 mL type I borosilicate glass vial with a 20 mm (b) (4) butyl rubber stopper and a 20 mm flip-off seal. Each CT-P13 drug product vial contains 100 mg CT-P13 drug substance as the active ingredient, 2.2 mg sodium dihydrogen phosphate monohydrate, 6.1 mg di-sodium hydrogen phosphate dihydrate, 500 mg sucrose and 0.5 mg polysorbate 80 as excipients which are ingredients commonly used for formulation of biopharmaceuticals. No excipients are of human or animal origin.

Long term stability studies of the drug product indicate no discernable quality changes or trends among the lots tested. Celltrion proposes a shelf-life of (b) (4) months at 2 – 8°C for CT-P13 DP. However, the current drug product stability data using Process B batches of CT-P13 support an expiry date of 42 months. The CMC team proposed a comment to that extent as detailed in Recommended Comments to Applicant section at the end of this document, and I agree.

The detailed assessment of the assay used to screen for visible particulates was deemed suboptimal in terms of number of vials tested. A revision to refine the assay was recommended by the CMC review team that will have to be addressed prior to licensing. The applicant agreed and has already implemented assay refinement and re-qualification. This was communicated to applicant at the facilities inspection close out and reiterated in an information request on April 14, 2015. Since the issue has not been addressed by the applicant at the time of this review, the CMC team proposed a deficiency comment to that extent as detailed in Recommended Comments to Applicant section at the end of this document, and I agree.

- **Analytical Similarity Assessment**

Initially, the CT-P13 development program was designed to demonstrate biosimilarity to EU-approved Remicade for non-US regulatory agencies. This program was supported by a 2-way analytical similarity assessment and a clinical program comparing CT-P13 against EU-approved Remicade. Of note, these studies were conducted prior to interactions with the US

Reference ID: 3775998

FDA. Subsequently, the CT-P13 program was repurposed to demonstrate biosimilarity to US-licensed Remicade. To support a scientific bridge to justify the relevance of the data generated using EU-approved Remicade to an assessment of biosimilarity and establish an acceptable bridge to the US-approved Remicade, a 3-way analytical similarity assessment was performed using batches of US-licensed Remicade, EU-approved Remicade and CT-P13. The biological assays cover a range of functions that reflect known and potential mechanisms of action *in vivo*.

Celltrion conducted the 3-way assessment in 3 stages. An abridged study was undertaken consisting of 3 batches of each product, followed by a detailed assessment of 6 – 7 batches of each product. Subsequently, an additional 3 batches of each product were analyzed in biological activity assays to provide sufficient power for statistical analyses using an "Equivalence Margin" based approach recommended by FDA at the BPD Type 4 meeting. A total of 13 batches of US-licensed Remicade, 11 batches of EU-approved Remicade, and 13 batches of CT-P13 drug product (DP) manufactured at the Celltrion Plant (b) (4) were employed for the 3-way quality similarity assessment submitted to the original BLA. For biological activity assays, 10 batches of each product were assessed by the equivalence approach. For other quality attributes, 6-7 batches of each product were assessed. During the review cycle, an additional 3-5 batches of each product type were analyzed for certain assays to boost statistical power of the analytical similarity exercise (e.g. TNF binding, protein content, see CMC review). Notably, the expiration dates for the lots of US-licensed Remicade, used in the analytical similarity assessment, were from February 2015 to March 2017, as compared with the range from 2014 through 2017 for EU-approved Remicade. CT-P13 lots were manufactured in 2012.

CMC Analytical Similarity Assessment

The analytical procedures used to demonstrate the analytical similarity of CT-P13, US-licensed Remicade and EU-approved infliximab include the routine lot release tests, extended characterization tests and tests that can be best described as research-grade for establishment of product mechanisms. They can be grouped into seven categories based on the product quality characteristics that they assessed as follows: primary structure, higher order structure, content, purity, charged isoforms, glycosylation and biological activity.

- Primary Structure

Using peptide mapping, intact mass, amino acid analysis/molar absorptivity, N- and C-terminal sequencing, Celltrion provided sufficient information to demonstrate that CT-P13 has the same primary amino acid structure as US-licensed Remicade.

- Higher Order Structure

A number of analytical approaches typically employed for antibodies were used to assess the secondary and tertiary structure of CT-P13, US-licensed Remicade and EU-approved Remicade. They included Fourier transform infrared spectroscopy (FTIR), circular dichroism (CD), differential scanning calorimetry (DSC), disulfide bond structure (free thiols) and an

Reference ID: 3775998

experimental approach called antibody array. No significant differences in the higher order structure were identified in the samples using these analytical approaches. Measures of CT-P13 secondary and tertiary structure provide evidence of consistent antibody manufacture and biochemical quality.

- Protein Content:

The protein content of reconstituted vials of CT-P13, US-licensed Remicade and EU-approved Remicade was determined using a spectrophotometer (i.e., A280). The batches used in the enhanced assessment (10 vials each) of EU-approved Remicade and US-licensed Remicade are the same average concentration (9.2 ± 0.3mg/mL). The concentrations of ten reconstituted vials of CT-P13 were found to be slightly higher on average (9.5 ± 0.14 mg/mL). This was confirmed during an analysis of additional product batches during the review cycle. In order to minimize the potential that CT-P13 could have a different strength than the US-licensed reference product, Celltrion has adjusted (b) (4) to more closely match the actual protein content of US-licensed Remicade and performed three successful process validation runs using the (b) (4).

- Purity

The biochemical/biophysical purity (i.e. absence of aggregates) of CT-P13, EU-approved Remicade and US-licensed Remicade were assessed using SEC-HPLC, SEC-MALS and AUC. Consistent inter-lot levels of intact monomer ~99.4% were measured using SEC-HPLC assay. The CT-P13 DP lots, and EU-approved Remicade and US-licensed Remicade lots, form only minor levels of high molecular weight (HMW) aggregates and low molecular weight (LMW) fragments even under stressed conditions, indicating that all three DPs do not aggregate significantly when held at labeled conditions. Overall, the data from the analysis show there are at most minor differences between the three products, and aggregate levels are routinely <1%. The CMC review team identified antibody fragments as product-related antibody H2L1 (two heavy chains, one light chain) forms which may impact NK cell-dependent ADCC and thus may be relevant to the observed differences in the ADCC assay between CT-P13 and US-licensed Remicade. The applicant did not provide information to determine whether the H2L1 variant that is present at relatively high levels in CT-P13 compared to US-licensed Remicade plays a role in decreasing NK-dependent ADCC activity. In addition, it is not known whether an H2L1 variant would be more immunogenic than the intact monoclonal antibody. Since this issue has not been addressed by the applicant at the time of this review, CMC team proposed a deficiency comment as detailed in Recommended Comments to Applicant section at the end of this document, and I agree.

- Charged Isoforms

Variability in the charge variants was observed, largely from C-terminal Lysine heterogeneity. This variability would not preclude a finding that CT-P13 is highly similar to U.S. licensed Remicade. The CMC review team also notes that this variability is not considered likely to

Reference ID: 3775998

have a significant clinical impact given the fact that the C-terminal Lys is clipped in the serum.[5]

- Glycosylation

Glycosylation was assessed using three assays: an LC-MS peptide mapping technique for site specific glycan analysis and an oligosaccharide analysis using HPAE-PAD. Monosaccharide analysis of neutral and amino sugars and sialic acid analysis were also undertaken. The pattern of the glycan data from the 3-way analysis differed from that in the two-way analysis in that a clearer trend in the 2-way analysis towards higher afucosylation (defined by G0 +Man5) in CT-P13 was not as obvious as shown in Table 1. Fucosylation is an important attribute of CT-P13, because the degree of fucosylation affects binding of CT-P13 to FcγRIIIa and its Fc-mediated effector function, including antibody-dependent cellular cytotoxicity (ADCC) which may have a role in the clinical activity of the product in inflammatory bowel disease. However, the pattern of different afucosylated glycoform profiles for CT-P13 and US-licensed Remicade (as measured by Man5+ G0 levels) observed in the 2-way data but not the 3-way analysis was not satisfactorily addressed by the applicant at the time of this review. The CMC team proposed a deficiency comment to that extent as detailed in Recommended Comments to Applicant section at the end of this document, and I agree.

Table 1. Differences in Glycan Analysis, FcγRIII Binding Affinity, and ADCC Assay, Between 2-Way and 3-Way Analytical Similarity Data

	3-Way Analysis			2-Way Analysis	
	CT-P13	US-Remicade	EU-Remicade	CT-P13	EU-Remicade
Afucosylated glycoforms (%)	5.2	5.8	6	5.9	9.7
FcγRIII binding affinity by SPR (%)	101	127	126	101	124
ADCC activity* (relative %)	101	120	122	99	122
ADCC assay using NK cells expressing the high affinity V allele of FcγRIIIa cells; SPR: surface plasmon resonance					

- Biological Activity

CMC Statistical Analytical Similarity Assessment

Given the importance of TNF binding and TNF neutralization potency measure, as the key biological activity attributes, data from these two assays were defined as Tier 1 attributes and evaluated with a more rigorous statistical testing approach. Based on the statistical analyses of the *in vitro* TNFα neutralization activity and the TNFα binding affinity by ELISA, the results support the demonstration that CT-P13 is highly similar to the US-licensed Remicade as shown in Table 2.

[5] Brorson K and Jia AY. 2014. Therapeutic monoclonal antibodies and consistent ends: terminal heterogeneity, detection, and impact on quality. Curr Opin Biotechnol 30:140-6

Reference ID: 3775998

Table 2. Analytical Similarity Equivalence Testing Results

Comparison	Mean difference	-1.5 σ_c	90% CI		+1.5σ_c	Equivalent
			Lower limit	Upper limit		
in vitro TNFα Neutralization Activity						
CT-P13 vs. US	-0.71	-8.18	-3.79	2.36	8.18	Yes
CT-P13 vs. EU	-0.84	-7.42	-3.83	2.15	7.42	Yes
EU vs. US	0.12	-8.18	-3.20	3.45	8.18	Yes
TNFα Binding Affinity (ELISA)						
CT-P13 vs. US	-2.50	-7.04	-5.09	0.09	7.04	Yes
CT-P13 vs. EU	-0.05	-6.34	-2.60	2.50	6.34	Yes
EU vs. US	-2.45	-7.04	-4.58	-0.31	7.04	Yes

Source: Adapted from Dr. Shen's CMC Statistical Review, Tables 4 and 6
Equivalence margins: ±1.5σc where "c" represents reference product variability as determined from Celltrion's analysis of the data

Mechanisms of Action (MOA)

The known and potential (likely or plausible), mechanisms of action of US-licensed Remicade are listed in Table 3.

Table 3. Known and Potential (Likely or Plausible) Mechanisms of Action of US-licensed Remicade in the Licensed Conditions of Use

MOA of Remicade[6],[7]	**RA**	**AS**	**PsA**	**PsO**	**CD, Pediatric CD**	**UC, Pediatric UC**
Mechanisms involving the Fab (antigen binding) region:						
Blocking TNFR1 and TNFR2 activity via binding and neutralization of s/tmTNF	Known	Known	Known	Known	Likely	Likely
Reverse (outside-to-inside) signaling via binding to tmTNF:	-	-	-	-	Likely	Likely
Apoptosis of lamina propria activated T cells	-	-	-	-	Likely	Likely
Suppression of cytokine secretion	-	-	-	-	Likely	Likely
Mechanisms involving the Fc (constant) region:						
Induction of CDC on tmTNF-expressing target cells (via C1q binding)	-	-	-	-	Plausible	Plausible
Induction of ADCC on tmTNF-expressing target cells (via FcγRIIIa binding expressed on effector cells)	-	-	-	-	Plausible	Plausible
Induction of regulatory macrophages in mucosal healing	-	-	-	-	Plausible	Plausible

ADCC: antibody-dependent cellular cytotoxicity; AS: ankylosing spondylitis; CD: Crohn's disease; CDC: complement-dependent cytotoxicity; MOA: mechanism of action; PsA: psoriatic arthritis; PsO: plaque psoriasis; RA: rheumatoid arthritis; UC: ulcerative colitis; sTNF: soluble TNF; tmTNF: transmembrane TNF

[6] Oikonomopoulos A et. al, Anti-TNF Antibodies in Inflammatory Bowel Disease: Do We Finally Know How it Works?, Current Drug Targets, 2013, 14, 1421-1432
[7] Tracey D et al, Tumor necrosis factor antagonist mechanisms of action: A comprehensive review, Pharmacology & Therapeutics 117 (2008) 244–279

Reference ID: 3775998

Celltrion provided experimental biological activity data to address each presumed mechanisms of action of US-licensed Remicade listed in Table 3, including:

- Fab (antigen binding) region of the antibody:
  - Binding to and neutralization of soluble (s)TNF:
    - Suppression of cytokine secretion
    - Suppression of apoptosis in Caco-2 cells, an *in vitro* IBD model
  - Binding to transmembrane (tm)TNF
  - Induction of reverse signaling in tmTNF-expressing target cells
    - Induction of apoptosis in tmTNF Jurkat cells
    - Suppression of cytokine secretion
- Fc (constant) region of the antibody:
  - Fc receptor binding:
    - FcRn
    - FcγRI, FcγRII, FcγRIIIa/b (V, high affinity and F, low affinity type)
  - Induction of CDC on tmTNF-expressing target cells (via C1q binding)
  - Induction of ADCC on tmTNF-expressing target cells (via FcγR binding expressed on effector cells)
  - Induction of regulatory macrophages and mucosal healing

The results from most of these *in vitro* experimental systems indicate that CT-P13 has a biological activity similar to that of EU-approved Remicade and US-licensed Remicade with the notable exception of FcγRIIIa/b binding affinity and in select ADCC assays which are discussed next.

FcγRIII Binding:

- Approximately 25% lower FcγRIIIb binding avidity for CT-P13 was observed only by high affinity V/V and V/F genotype NK cells. This was seen both by a highly sensitive and precise instrument called surface plasmon resonance (SPR) and in an *in vitro* system using enriched NK cells in the presence of 1% bovine serum albumin (BSA) as a conditioning medium. The difference in NK-cell binding was completely abolished when instead of BSA, a 50% serum was used, probably because the serum contains competing antibodies.
- No differences were seen in FcγRIII binding to neutrophils, which also express predominantly FcγRIII.

ADCC Activity:
ADCC is a cell killing activity mediated through FcγR receptors. ADCC can be mediated by many types of effector cells, including NK cells, monocytes and other white blood cells. Different effector types may be more reliant on one receptor type or the other; NK cells mostly use FcγRIII to bridge to the target cells. These different cell types may be more predominant in one tissue (e.g., the gut) vs. others (e.g., joint synovia). ADCC assays utilize two cell types: (1) "effector cells" which possess FcRs on their surface that are activated to kill other cells and (2) "target cells", which possess cell surface molecules (in the case tmTNFα) which are bound by antibody that recruit the "effector" cells through their cell surface FcRs.

Reference ID: 3775998

- 20% lower ADCC activity with CT-P13, as compared with US-licensed and EU-approved Remicade were seen in some but not all ADCC assays. The experimental system in which differences in ADCC were observed, while sensitive, may not be fully representative of *in vivo* conditions as it uses transfected Jurkat cells as targets, which overexpress tmTNFα, and purified NK cells as effector cells. Furthermore, the ADCC differences were abolished when:
  - Peripheral blood mononuclear cells (PBMC) or whole blood, instead of the purified NK cells, were used as effector cells
  - LPS-stimulated monocytes were used, instead of the TNF overexpressing Jurkat cells, as target cells (with either PBMC or NK cells as effector cells).

Importantly, while the differences in FcγRIIIa/b binding affinity and ADCC activity between CT-P13 as compared with US-licensed Remicade and EU-licensed Remicade appear consistent between the 2-way and 3-way similarity assessment based on the limited number of batches tested. In contrast, this observation is inconsistent with the 3-way analysis of afucosylation in that no consistent pattern of differences was observed between the three products (see Table 1). This leads to residual uncertainty regarding the consistency and interpretation of the analytical data to support the conclusion that CT-P13 is highly similar to US-licensed Remicade. Since this issue has not been adequately addressed by the applicant at the time of this review (i.e. an explanation of why a difference in FcγRIIIa/b binding affinity and ADCC activity would exist in the absence of a clear pattern of glycoform differences), the CMC team recommended a deficiency comment to that extent as detailed in Recommended Comments to Applicant section at the end of this document, and I agree.

It is unclear whether the differences observed in the assays for FcγRIIIa binding and ADCC in tmTNF-overexpressing inflammatory cells, if confirmed, are relevant to clinical activity and/or would likely be associated with a clinically meaningful difference between CT-P13 and US-licensed Remicade in certain conditions of use. At the time of this review however, I do not have sufficient information on the consistency of the apparent FcγRIIIa binding/ADCC differences to determine whether these represent true differences between CT-P13 and US-licensed Remicade.

- **Facilities review/inspection**

A pre-license inspection at Celltrion Plant [redacted] (b) (4) at the applicant site in The Republic of Korea was conducted on February 23 – March 6, 2015 for this BLA. The inspection team issued a fifteen-item Form FDA 483 to the firm with the following observation summaries which the applicant agreed to correct:

1) Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established and followed;
2) A procedure has not been established for performing identity testing on the contents of a final CT-P13 drug product vial of each lot after all labeling operations have been completed as required by 21CFR610.14;
3) Alert limits for bioburden and endotoxin are not established for CT-P13 drug substance [redacted] (b) (4);

Reference ID: 3775998

4) Qualification studies for the Lyomax 19 lyophilizer, PR-LYO-F300 are not adequate;
5) The visual inspection program (FF24010) for CT-P13 drug product vials is inadequate;
6) The media fill program (CP2205) is deficient in that acceptance criterion for yield has not been established for media fills;
7) The investigation for Deviation DE-P2-12-246 is inadequate;
8) Bioburden excursions for CT-P13 drug substance are not adequately investigated;
9) Qualification of assays conducted in the Research and Development Laboratory to evaluate infliximab biosimilarity for regulatory purposes was documented retrospectively;
10) The methylene blue dye penetration test used to evaluate CT-P13 drug product container closure integrity is inadequate;
11) The (b) (4) endotoxin test for drug substance is not adequately conducted;
12) Numerous leaks (b) (4) the bioreactor have occurred since 2013 and appear to be ongoing;
13) The disinfectant efficacy study (Report GR-QC-15-003.AD1) conducted to validate disinfectants used for (b) (4) cleaning is inadequate;
14) Establishment of the reliability of the stopper supplier's Certificate of Analysis is deficient in that the test results are not appropriately validated at appropriate intervals;
15) The raw material specifications for CT-P13 are inadequate.

The initial classification of the inspection was voluntary action indicated (VAI). The final evaluation of the compliance status of the facility is pending at the time of this review.

- **Other notable issues (resolved or outstanding)**

The CMC review team recommended, and I agree, that this 351 (k) BLA application not be approved at this time due to deficiencies in the analytical biosimilarity assessment that currently preclude a determination that this product is “highly similar” to the reference product, as outlined in the proposed comments to applicant below.

In the course of the immunogenicity review, differences in sub-visible particulates in the range of 1 to 5 µm in size between CT-P13, US-licensed Remicade and EU-approved Remicade lots used in study 1.4 were observed. The proteinaceous sub-visible particulates of this size are a product quality attribute that may be associated with enhanced immunogenicity.[8] Since the issue has not been addressed by the applicant at the time of this review, the Immunogenicity review team proposed a comment to that extent as detailed in subsection in Recommended Comments to Applicant section at the end of this document, and I agree.

4. Nonclinical Pharmacology/Toxicology

Pharm-Tox Reviewer: Matthew Whittaker, Ph.D.; Supervisor: Timothy Robison, Ph.D.

[8] Rosenberg. 2006. Effects of protein aggregates: an immunologic perspective. AAPS J. 4:E501-7

Reference ID: 3775998

The CT-P13 nonclinical development program was adequate to support clinical development. Two key nonclinical toxicology/toxicokinetic studies were submitted in support of the BLA: (1) a single dose toxicokinetic (TK) study in Sprague-Dawley (SD) rats comparing CT-P13 vs. EU-approved infliximab and (2) a 2-week toxicity/TK study in SD rats comparing CT-P13 vs. EU-approved infliximab. During pre-submission communications, the Agency acknowledged the limitations of animal studies as infliximab is only active in chimpanzees and has advised Celltrion that additional animal studies were not recommended based upon the available extensive human experience with infliximab.

Collectively, there was no evidence in nonclinical studies conducted in SD rats to indicate potential clinical safety concerns associated with CT-P13 administration. The TK profile of CT-P13 was comparable to that of EU-approved infliximab in SD rats. The pharmacology and animal data submitted to the BLA support a demonstration of biosimilarity (i.e., comparable achieved exposures and similar safety) between CT-P13 and EU-approved Remicade from the nonclinical Pharmacology and Toxicology perspective. The Pharmacology and Toxicology review team recommended approval of the BLA from the nonclinical perspective without the need for additional animal studies. There are no outstanding issues from the nonclinical Pharmacology and Toxicology perspective.

5. Clinical Pharmacology/Biopharmaceutics

Clinical Pharmacology Reviewer: Lei He, Ph.D.
Clinical Pharmacology Team Leader (acting): Ping Ji, Ph.D.

- **General clinical pharmacology/biopharmaceutics considerations**

The applicant submitted pharmacokinetic data from two dosing regimens in two distinct patient populations (3 mg/kg in combination with MTX in patients with RA and 5 mg/kg as monotherapy in patients with AS) comparing CT-P13 and EU-approved Remicade, and single dose of 5 mg/kg in healthy subjects comparing CT-P13, EU-approved Remicade, and US licensed Remicade.

Pharmacokinetic (PK) similarity of CT-P13 to US-licensed Remicade was evaluated in one 3-way PK similarity study that compared the PK, safety, tolerability, and immunogenicity of single dose 5 mg/kg of either CT-P13, EU-approved Remicade and US-licensed Remicade in healthy subjects (study 1.4). The study was required by the FDA to provide needed PK bridging data, in addition to the analytical bridging, to scientifically justify the relevance of the clinical comparative data from the clinical development program which used exclusively EU-approved Remicade to the assessment of biosimilarity to the US-licensed Remicade (for additional considerations on the use of data generated using a non-US-licensed comparator product, refer to Section Background, The Reference Product (above).

Reference ID: 3775998

Description of Relevant Clinical Pharmacology Studies

The PK of CT-P13 following IV administration has been characterized in studies using either US-Remicade (the reference product) or EU-Remicade as the comparator. The summary of each relevant study design pertinent to the PK evaluation is provided below:

- Study 1.4 was a randomized , double-blind, three-arm, parallel-group study following a single dose of 5 mg/kg through a 2-hr IV infusion to compare the PK, safety, tolerability, and immunogenicity of CT-P13, EU-Remicade, and US-Remicade in healthy subjects (N=71/arm). The PK endpoints evaluated in this study were AUCinf, AUC0-last, and Cmax. Immunogenicity serum samples were collected at screening/predose and at end-of-study visit (Day 57) for assessment of the anti-drug antibodies (ADA) and neutralizing antibodies (nAb).

- Study 1.1 was a randomized, double-blind, parallel-group, Phase 1 study following multiple doses of 5 mg/kg through a 2-hr IV infusion to demonstrate the PK similarity at steady state between CT-P13 and EU-Remicade in patients with active AS (N=125/group). The PK endpoints evaluated in this study were steady state exposure metrics, AUCτ,ss and Cmax,ss, between week 22 and 30. Immunogenicity serum samples were collected at screening/predose and Weeks 14, 30, and 54.

- Study 3.1 was a randomized, double-blind, parallel-group, Phase 3 study following multiple doses of 3 mg/kg through a 2-hr IV infusion to demonstrate the similarity in efficacy and safety between CT-P13 and EU-Remicade when co-administered with methotrexate in patients with active RA (N=606). Sparse PK samples were collected pre-dose, and at 2 hours (end of infusion) and 3 hours (1 hour after the end of infusion) following each of the multiple doses for PK similarity comparison between CT-P13 and EU-Remicade. Immunogenicity serum samples were collected at screening/predose and Weeks 14, 30, and 54.

Results of Clinical Pharmacology Studies

Study 1.4: Pharmacokinetics Results

In the dedicated PK study 1.4, the pairwise comparisons of CT-P13, US-licensed Remicade and EU-approved Remicade met the pre-specified acceptance criteria for PK similarity (90% CIs for the ratios of geometric mean of AUCinf, AUClast, and Cmax, within the interval of 80% to 125%) as summarized in Table 4 and depicted in Figure 1. These data establish a PK bridge to justify the relevance of the data generated using EU-approved Remicade.

Reference ID: 3775998

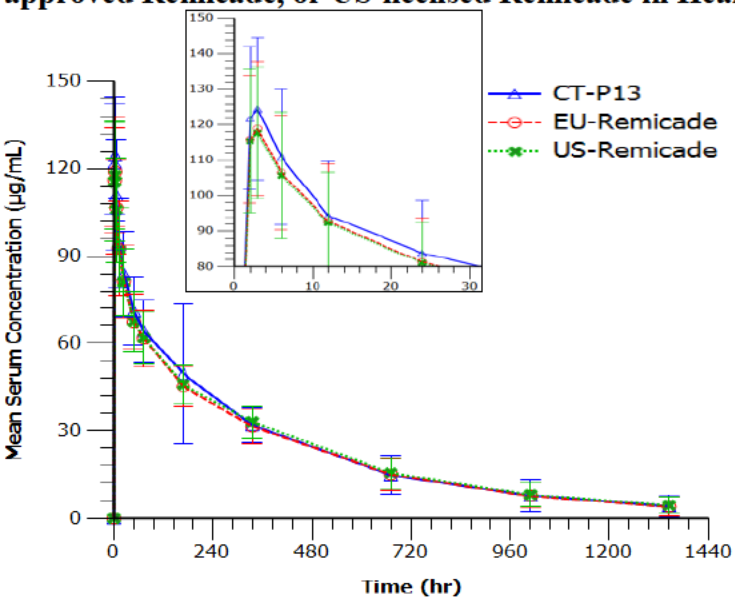
Table 4. PK Analysis of the 3-Way PK Bridging/Similarity Study 1.4

Comparison	Parameter	GMR%	90% CI (%)
CT-P13 vs US-licensed Remicade	**Cmax**	105.7	(100.8, 110.8)
	AUC0-t	101.4	(95.1, 108.1)
	AUC0-inf	102.3	(95.1, 110.0)
CT-P13 vs EU-approved Remicade	**Cmax**	106.9	(102.0, 112.1)
	AUC0-t	98.2	(92.3, 104.5)
	AUC0-inf	98.8	(92.1, 106.0)
EU-approved Remicade vs US-licensed Remicade	**Cmax**	100.9	(96.8, 105.8)
	AUC0-t	96.9	(91.7, 102.4)
	AUC0-inf	96.6	(90.4, 103.3)

Source: Adapted from Dr. He's Clinical Pharmacology Review, Table 1
CI: confidence interval; GMR: geometric mean ratio

While the pre-specified acceptance criteria for PK similarity were met, it was noted that exposure as measured by Cmax was higher for CT-P13 than for EU-approved Remicade and US-licensed Remicade. This was attributed to the inherent variability of Cmax sampling and the slightly higher (approximately 3%) total protein content of CT-P13 as detailed in Section CMC above.

Figure 1. Infliximab PK Profiles Following a Single IV Dose 5 mg/kg of CT-P13, EU-approved Remicade, or US-licensed Remicade in Healthy Subjects (Study 1.4)



Source: Adapted from Dr. He's Clinical Pharmacology Review, Figure 1

Study 1.4: Immunogenicity Results

The incidence of anti-drug antibody (ADA) formation on Day 57 in healthy subjects using ELISA was 26.7%, 25.3%, and 11.4% for CT-P13, EU-approved Remicade, and US-licensed Remicade, respectively. When testing ADA by ECLA, the assay used in rest of the clinical studies, the rates were 14%, 7%, and 2.9% respectively. The implications of the observed

Reference ID: 3775998

immunogenicity numerical differences seen in study 1.4 for the totality of the evidence are discussed in detail in section Safety, Immunogenicity below.

Study 1.1 and 3.1 Pharmacokinetics Results

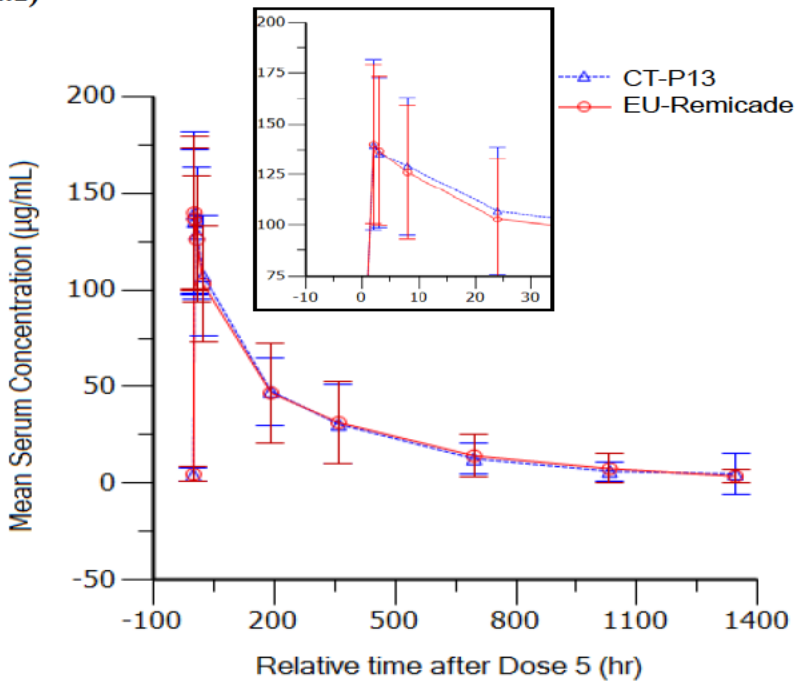
Similar PK, safety, and immunogenicity were demonstrated for CT-P13 and EU-approved Remicade in two different usage scenarios, i.e. in patients with RA (3 mg/kg of infliximab with concomitant use of methotrexate) and in patients with AS study (use of the higher dose of 5 mg/kg, but without concomitant immunosuppressive therapy). In the supporting PK biosimilarity study 1.1 in AS, the 90% CIs for CT-P13 vs. EU-approved Remicade geometric mean ratios of Cmax and AUCtau were contained within the similarity range of 80% –125% as summarized in Table 5 and depicted in Figure 2.

Table 5. PK similarity analysis of Study 1.1 Using Average Bioequivalence Approach

CT-P13 (T) vs EU-approved Remicade (R)						
Parameter	**LSM (T)**	**N**	**LSM (R)**	**N**	**GMR (%)**	**90% CI (%)**
Cmax	149.90	119	144.79	116	103.5	(97.5, 109.9)
AUCss	32155.86	119	30739.38	116	104.6	(94.8, 115.4)

Source: Adapted from Dr. He's Clinical Pharmacology Review, Table 7
CI: confidence interval; GMR: geometric mean ratio; The units of Cmax and AUC are µg/mL and µg*hr/mL, respectively

Figure 2. Infliximab PK Profiles at Steady State Between Week 22 and 30 Following Multiple IV Doses (5 mg/kg) of CT-P13 or EU-approved Remicade in AS Patients (Study 1.1)



Source: Adapted from Dr. He's Clinical Pharmacology Review, Figure 2

Reference ID: 3775998

In addition, consistent with the PK data from studies 1.4 in healthy volunteers and study 1.1 in patients with AS, the trough and peak concentrations of CT-P13 were comparable to those of EU-approved Remicade in RA patients in study 3.1 (data not shown).

Relevance of the PK Data to Indications Not Studied in CT-P13 Program

The clinical pharmacology review team also assessed the relevance of the PK findings from the above studies to the conditions of use not studied in the clinical program, including JIA, plaque psoriasis, ulcerative colitis, and Crohn's disease. The PK of CT-P13 is generally comparable across various populations including healthy subjects and patients with RA and AS. Similarly, the PK of EU-approved Remicade and/or US-licensed Remicade are also comparable across various populations including healthy subjects and patients with RA, AS, JIA, plaque psoriasis, ulcerative colitis, and Crohn's disease thus supporting the relevance of the PK findings from the CT-P13 clinical program to all the indications for which the applicant is seeking licensure.

Conclusions

Overall, the submitted clinical pharmacology studies are adequate to:

1) Establish a PK bridge to justify the relevance of the data generated using EU-approved Remicade
2) Justify the relevance the PK findings from the CT-P13 clinical program to all the indications for which the applicant is seeking licensure
3) Support a conclusion of no clinically meaningful differences between CT-P13 and US-licensed Remicade.

The Office of Clinical Pharmacology has determined that PK similarity has been established between CT-P13 and US-licensed Remicade, and the PK results add to the totality of evidence to support a demonstration of no clinically meaningful differences between CT-P13 and US-licensed Remicade. I concur with this recommendation.

6. Clinical Microbiology

Microbiology Reviewer: Bo Chi, Ph.D.; Bioburden Control Reviewer: Maria Candauchacon, Ph.D. Microbiology Supervisor: Patricia Hughes, Ph.D.

The microbiology review team concluded that the drug product is recommended for approval from sterility assurance and product quality microbiology perspective. I concur with this recommendation.

7. Clinical/Statistical- Efficacy

Clinical Primary Reviewer: Juwaria Waheed, M.D.

Reference ID: 3775998

Statistical Primary Reviewer: Gregory Levin, Ph.D., Statistical Team Leader: Ruthanna Davi, Ph.D.

Overview of the Clinical Program

The applicant submitted results from eight completed clinical studies. A summary of the key design features of these studies is provided in Table 6. Study 1.4 (discussed in Section Clinical Pharmacology/Biopharmaceutics above) was a randomized, double-blind, parallel-group, single-dose clinical study in 213 healthy volunteers to compare the pharmacokinetic (PK) profiles of CT-P13, EU-Remicade, and US-Remicade. Study 3.1 was a randomized, double-blind, parallel-group clinical study to compare the safety and efficacy of CT-P13 and EU-Remicade in 606 patients with active RA who had an inadequate response to methotrexate (MTX). Study 3.2 was an open-label, single-arm extension study in 302 RA patients who had completed Study 3.1. Study 1.2 was a randomized, double-blind, parallel- group pilot study to compare CT-P13 and EU-Remicade in 19 RA patients in the Philippines. Study 3.3 was a randomized, double-blind, parallel- group study to compare CT-P13 and EU-Remicade in 15 RA patients in Russia. Study B1P13101 was a randomized, double-blind, parallel-group clinical study to compare the PK profiles of CT-P13 and EU-Remicade in 108 Japanese patients with active RA who had an inadequate response to MTX. Study 1.1 was a randomized, double-blind, parallel-group clinical study to perform PK, safety, and efficacy comparisons of CT-P13 and EU-Remicade in 250 patients with AS. Study 1.3 was an open-label, single-arm extension study in 174 AS patients who had completed Study 1.1. There are also a number of ongoing studies.

Study 3.1 in RA was the comparative clinical study in which a comparison of efficacy and safety was the primary objective providing the primary evidence to support the conclusion of no clinically meaningful differences between CT-P13 and US-licensed Remicade. Supportive safety and efficacy data were provided by the rest of the clinical studies, including study 1.1 in a different population of patients with AS using a different approved dosing regimen.

Reference ID: 3775998

Table 6. Key Design Features of CT-P13 Clinical Studies

Protocol ***Duration*** (Dates conducted)	**Design** ***Objectives***	**Patient Population** ***Total Number***	**Treatment Arms**	**Number per arm**
Controlled Studies in Patients				
CT-P13 3.1 (Global, ex-US) *54 weeks* (12/10-07/12)	R, DB, PG Comparative Clinical Study: *Efficacy, Safety, PK, Immunogenicity*	Moderate to Severe RA, MTX-IR *N=606*	CT-P13 3 mg/kg+ MTX EU-approved Remicade + MTX	n=302 n=300
CT-P13 1.1 (Global, ex-US) *54 weeks* (12/10-07/12)	R, DB, PG *PK, Efficacy, Safety, Immunogenicity*	Moderate to severe AS *N=250*	CT-P13 5 mg/kg EU-approved Remicade	n=128 n=122
B1P13101 (Japan) *54 weeks* (10/11-06/13)	R, DB, PG *PK, Efficacy, Safety, Immunogenicity*	Moderate to Severe RA, MTX-IR *N=108*	CT-P13 3 mg/kg+ MTX EU-approved Remicade + MTX	n=51 n=53
CT-P13 1.2 (Philippines) *54 weeks* (04/10-08/12)	R, DB, PG Pilot Study: *Efficacy, Safety*	Moderate to Severe RA, MTX-IR *N=19*	CT-P13 3 mg/kg+ MTX EU-approved Remicade + MTX	n=9 n=9
CT-P13 3.3 (Russia) *54 weeks* (12/12-10/13*)	R, DB, PG Local Registration Study: *Efficacy, Safety*	Moderate to Severe RA, MTX-IR *N=15*	CT-P13 3 mg/kg+ MTX EU-approved Remicade + MTX	n=6 n=9
Controlled Studies in Healthy Volunteers				
CT-P13 1.4 *Single Dose* (10/13-02/14)	R, DB, PG, SD *3-way PK Bridging PK, Safety, Immunogenicity*	Healthy volunteers *N=213*	CT-P13 5 mg/kg EU-approved Remicade 5 mg/kg US-licensed Remicade 5 mg/kg	n=71 n=71 n=71
Extension Studies				
CT-P13 3.2 *(~1year)* (02/12-07/13)	OLE: *Safety, Immunogenicity*	RA, Enrolled from controlled study CT-P13 3.1 *N=302*	CT-P13 maintenance CT-P13 transitioned from EU-approved Remicade	n=158 n=144
CT-P13 1.3 *(~1year)* (03/12-06/13)	OLE: *Safety, Immunogenicity*	AS, Enrolled from controlled study CT-P13 1.1 *N=174*	CT-P13 maintenance CT-P13 transitioned from EU-approved Remicade	n=88 n=86

[1]EU-approved Remicade;[2]US-licensed Remicade; *-30-week data; DB: double blind, IR: inadequate responder; MTX: methotrexate, OLE: open label extension, PG: parallel-group, PK: pharmacokinetics, R: randomized, SD: single dose

Brief Description of Efficacy Endpoints

Comparative Clinical Study 3.1 in RA

The prespecified primary efficacy endpoint was the proportion of patients achieving an ACR20 response at Week 30, as a well validated outcome measure in RA. In 1995, the American College of Rheumatology (ACR) published a definition of improvement for clinical trials in rheumatoid arthritis, which has since been used in drug development trials to demonstrate evidence of efficacy for signs and symptoms of RA.[9] The ACR20 response is calculated as a ≥20% improvement in:

- tender joint count (of 68 joints) and
- swollen joint count (of 66 joints) and
- 3 of the 5 remaining ACR core set measures
    - Patient Global Assessment of Arthritis on a visual analog scale (VAS)

[9] DT Felson, et al., Arthritis & Rheum, 1995 June, 38(6):727-735

Reference ID: 3775998

- Physician Global Assessment of Arthritis on a VAS
- Patient Assessment of Pain on a VAS
- Patient Assessment of Physical Function (e.g. Health Assessment Questionnaire)
- Acute Phase Reactant (Erythrocyte Sedimentation Rate or C-reactive protein)

Fifty percent and 70 percent improvement (ACR50 and ACR70) are similarly calculated using these higher levels of improvement.

Secondary efficacy endpoints included the components used to define ACR20 response, time to onset of ACR20 response, the Disease Activity Score in 28 joints (DAS28), EULAR response, ACR50 response, ACR70 response, Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), total van der Heijde radiographic joint score, SF-36 total score, fatigue (SF-36 vitality subscale score), and the number of patients requiring salvage treatments. Most were evaluated at Weeks 14, 30, and 54.

The determination of a similarity margin is a critical aspect of the design of the comparative clinical study because it determines the null hypothesis being tested in the primary analysis, i.e., the differences in efficacy that the study will need to rule out at an acceptable significance level.

Discussion on Similarity Margin

Study 3.1 had a pre-specified similarity margin of ±15% and was completed prior to Celltrion's interactions with FDA. In response to comments from FDA indicating that the margin was not acceptable, the applicant provided justification for a revised margin of ±13% based on a meta-analysis of historical data from randomized clinical trials of infliximab and the goal of preserving at least 50% of the effect size of the reference product. As discussed in Dr. Levin's statistical review, the Agency does not agree with the applicant's selection of historical trials as, unlike the meta-analysis conducted by the Agency (see Table 7), the applicant did not include one important study (Schiff et al, 2008) in their meta-analysis. The agency believes that a similarity margin of ±12% is more appropriate for this study. The agency's recommendation for a ±12% similarity margin is aimed at weighing the clinical importance of different losses in effect against the feasibility of different study sizes. In a comparative clinical study designed with 90% power to reject absolute differences greater than 12% in magnitude, observed differences larger than approximately 6% will result in failure to establish similarity, as the 90% confidence interval for the estimated difference will not rule out the 12% margin. Therefore, the comparative clinical study will be able to rule out differences in ACR20 response greater than 12% with high (at least 95%) statistical confidence, and will be able to rule out differences greater than around 6% with moderate (at least 50%) statistical confidence. The lower bound of the proposed similarity margin (-12%) also corresponds to the retention of approximately 50% of conservative estimates of treatment effect sizes relative to placebo for infliximab.

Reference ID: 3775998

Table 7. Meta-analysis of Historical Effect of Infliximab on ACR20 Response in Randomized Clinical Trials of Patients with Active RA Despite Treatment with MTX

		MTX+Placebo		MTX+Infliximab		
Study	Week	N	ACR20 Response	N	ACR20 Response	Treatment Difference
Maini et al, 1999	30	88	20%	86	50%	30%
Westhoven et al, 2006	22	361	24%	360	55%	31%
Schiff et al, 2008	28	110	42%	165	59%	18%
Zhang et al, 2006	18	86	49%	87	76%	27%
Abe et al, 2006	14	47	23%	49	61%	38%
Meta-Analysis (Fixed Effect[1]): Difference (95% CI)						28.4% (23.6%, 33.3%)
Meta-Analysis (Random Effect[2]): Difference (95% CI)						28.3% (22.6%, 34.1%)

Source: Adapted from Dr. Levin's Statistical Review, Table 2
[1]Based on Mantel-Haenszel weights
[2]Based on DerSimonian-Laird approach

PK and Efficacy Study 1.1 in AS

The primary objective was to demonstrate comparable PK at steady state between CT-P13 and EU-Remicade which was discussed in Section Clinical Pharmacology/Biopharmaceutics. Secondary objectives were to compare CT-P13 and EU-Remicade with respect to long-term safety and efficacy endpoints. Efficacy endpoints included the Assessment of SpondyloArthritis International Society (ASAS) 20% improvement scale (ASAS20), ASAS40, BASDAI score, Bath Ankylosing Spondylitis Functional Index (BASFI) score, Bath Ankylosing Spondylitis Metrology Index (BASMI) score, chest expansion, and SF-36 total score, assessed at Weeks 14, 30, and 54 (or an end-of-study visit for patients who stopped treatment early). The ASAS20 response is defined as an improvement of at least 20% and an absolute improvement of at least 1 unit on a 0 to 10 scale from baseline in at least 3 of the following domains:

- Patient global assessment of disease status
- Patient assessment of spinal pain
- Function according to BASFI
- Morning stiffness determined using the last 2 questions of BASDAI

Study Conduct

Treatment groups in the studies were generally balanced with respect to demographics and baseline characteristics. None of the study sites was in the US. In study 3.1, the average disease activity score (DAS28 [CRP]; scale: 0-10) was 5.8, consistent with the target population of patients with moderate-to severely active RA. Similarly study 1.1 recruited AS patients with moderate to severely active disease with an average disease activity score (BASDAI; scale: 0-10) 6.7. The design of the clinical studies was such that subjects who stopped treatment early were also withdrawn from the study and not followed for the rest of the study duration. As a result, there was substantial patient dropout as shown in Table 8, contributing to missing data. The overall proportions of discontinuation and drop out by

Reference ID: 3775998

category, including adverse events or lack of efficacy, were similar between CT-P13 and EU-approved Remicade arms in both study 3.1 and study 1.1. However, to account for the missing data, sensitivity analyses were conducted as detailed in subsection *Missing Data* below.

Table 8. Patient Disposition in Controlled Studies 3.1 in RA and 1.1 in AS

	Rheumatoid Arthritis Study 3.1		Ankylosing Spondylitis Study 1.1	
	CT-P13 3mg/kg n (%)	EU-approved Remicade 3mg/kg n (%)	CT-P13 5mg/kg (n=125) n (%)	EU-approved Remicade 5mg/kg n (%)
ITT Population				
• Screened	302 (100)	304 (100)		
• Randomized	300 (99)	302 (99)	125 (100)	125 (100)
• Completed entire study	233 (77)	222 (73)	106 (85)	104 (83)
• Total Discontinued	69 (23)	82 (27)	19 (15)	21 (17)
Primary reason for Discontinuations				
• Lack of efficacy	10 (3)	6 (2)	2 (2)	0
• Adverse event	31 (10)	41 (14)	10 (8)	8 (6)
• Death	0	1 (<1)	0	2 (2)
Other withdrawals				
• Protocol violation	2 (<1)	2 (<1)	0	1 (<1)
• Withdrew consent	16 (5)	21 (7)	3 (2)	6 (5)
Adapted from Dr. Waheed's Clinical Review, Table 11				

Efficacy findings

Comparative Clinical Study 3.1

Study 3.1 met its pre-specified primary endpoint. Approximately 60.9% of patients randomized to CT-P13 and 58.9% of patients randomized to EU-approved Remicade remained in the study and achieved an ACR20 response at Week 30, for an estimated absolute difference between treatments of 2.0% (90% CI: -4.6%, +8.7%; 95% CI: -5.8%, +9.9%). The 90% CI ruled out the margin of ±13% proposed by the applicant, in addition to the margin of ±12% that the Agency has determined reasonable (see *Discussion of Similarity Margin* subsection above).

In a sensitivity analysis using the per-protocol population (patients who completed the study and adhered to the protocol), 73.4% and 70.1% responded on CT-P13 and EU-approved Remicade, respectively, for an estimated difference of 3.3% (90%: -3.4%, +10.0%). The primary analysis was further supported by the mean changes from baseline in the components of the ACR composite endpoint and the disease activity score (DAS28), ACR50 and ACR70 response rates, which were also similar between the arms in all randomized patients who completed the study and the per-protocol population.

While radiographic endpoints are generally not expected for comparative clinical studies in RA, the applicant has included radiographic assessment in study 3.1 using the change from baseline in total van der Heijde radiographic joint score at Week 54. Original analysis of joint

Reference ID: 3775998

damage progression showed a similar decrease in the modified sharp score at Week 54 for CT-P13 compared to EU-approved Remicade in study 3.1 (difference: 2.6; 95% CI: -2.7, 7.9) but the within-group mean changes on the two arms (-28.5 and -31.9) was significantly larger compared to historical studies with infliximab (where the change was closer to zero). The applicant, therefore, conducted a post-hoc re-evaluation of the radiographs from baseline and Week 54 using a similar approach as used in the historical studies with infliximab. In the original assessment, a single reader evaluated a patient's radiographs with knowledge of the chronological order of the images. The re-evaluation utilized two independent readers without knowledge of the order of the radiographs, evaluating paired, rather than individual radiographs of the patient. Based on that re-evaluation, the average changes on the two arms remained similar, and the within-group changes from baseline were more in line with those of historical trials. However, the fact that a post hoc reassessment was needed precludes definitive conclusion regarding the radiographic data.

PK and Efficacy Study 1.1 in AS

The results from the primary PK analysis in study 1.1 were discussed in Section Clinical Pharmacology/Biopharmaceutics. According to the applicant's planned efficacy analysis in the subset of patients remaining in study 1.1 at Week 30, approximately 70.5% of patients randomized to CT-P13 and 72.4% of patients randomized to EU-Remicade achieved an ASAS20 response, for an estimated odds ratio comparing treatments of 0.91 (95% CI: 0.51, 1.62). A supportive FDA analysis in all randomized patients, 63.2% of patients on CT-P13 and 67.2% on EU-Remicade remained in the study and achieved an ASAS20 response at Week 30, for an estimated difference of -4.0% (95% CI: -15.9%, 8.0%) indicating similar efficacy in AS using a 5 mg/kg dosing regimen without background immunosuppression.

Missing Data

As noted in subsection *Study Conduct* above, a substantial proportion of subjects dropped out of studies 3.1 and 1.1 due primarily to study design where subjects who discontinued treatment early were not followed for the duration of the study. To investigate the impact of these missing data on the primary analysis, the FDA statistical review team conducted tipping point analyses to explore the sensitivity of results to violations in assumptions about the missing data (i.e., to various missing-not-at-random assumptions). These tipping point sensitivity analyses largely support the findings of the key efficacy analyses in Study 3.1 (data not shown).

- **Discussion of statistical and clinical efficacy reviews with explanation for CDTL's conclusions and ways that any disagreements were addressed.**

In summary, the applicant has provided statistically robust comparative efficacy data demonstrating similar efficacy between CT-P13 and EU-approved Remicade in patients with moderate-to-severe RA despite methotrexate, using 3 mg/kg dosing on methotrexate background, and in patients with moderate-to-severe AS, using 5 mg/kg dosing monotherapy. The primary analysis was supported by the analysis of key secondary endpoints and sensitivity analyses accounting for the missing data. The FDA statistical and clinical review teams

Reference ID: 3775998

concluded, and I concur, that the results from the CT-P13 clinical program support a conclusion of no clinically meaningful differences between CT-P13 and US-licensed Remicade in the indications studied, provided that the bridge between EU-approved Remicade and US-licensed Remicade is confirmed.

- **Includes discussion of notable efficacy issues both resolved and outstanding**

None.

8. Safety

Clinical Primary Reviewer: Juwaria Waheed, M.D.
Statistical Primary Reviewer: Gregory Levin, Ph.D., Statistical Team Leader: Ruthanna Davi, Ph.D.

- **Studies contributing to safety analyses**

A summary of the studies contributing to the primary safety analyses may be found in Table 9. These studies include: one comparative clinical study in patients with RA (study 3.1), one comparative PK and efficacy study in patients with AS (study 1.1), three supportive clinical studies in patients with RA (studies B1P13101 conducted in Japan, 1.2 conducted in the Philippines, and 3.3 conducted in Russia), and one single-dose study in healthy volunteers (study 1.4). Additional safety data were submitted from long-term extension study 3.2 which enrolled RA patients from the controlled study 3.1, and study 1.3 which enrolled AS patients from the controlled study 1.1. These studies also provided safety and immunogenicity data on patients transitioning from EU-approved Remicade to CT-P13 to assess for potential safety concerns, including hypersensitivity and anaphylaxis, which may arise from the clinically relevant scenario of non-treatment naïve patients who transition to CT-P13.

Reference ID: 3775998

Table 9. Summary of CT-P13 Studies with Associated Long-Term Extension

Protocol ***Duration***	**Patient Population** ***Total Number***	**Treatment Arms**	**Number per arm**
Controlled Studies in Patients			
CT-P13 3.1 (Global, ex-US) *54 weeks*	Moderate to Severe RA, MTX-IR *N=606*	CT-P13 3 mg/kg+ MTX EU-approved Remicade + MTX	n=302 n=300
CT-P13 1.1 (Global, ex-US) *54 weeks*	Moderate to severe AS *N=250*	CT-P13 5 mg/kg EU-approved Remicade	n=128 n=122
B1P13101 (Japan) *54 weeks*	Moderate to Severe RA, MTX-IR *N=108*	CT-P13 3 mg/kg+ MTX EU-approved Remicade + MTX	n=51 n=53
CT-P13 1.2 (Philippines) *54 weeks*	Moderate to Severe RA, MTX-IR *N=19*	CT-P13 3 mg/kg+ MTX EU-approved Remicade + MTX	n=9 n=9
CT-P13 3.3 (Russia) *54 weeks**	Moderate to Severe RA, MTX-IR *N=15*	CT-P13 3 mg/kg+ MTX EU-approved Remicade + MTX	n=6 n=9
Three-way PK Similarity Study in Healthy Volunteers			
CT-P13 1.4 *Single Dose*	Healthy volunteers *N=213*	CT-P13 5 mg/kg EU-approved Remicade 5 mg/kg US-licensed Remicade 5 mg/kg	n=71 n=71 n=71
Extension Studies			
CT-P13 3.2 *(~1year)*	RA, Enrolled from controlled study CT-P13 3.1 *N=302*	CT-P13 maintenance CT-P13 transitioned from EU-approved Remicade	n=158 n=144
CT-P13 1.3 *(~1year)*	AS, Enrolled from controlled study CT-P13 1.1 *N=174*	CT-P13 maintenance CT-P13 transitioned from EU-approved Remicade	n=88 n=86
*-30-week data; DB: double blind, IR: inadequate responder; MTX: methotrexate, PK: pharmacokinetics			

For patients discontinuing treatment, serious adverse events (SAE) were reported starting from the time the patient provided informed consent (prior to receiving investigational product) through and including 8 weeks after the last administration of the investigational product. The safety data were presented both in the individual study reports for each study, and as pooled safety for the adverse events of special interest (AESI). Additional supportive safety information was provided in the 120-day safety update from the ongoing postmarketing surveillance and observational studies in RA and IBD.

- **Adequacy of the database, major findings/signals, special studies**

As of the original submission data cut-off (January 21, 2014), the extent of the safety database comprised of 803 subjects of whom 213 healthy volunteers. Patients with RA received 3 mg/kg CT-P13 or EU-approved Remicade in combination with methotrexate and folic acid and patients with AS received 5 mg/kg CT-P13 or EU-approved Remicade, for over one year. Healthy subjects received a single dose of 5 mg/kg CT-P13, EU-approved Remicade or US-licensed Remicade. Overall, the safety database is adequate to provide a reasonable comparative safety assessment, using two approved dosing regimens in two distinct patient populations, to support a determination of no clinically meaningful differences between CT-P13 and US-licensed Remicade, provided that the bridge between EU-approved Remicade and US-licensed Remicade is confirmed.

Reference ID: 3775998

- **General discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests.**

No new safety signals were identified in the CT-P13 group compared to the known adverse event profile of US-licensed Remicade. The incidence of adverse events, serious adverse events, adverse events of special interest, and death are summarized in Table 10. The overall incidences of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and AEs leading to discontinuation, infections, infusion-related reactions and anaphylaxis, were similar between CT-P13 and the comparator products.

Table 10. Overview of Deaths, SAEs, and Events of Interest in Studies 3.1 in RA, 1.1 in AS, and 1.4 in Healthy Volunteers

	Rheumatoid Arthritis Study 3.1		Ankylosing Spondylitis Study 1.1		Healthy Volunteers Study 1.4		
	CT-P13 3mg/kg (n=302)	EU-Remi 3mg/kg (n=300)	CT-P13 5mg/kg (n=128)	EU-Remi 5mg/kg n=122)	CT-P13 5mg/kg (n=71)	EU-Remi 5mg/kg (n=71)	US-Remi 5mg/kg (n=71)
Total # of TEAEs # of pts with ≥1 TEAE, n (%)	732 213 (71)	738 211 (70)	362 95 (74)	375 82 (67)	67 37 (42)	28 21 (30)	54 33 (46)
Total # of SAEs # of pts with ≥1 SAE, n (%)	49 42 (14)	39 3 (10)	12 10 (8)	11 8 (7)	1 1 (1)	1 1 (1)	0 0
TEAEs leading to discontinuation # of pts (%)	40 33 (11)	52 47 (16)	12 11 (9)	9 9 (7)	0	0	0
Infections, n # of pts with ≥1 infection, n (%)	237 127 (42)	231 137 (46)	91 55 (43)	107 49 (40)	18 18 (25)	12 12 (17)	26 24 (34)
Serious Infections (SIE), n # of pts with ≥ 1SIE, n (%)	13 13 (4)	8 7 (2)	2 2 (2)	4 3 (3)	0	0	0
Infusion-related reactions (IRR) # of pts with IRR, n (%)	12 10 (3)	11 11 (4)	0 0	4 4 (3)	0	0	0
Anaphylaxis, n (%)	6 (2)	4 (1)	1 (<1)	3 (2)	0	0	0
Death, n	0	1	1	1	0	0	0

EU-Remi: EU-approved Remicade; US-Remi: US-licensed Remicade; SAE: serious adverse event; TEAE: treatment-emergent adverse events
Source: Adapted from Dr. Waheed's clinical review, Table 22

Death

As of the 120-day safety update (data cut-off 19 Jul 2014), a total of 4 deaths were reported in the CT-P13 clinical development program, two in each CT-P13 and EU-approved Remicade groups. Details of each case are summarized below by study and treatment group:

- Study 3.1, EU-approved Remicade: A 59-year-old female patient with a long-standing history of hypertension and RA died of sudden death after 379 days on treatment. The cause of death was unknown.
- Study 3.2, CT-P13 maintenance group: A 44-year-old male patient with RA died after 578 days of treatment following appendectomy with peritonitis. The cause of death was suspected peritonitis, and multiorgan failure.
- Study 1.1, EU-approved Remicade: A 38-year-old patient died in a car accident.
- Study 1.1, CT-P13: A 25-year-old patient died in a car accident as a passenger.

Reference ID: 3775998

Nonfatal Serious Adverse Events (SAE)

The proportion of patients who experienced at least one SAE was similar between the two treatment groups, CT-P13 and EU-approved Remicade during the controlled period of clinical studies as detailed in Table 10 above. The most frequently reported SAEs were infections and infusion-related reactions and were similar between both treatment groups. SAEs across the system organ classes showed a similar distribution with minor numerical differences between each group. There was no notable difference in the incidence of SAEs following transition of RA and AS patients from EU-approved Remicade to CT-P13 in the extension studies. The different SOCs of SAEs or the pattern of SAEs in the studies comparing CT-P13 and EU-approved Remicade was consistent with the known safety profile of the reference product, US-licensed Remicade.

Discontinuations due to Adverse Events

The proportion of patients discontinuing due to an adverse event was similar between CT-P13 and EU-approved Remicade as detailed in Table 10 above. Infections were the most common reason for discontinuation in studies 3.1 and 1.1 (approximately 3% in the CT-P13 groups compared to 5% in the EU-approved Remicade groups). Infusion-related reactions, and drug hypersensitivity, including anaphylaxis, were the next leading cause of treatment discontinuation in the same studies (with combined rates of approximately 3% in CT-P13, and 5% in the EU-approved Remicade groups). In the extension studies 1.3 and 3.2, generally fewer patients discontinued therapy after transitioning from EU-approved Remicade than those who continued on CT-P13. Adverse events of infections and infusion-related reactions and hypersensitivity are discussed in further detail in separate sections below.

Adverse Events of Special Interest (AESI)

For AESI, which included infections, serious infections, pneumonia, active tuberculosis (TB), latent TB, infusion related reactions, anaphylactic reactions, serious hepatobiliary events, drug induced liver injury, malignancy and lymphoma, Celltrion provided pooled analyses of crude percent rates and exposure-adjusted incidence rates. To account for the differences in the study designs, e.g. study patient populations and dosing regimens, the FDA conducted supplementary analysis of the safety data from the core studies (studies 3.1 and 1.1 and their long-term extension studies 3.1 and 1.3), of the study-specific estimated differences between groups with respect to adverse events of special interest. Of note, electronic datasets for the Japanese study B1P13101 were not submitted as they were not accessible to the applicant as discussed at the BPD Type 4 meeting, and were not included in this integrated analysis. Table 11 provides a summary of the comparative analysis of AESI during the controlled studies 3.1 in RA and 1.1 in AS. The relative risk of an AESI comparing CT-P13 and EU-approved Remicade, was calculated based on DerSimonian-Laird random effects meta-analysis, and there were no significant differences between the treatment groups (although the confidence intervals for the relative risks of the more rare events are quite wide). Similar analysis for the extension studies 3.2 in RA and 1.3 in AS, summarized in Table 12, show that the risk of an AESI was also similar between patients who transition from EU-approved Remicade to CT-P13 and those who continued CT-P13 treatment.

Reference ID: 3775998

Table 11. Adverse Events of Special Interest - Controlled Studies 3.1 in RA and 1.1 in AS

	Rheumatoid Arthritis Study 3.1				Ankylosing Spondylitis Study 1.1				Integrated RR (95% CI)[3]
	CT-P13 (N=302)		EU-approved Remicade (N=300)		CT-P13 (N=128)		EU-approved Remicade (N=122)		
	n (%)[1]	Rate[2]	n (%)[1]	Rate[2]	n (%)[1]	Rate[2]	n (%)[1]	Rate[2]	
Latent TB	28 (9)	9.3	26 (9)	8.6	10 (8)	7.3	6 (5)	4.6	1.2 (0.7, 1.8)
Active TB	3 (1)	0.9	0	0.0	2 (2)	1.4	1 (1)	0.7	3.2 (0.5, 20.4)
Infection	127 (42)	53.8	137 (46)	60.4	55 (43)	52.5	49 (40)	48.4	1.0 (0.8, 1.1)
Serious Infection	13 (4)	4.2	7 (2)	2 2	2 (2)	1.4	3 (3)	2.2	1.4 (0.6, 3.5)
Pneumonia	8 (3)	2.5	5 (2)	1.6	2 (2)	1.4	0	0.0	1.8 (0.6, 5.1)
Malignancy and Lymphoma	3 (1)	0.9	4 (1)	1 3	2 (2)	1.4	0	0.0	1.2 (0.2, 5.7)
Infusion-related Reaction	30 (10)	9.8	43 (14)	14.8	11 (9)	8.2	15 (12)	11.8	0.7 (0.5, 1.0)
Vascular disorder	25 (8)	8.3	16 (5)	5 3	4 (3)	2.9	1 (1)	0.7	1.7 (0.9, 3.0)
Cardiac disorder	5 (2)	1.6	12 (4)	3 9	5 (4)	3.6	6 (5)	4.6	0.6 (0.3, 1.2)
Opportunistic Infection	4 (1)	1.3	6 (2)	1 9	0	0.0	2 (2)	1.5	0.6 (0.2, 1.8)

Source: FDA safety analysis
[1] Number of patients with event (percent)
[2] Incidence rate of first event per 100 person-years
[3] Relative risk of event (95% confidence interval) comparing CT-P13 with EU-approved Remicade based on DerSimonian-Laird random effects meta-analysis of results from Studies 1.1 and 3.1
[4] Definitions of Adverse Events of Special Interest:
Latent TB: All preferred terms with latent tuberculosis or Mycobacterium tuberculosis complex test
Active TB: All preferred terms with tuberculosis not classified as latent TB
Infection: All events in infections and infestations system organ class
Serious Infection: All events in infections and infestations system organ class classified as serious
Pneumonia: All preferred terms with pneumonia, bronchopneumonia, lobar pneumonia, or lower respiratory tract infection
Malignancy and Lymphoma: All preferred terms with cancer, carcinoma, lymphoma, neoplasm, or Myeloproliferative disorder
Infusion-related Reaction: See applicant's ISS SAP Appendix 2 for definition
Vascular Disorder: All events in vascular disorders system organ class
Cardiac Disorder: All events in cardiac disorders system organ class
Opportunistic Infection: All preferred terms with Herpes zoster, Oesophageal candidiasis, Oral candidiasis, or Varicella

Reference ID: 3775998

Table 12. Adverse Events of Special Interest - Extension Studies 3.2 in RA and 1.3 in AS

	Rheumatoid Arthritis Study 3.2				Ankylosing Spondylitis Study 1.3				Integrated RR (95% CI)[3]
	CT-P13 → CT-P13 (N=159)		EU-Remi →CT-P13 (N=143)		CT-P13 → CT-P13 (N=90)		EU-Remi → CT-P13 (N=84)		
	n (%)[1]	Rate[2]	n (%)[1]	Rate[2]	n (%)[1]	Rate[2]	n (%)[1]	Rate[2]	
Latent TB	11 (7)	5.0	7 (5)	3.4	5 (6)	4.1	7 (8)	5.3	1.0 (0.3, 3.2)
Active TB	0	0.0	0 (0.0)	0.0	1 (1)	0.8	1 (1)	0.7	1.1 (0.1, 16.9)
Infection	50 (31)	32.3	47 (33)	34.9	23 (26)	25.4	29 (35)	30.5	1.1 (0.9, 1.5)
Serious Infection	4 (3)	1.7	3 (2)	1.4	2 (2)	1.5	1 (1)	0.7	0.7 (0.2, 2.6)
Pneumonia	1 (1)	0.4	0	0.0	0	0.0	0	0.0	NA
Malignancy and Lymphoma	1 (1)	0.4	4 (3)	1 9	1 (1)	0.8	0	0.0	1.7 (0.1, 18.6)
Infusion-related Reaction	11 (7)	5.0	4 (3)	1 9	7 (8)	5.7	6 (7)	4.5	0.6 (0.3, 1.4)
Vascular disorder	4 (3)	1.7	3 (2)	1.4	3 (3)	2.3	2 (2)	1.4	0.8 (0.3, 2.4)
Cardiac disorder	1 (1)	0.4	1 (1)	0 5	4 (4)	3.2	3 (4)	2.1	0.9 (0.2, 3.2)
Opportunistic Infection	1 (1)	0.4	1 (1)	0 5	1 (1)	0.8	1 (1)	0.7	1.1 (0.2, 7.7)

Source: FDA safety analysis
[1] Number of patients with event (percent)
[2] Incidence rate of first event per 100 person-years
[3] Relative risk of event (95% confidence interval) comparing transition from EU-approved Remicade to CT-P13 with CT-P13 maintenance based on DerSimonian-Laird random effects meta-analysis of results from Studies 1.3 and 3.2
[4] Definitions of Adverse Events of Special Interest:
Latent TB: All preferred terms with latent tuberculosis or Mycobacterium tuberculosis complex test
Active TB: All preferred terms with tuberculosis not classified as latent TB
Infection: All events in infections and infestations system organ class
Serious Infection: All events in infections and infestations system organ class classified as serious
Pneumonia: All preferred terms with pneumonia, bronchopneumonia, lobar pneumonia, or lower respiratory tract infection
Malignancy and Lymphoma: All preferred terms with cancer, carcinoma, lymphoma, neoplasm, or Myeloproliferative disorder
Infusion-related Reaction: See applicant's ISS SAP Appendix 2 for definition
Vascular Disorder: All events in vascular disorders system organ class
Cardiac Disorder: All events in cardiac disorders system organ class
Opportunistic Infection: All preferred terms with Herpes zoster, Oesophageal candidiasis, Oral candidiasis, or Varicella

Infections

In the CT-P13 clinical development program, the overall incidence and types of infections were similar between CT-P13 and EU-approved Remicade. During the controlled periods of the CT-P13 clinical studies, 15/430 (3.4%) patients treated with CT-P13, compared to 10/422 (2.4%) patients treated with EU-approved Remicade experienced serious infection. This difference was driven by numerical imbalance in cases of TB and pneumonia as discussed below.

Active tuberculosis (TB)
In the controlled studies 5 cases of active TB were reported in CT-P13 treated patients (3 in RA, and 2 in AS) compared to 1 case of active TB in the EU-approved Remicade group in AS patient. Two additional cases were reported during the extension study 1.3 in AS, one in a patient who continues CT-P13 and one in a patient who transitioned from EU-approved Remicade to CT-P13. Two cases of active TB were also reported in the supportive study 1.2 in the Philippines. Most of the cases occurred in endemic areas. Of note, three patients from Philippines (Study 3.1 – 1 patient; and study 1.2 – 2 patients) treated with CT-P13, received a clinical diagnosis of TB based on investigator's judgment without a histopathological or microbiological confirmation of presence of M. tuberculosis in clinical samples. Tuberculosis

Reference ID: 3775998

is a well-recognized safety risk with TNF inhibition, including with infliximab. The slight numerical imbalance in the incidence of TB between CT-P13 and EU-approved Remicade is likely to reflect a chance finding. Furthermore, the numerical imbalance in the cases of active TB between the two treatment groups cannot be explained by the known analytical or functional differences between the molecules.

Pneumonia
During the controlled safety period in studies 3.1 and 1.1, 10 cases of pneumonia (8 in RA and 2 in AS patients respectively) were reported in CT-P13 treated subjects (2%) compared to 5 cases of pneumonia (RA patients only) in the EU-approved Remicade group (1%). Only one case of pneumonia was reported in the extension studies that occurred in the CT-P13 maintenance group in the RA study. The numerical differences between the two treatment groups were small and this imbalance was not observed in the Japanese RA study B1P13101 where 2 patients developed pneumonia in the CT-P13 group (4%) versus 4 patients in the EU-approved Remicade group (8%). Serious infections, including pneumonia, are a well-recognized safety risk with TNF inhibition, including with infliximab.

Overall, the incidence and pattern of infections observed in the CT-P13 clinical program are consistent with the safety profile of the US-licensed Remicade and do not indicate a new safety concern. Dr. Waheed and I agree that the observed numerical imbalance in active TB and pneumonia does not indicate a clinically meaningful difference between CT-P13 and US-licensed Remicade.

Vascular Disorders

Small numerical differences were reported in the Vascular Disorders SOC driven by hypertension. Overall, 19 (4%) and 11 (3%) patients reported hypertension in the CT-P13 and EU-approved Remicade groups respectively, in the controlled studies 1.1 and 3.1. The majority of the adverse events were mild or moderate and were explained by higher baseline incidence of hypertension in CT-P13 group. Among patients with no baseline hypertension, the incidence of new onset hypertension was similar between CT-P13 and EU-approved Remicade treated patients. This imbalance was not associated with differences in major cardio-vascular outcomes in the CT-P13 clinical program where 2 cases of myocardial infarction were reported in each treatment group.

Infusion-Related Reactions and Drug Hypersensitivity

Infusion-related reactions were defined as: (1) Hypersensitivity, drug hypersensitivity, anaphylactic shock, anaphylactic reaction or infusion-related reaction with a possible, probably or definite relationship to study medication, or (2) TEAE term related to hypersensitivity or infusion-related reactions with a possible, probably or definite relationship to study medication, or (3) Signs and/or symptoms related to hypersensitivity or infusion-related reactions for which the TEAE start date matches an infusion date and classified as “possible, probably or definite” relationship to study drug. In the CT-P13 controlled studies 1.1 and 3.1, 41/430 (10%) patients in the CT-P13 group and 58/422 (14%) patients in the EU-approved Remicade group experienced infusion-related reaction or drug hypersensitivity. Importantly,

Reference ID: 3775998

the incidence of such reactions did not increase after patients transitioned from EU-approved Remicade to CT-P13 (10/227 or 4%) compared to patients who continued on CT-P13 (18/249 or 7%) in studies 3.2 and 1.3.

Anaphylaxis

Based on pre-submission discussions and recommendations by the Agency, Celltrion conducted analysis of the safety database to identify cases of anaphylaxis defined by the criteria described by Sampson et al. (2006). In the CT-P13 controlled studies 1.1 and 3.1, 7/430 (1.6%) patients in the CT-P13 group and 7/422 (1.7%) patients in the EU-approved Remicade group experienced anaphylaxis. Importantly, there were no cases of anaphylaxis in patients who transitioned from EU-approved Remicade to CT-P13 in the extension studies 3.2 and 1.3.

The analysis of the overall incidence of infusion-related reaction or drug hypersensitivity, including anaphylaxis, indicate that transitioning of non-treatment naïve patients to CT-P13 is not likely to result in clinically significant reactions. These results are also consistent with the similar incidence of anti-drug antibodies between patients who transitioned from EU-approved Remicade to CT-P13 compared to patients who continued on CT-P13 in the same extension studies 3.2 and 1.3 as detailed in Section Immunogenicity below.

Common AE

Adverse events in the Infections and Infestations SOC were the most common adverse events in the CT-P13 development program with event rates similar between CT-P13 and the comparator products. The most frequently reported infections included nasopharyngitis, upper respiratory tract infection, latent tuberculosis (latent TB), urinary tract infection. Adverse events in the Investigations SOC, ALT and AST elevations, were the next most common adverse events, followed by Gastrointestinal SOC with diarrhea, abdominal pain and nausea, and Nervous System SOC with headache and dizziness, with similar incidence rates across all treatment groups in the controlled periods of the studies. The common adverse event profile remained consistent during the long-term extension studies 1.3 and 3.2, and comparable between subjects who transitioned from EU-approved Remicade to CT-P13 and those who continued on CT-P13.

Laboratory Abnormalities, Vital Signs and Electrocardiograms (ECGs)

Cases of CTCAE Grade 3 and 4 cytopenia, ALT and AST abnormalities were reported sporadically in the CT-P13 clinical studies with similar rates between CT-P13 and the comparator products. The distribution of laboratory findings, vital signs and electrocardiogram (ECGs) findings was balanced between the CT-P13 and EU-approved Remicade groups. No new or unexpected laboratory findings were reported in CT-P13 clinical program.

- **Immunogenicity**

Clinical Pharmacology Reviewer: Lei He, Ph.D.

Reference ID: 3775998

Clinical Pharmacology Team Leader (acting): Ping Ji, Ph.D.
Clinical Primary Reviewer: Juwaria Waheed, M.D.
Immunogenicity Reviewer: William Hallett, Ph.D.
Immunogenicity Team Leader (acting): Harold Dickensheets, Ph.D.

Immunogenicity was assessed using a validated ELISA method (study 1.4) and ECLA assay (studies 1.4, 1.1, and 3.1). The incidence rates of anti-drug antibody (ADA) formation in CT-P13 clinical program is summarized in Table 13 by assay and time point of assessment.

Table 13. Comparison of Immunogenicity Across CT-P13 Clinical Studies (Study 1.4 in Healthy Subjects, Study 1.1 in Patients with AS, and Study 3.1 in Patients with RA)

Assay	Timepoint	Study 1.4 in Healthy Subjects (5 mg/kg single dose)			Study 1.1 in AS (5 mg/kg at week 0, 2, 6, and then q8w to week 54)		Study 3.1 in RA (3 mg/kg at week 0, 2, 6, and then q8w to week 54)		Study 1.3 in AS (5 mg/kg q8w)		Study 3.2 in RA (3 mg/kg q8w)	
		CT-P13 (N=70)	EU (N=71)	US (N=70)	CT-P13 (N=125)	EU (N=125)	CT-P13 (N=302)	EU (N=304)	CT-P13 to CT-P13 (N=90)	EU to CT-P13 (N=84)	CT-P13 to CT-P13 (N=159)	EU to CT-P13 (N=143)
ECLA	Predose	--	--	--	2 (2%)	1 (<1%)	9 (3%)	6 (2%)	2 (2%)*	1 (<1%)*	7 (4%)*	4 (3%)*
	Week 8	10 (14.3%)	5 (7%)	2 (2.9%)	--	--	--	--	--	--	--	--
	Week 14	--	--	--	11 (9%)	13 (11%)	69 (23%)	70 (23%)	--	--	--	--
	Week 30	--	--	--	32 (25%)	25 (20%)	122 (40%)	122 (40%)	--	--	--	--
	Week 54	--	--	--	25 (20%)	28 (23%)	124 (41%)	108 (36%)	--	--	--	--
	Week 78	--	--	--	--	--	--	--	21 (23%)	25 (30%)	71 (44%)	66 (46%)
	Week 102	--	--	--	--	--	--	--	21 (23%)	23 (27%)	64 (40%)	64 (45%)
ELISA	Predose	4 (5.6%)	0	1 (1.4%)	--	--	--	--	--	--	--	--
	Week 8	19 (26.8%)	18 (25.4%)	8 (11.4%)	--	--	--	--	--	--	--	--

Source: Adapted from Dr. Waheed's Clinical Review, Table 29; *reflects the incidence of ADA positivity at the screening/predose visit in index clinical studies 1.1 and 3.1 of the patients who enrolled in the extension studies 1.3 and 3.2

Immunogenicity Results from Study 1.4

Study 1.4 is the only study comparing immunogenicity of CT-P13 with US-licensed Remicade, and evaluated immunogenicity after a single dose of 5 mg/kg. This study enrolled 213 healthy volunteers with 71 subjects in each treatment group: CT-P13, EU-approved Remicade and US-licensed Remicade. While the study met its primary objective of demonstrating PK similarity between the three products, some numerical differences were seen in the incidence and titer of ADA formation (Table 13):

- ADA positives by ELISA: CT-P13 19/71 patients (27%), EU-approved Remicade – 18/71 patients (25%) and US-Remicade – 8/71 patients (11%). The ELISA was used to re-analyze the samples in this study because ECLA had a higher degree of drug interference

Reference ID: 3775998

- ADA positives by ECLA (used in the rest of the clinical program): CT-P13 10/71 patients (14%), EU-approved Remicade – 5/71 patients (7%) and US-Remicade – 2/71 patients (3%)

Screening assay ADA titers were overlapping between US-licensed and EU-approved Remicade, but trended higher (though still overlapping) with CT-P13. All of the screening assay positive ADAs were confirmed to be neutralizing antibodies. The neutralizing antibody titers were also numerically higher when CT-P13 was compared to either US-licensed Remicade or EU-approved Remicade. However, no assay-related or subject-related factors could be identified to explain the reported differences. Detailed review of the potential product-related factors that could have contributed to the observed differences in ADA formation in study 1.4 identified a relatively higher content of subvisible particulates (1 to 5 µm) in CT-P13 compared to US-licensed Remicade lots used in study 1.4.

Overall, the observed differential ADA formation in study 1.4 did not impact the PK similarity among the three products as shown in Table 4 and Figure 1 above. To further investigate the potential clinical impact of the observed ADA differences, the FDA clinical pharmacology review team examined the relationship between ADA and exposure parameters. The numerical differences in ADA titers did not appear to impact the PK similarity between these three treatment groups. Looking at the ADA positive subgroup alone, the 90% IC of geometric mean ratios for AUC0-t and C0-inf were within the acceptance range of 80-125% for all three comparisons, as shown in Table 14. While the 90% CI of Cmax was slightly high in this subgroup, this is probably a statistical anomaly and unlikely to be related to ADA formation, which would be expected to decrease exposure, if anything.

Table 14. Analysis of PK Parameters of Infliximab in Study 1.4 in the ADA Positive Subgroup

Parameter	LSM (T)	N	LSM (R)	N	GMR Ratio (%)	90% CI (%)
CT-P13 (T) vs US-licensed Remicade (R)						
Cmax	127.88	19	107.08	8	119.4	(103.8, **137.4**)
AUC0-t	25778.23	19	26308.54	8	98.0	(83.6, 114.8)
AUC∞	26241.01	19	27220.39	8	96.4	(81.6, 113.9)
CT-P13 (T) vs EU-approved Remicade (R)						
Cmax	127.88	19	123.66	18	103.4	(92.4, 115.7)
AUC0-t	25778.23	19	26274.80	18	98.1	(85.9, 121.1)
AUC∞	26241.01	19	26561.97	18	98.8	(86.2, 113.3)
EU-approved Remicade (T) vs US-licensed Remicade (R)						
Cmax	123.66	18	107.08	8	115.5	(101.7, **131.1**)
AUC0-t	26274.80	18	26308.54	8	99.9	(82.9, 120.3)
AUC∞	26561.97	18	27220.39	8	97.6	(80.3, 118.5)

Source: Adapted from Dr. He's Clinical Pharmacology Review, Table 15
CI: confidence interval; GMR: geometric mean ratio

In support of the similar immunogenic potential of CT-P13 to the US-licensed Remicade and EU-approved Remicade, the applicant provided experimental data showing that ADA to EU-approved Remicade from IBD patients cross-react similarly with US-Remicade and CT-P13

Reference ID: 3775998

by ELISA, indicating the three products have similar immune-dominant epitopes, consistent with a similar immunogenic potential. These data also suggest that the immune response difference observed in study 1.4 is not likely to be assay-related.

Immunogenicity Results from Study 3.1 and Study 1.1

Infliximab is known to be immunogenic and anti-infliximab antibodies have implications on both safety and efficacy. To examine the impact of immunogenicity on comparative safety and efficacy, ADAs were measured at pre-specified time points throughout the controlled clinical studies 3.1 and 1.1, and the extension studies 3.2 and 1.3. Using ECLA assay, in studies 3.1 in RA and 1.1 in AS patients, the rates of immunogenicity, assessed as the proportion of anti-drug antibody (ADA) positive patients, were similar between the CT-P13 and EU-licensed Remicade treatment groups for the duration of the studies with nearly all being neutralizing antibodies. In the two extension studies 3.2 and 1.3, the rates of ADA positivity were also similar between patients who transitioned from EU-approved Remicade to CT-P13 and those who remained on CT-P13. Further, the impact of immunogenicity on safety and efficacy in the controlled studies was similar between CT-P13 and EU-approved Remicade. As expected, the incidence of infusion related reactions was higher in ADA-positive compared to ADA-negative patients, as summarized in Table 15. However, within each ADA subpopulation there were no notable differences between CT-P13 and EU-approved Remicade.

Table 15. Incidence of Infusion-related Reactions and Anaphylaxis by ADA Status-Controlled Studies (All-Randomized Population)

		Rheumatoid Arthritis Study 3.1		**Ankylosing Spondylitis Study 1.1**		**Total**	
	ADA Seroconversion Subgroup	CT-P13 3mg/kg (n=302)	EU-Remi 3mg/kg (n=300)	CT-P13 5mg/kg (n=128)	EU-Remi 5mg/kg n=122)	CT-P13 (n=430)	EU-Remi (n=422)
Infusion Related Reaction	ADA +	23/169 (14%)	35/164 (21%)	6/44 (14%)	11/39 (28%)	29/213 (14%)	46/203 (23%)
	ADA -	7/133 (5%)	8/135 (6%)	5/84 (6%)	4/83 (5%)	12/217 (6%)	12/218 (6%)
Anaphylaxis	ADA +	4/169 (2%)	2/164 (1%)	1/44 (2%)	3/39 (8%)	5/213 (2%)	5/203 (3%)
	ADA -	2/133 (2%)	2/135 (2%)	0/84	0/83	2/217 (1%)	2/218 (1%)
Source: Adapted from Dr. Waheed's Clinical Review, Table 30							

Similarly, in the comparative clinical study 3.1, lower proportions of patients achieved ACR20 response in the ADA-positive subgroups as shown in Table 16. However, within each ADA subpopulation there were no notable differences between CT-P13 and EU-approved Remicade.

Reference ID: 3775998

Table 16. ACR20 Responder Rates by ADA Status in Study 3.1 (All-Randomized Population)

ADA Seroconversion Subgroup	Treatment	ACR20 Response Rate		
		Week 14	Week 30	Week 54
ADA Positive	CT-P13 3mg/kg	38/69 (55%)	74/121 (61%)	77/123 (63%)
	EU-Remicade 3mg/kg	38/70 (54%)	75/123 (61%)	65/109 (60%)
ADA Negative	CT-P13 3mg/kg	148/202 (73%)	106/129 (83%)	95/112 (85%)
	EU-Remicade 3mg/kg	135/202 (67%)	100/132 (76%)	90/111 (81%)
Source: Adapted from Dr. Waheed's Clinical Review, Table 31				

Collectively, these data indicate that the ADA formation does not differentially impact safety or efficacy between patients treated with CT-P13 and EU-approved Remicade.

- **Discussion of primary reviewer's comments and conclusions**

Dr. Waheed and I are in agreement that the currently submitted safety data and analyses are adequate to inform the conclusion of no clinically meaningful differences between CT-P13 and EU-approved Remicade in patients with RA and AS. The safety database submitted for CT-P13 is adequate to provide a reasonable descriptive comparison between the two products. The analysis of the data indicates a safety profile similar to that of US-licensed Remicade. There were no notable differences between CT-P13 and EU-approved Remicade in treatment-emergent adverse events, serious adverse events, adverse events leading to discontinuations, and deaths between the treatment groups. A numerical imbalance in serious infections, driven by several cases of tuberculosis and pneumonia, was observed in the controlled studies. The differences were small, and serious infections, including tuberculosis, are well-recognized risks with TNF-inhibition as indicated in the Boxed warning of this class of biological products. No cases of drug-induced liver injury were reported in CT-P13 clinical program. No new safety signals have been identified. The FDA safety analysis is in agreement with the applicant's.

- **Highlight differences between CDTL and review team with explanation for CDTL's conclusion and ways that the disagreements were addressed**
- **Discussion of notable safety issues (resolved or outstanding)**

In the course of the immunogenicity review, differences in sub-visible particulates between CT-P13, US-licensed Remicade and EU-approved Remicade lots used in study 1.4 were observed. The CMC and Immunogenicity review teams expressed concerns that these results may suggest analytical differences exist between CT-P13, US-licensed Remicade and EU-approved Remicade, which if real, could impact the adequacy of the analytical bridge between the three products. Thus, they proposed the following to be conveyed as deficiency comments:

Reference ID: 3775998

1) *You provided data from a limited number of lots showing lower levels of subvisible particulates in the range of 1 to 5 microns in US-licensed Remicade compared to both CT-P13 and EU-approved infliximab. These apparent differences may be due to the limited number of lots of CT-P13, US-licensed Remicade and EU-approved infliximab used to perform the analysis. However, these results do not preclude that analytical differences may exist between US-licensed Remicade and EU-approved infliximab, which, if confirmed, could impact the assessment of the adequacy of the analytical bridge among the three products. To address this concern, provide the results of subvisible particulate analysis from additional CT-P13, US-licensed Remicade and EU-approved infliximab lots.*

2) *You conducted comparative clinical study CT-P13 1.4 to assess the immunogenicity of CT-P13 and US-licensed Remicade, and differences were observed in immunogenicity incidence rates between these products. This single dose, healthy volunteer study suggests a potential trend towards increased neutralizing immunogenic responses in CT-P13-treated subjects compared to the pooled group of subjects receiving either U.S.-licensed Remicade or EU-approved infliximab [27% vs. 19%, respectively (90% confidence Interval: -2.5%, +20%)]. Differences are also observed in binding antibody titers (mean transformed titers 4.74 vs 3.63 in CT-P13 and US-Remicade samples, respectively) and neutralizing antibody titers (mean transformed titers 3.42 vs 2.63, respectively. To address these differences, provide a rationale for why the results from study CT-P13 1.4 are in alignment with the conclusion that the immunogenicity profiles of CT-P13 and US-licensed Remicade are similar.*

I agree with the CMC/Immunogenicity review team that the applicant should provide additional information/analyses on subvisible particles from additional CT-P13, US-licensed Remicade and EU-approved Remicade lots and to provide additional justification that the differences in immunogenicity rates are not a reflection of differences in product quality attributes (subvisible particulates and other attributes). However, in the event the applicant provides sufficient information to demonstrate that CT-P13 and US-licensed Remicade are analytically highly similar, I do not believe that the observed imbalance in immunogenicity rates, on its own, is sufficient to preclude the conclusion of no clinically meaningful differences between CT-P13 and US-licensed Remicade.

In considering the significance of the numerical imbalances in the incidence and titer of ADA seen in study 1.4, I considered the following:

- The imbalance in ADA incidence and antibody titers seen in study 1.4 was not associated with a difference in PK.
- The low incidence of immunogenicity with US-licensed Remicade (3% by ECLA or 11% by ELISA) in study 1.4, is not consistent with the published data (Udata et al 2014) comparing US-licensed Remicade and EU-approved Remicade showed similarly high immunogenicity after a single-dose (28% and 33% ADA positive, respectively) in healthy volunteers and the 10 to 50% immunogenicity rates reported in the US-licensed Remicade USPI. This raises questions about whether study 1.4 results might be an artifact of sampling a limited range of US-licensed Remicade lots.
- Using the same ECLA assay, the apparent differences in immunogenicity between CT-P13 and EU-approved Remicade observed in study 1.4 (14.3% vs 7%, respectively)

Reference ID: 3775998

were not consistent with the similar immunogenicity rates between the two products at all time points in the larger clinical studies 3.1 and 1.1 where two distinct patient populations, RA and AS, were administered two different approved dosing regimens (either 3 mg/kg of study product on the background of methotrexate or a monotherapy of 5 mg/kg of study product, respectively) (see Table 13).

- The ADA formation impacted safety and efficacy similarly in CT-P13 and EU-approved Remicade treated patients in clinical studies 3.1 and 1.1 (see Table 15 and Table 16).
- Immunogenicity and hypersensitivity reactions did not appear to increase after a single transition from EU-approved Remicade to CT-P13 in studies 3.2 and 1.2 (see Table 13).

Therefore, there is sufficient data supporting similar immunogenicity between CT-P13 and EU-approved Remicade and that immunogenicity does not result in clinically meaningful differences between these products. While study 1.4 is the only data available to compare the immunogenicity of CT-P13 vs. US-licensed Remicade, publically available data on the immunogenicity of US-licensed Remicade suggest that the results of study 1.4 are not consistent with what is known of the immunogenicity of US-licensed Remicade. Publically available data also support similar immunogenicity between EU-approved Remicade and US-licensed Remicade. In light of these additional contextual pieces, I do not believe the results of study 1.4 are likely to represent real or clinically meaningful differences between US-licensed Remicade and CT-P13. Thus, I did not agree with the proposed immunogenicity deficiency Comment #2 above, or that the apparent differences in immunogenicity rates should on their own, preclude the approval of CT-P13 as a biosimilar. After further internal discussions (which occurred after the CMC and Immunogenicity reviews were archived), and correction of the data on neutralizing antibody titers which resulted in a smaller difference between CT-P13 and US-licensed Remicade (see Immunogenicity review amendment), the CMC and Immunogenicity review teams were in alignment with the clinical and clinical pharmacology teams' view that the difference in immunogenicity rates did not rise to the level of a deficiency which would preclude approval. Comment #2 was modified and included as an additional comment as detailed in the Recommended Comments to Applicant section at the end of this document.

9. Extrapolation of Data to Support Biosimilarity in Other Conditions of Use

Celltrion seeks licensure for all indications for which US-licensed Remicade is licensed (listed in the Introduction section above). The CT-P13 clinical program however, provides clinical efficacy and safety data primarily from clinical studies in patients with RA, and AS. There were no clinical studies in the remaining indications being sought for licensure.

As described in the Guidance for Industry: "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009", as a scientific matter, the FDA has determined that differences between conditions of use

Reference ID: 3775998

(including indications) with respect to the factors addressed in a scientific justification for extrapolation do not necessarily preclude extrapolation. If a biological product meets the statutory requirements for licensure as a biosimilar product under section 351(k) of the PHS Act based on, among other things, data derived from a clinical study or studies sufficient to demonstrate safety, purity, and potency in an appropriate condition of use, the potential exists for that product to be licensed for one or more additional conditions of use for which the reference product, i.e. US-licensed Remicade, is approved.[10] The applicant needs to provide sufficient scientific justification for extrapolation, which should address, for example, the following issues for the tested and extrapolated conditions of use:

- The mechanism(s) of action (MOA), if known or can reasonably be determined, in each condition of use for which licensure is sought
- The pharmacokinetics (PK) and bio-distribution of the product in different patient populations
- The immunogenicity of the product in different patient populations
- Differences in expected toxicities in each condition of use and patient population
- Any other factor that may affect the safety or efficacy of the product in each condition of use and patient population for which licensure is sought.

Consistent with the principles outlined in the above FDA guidance, Celltrion has provided a justification for the proposed extrapolation to all indications approved for US-licensed Remicade, as summarized in this section.

Extrapolation of Data to Support Biosimilarity in PsO, PsA

The primary MOA of infliximab is direct binding and blocking of TNF receptor-mediated biological activities. Infliximab binds to both soluble (s) and transmembrane (tm) TNF, thus blocking TNF binding to its receptors TNFR1 and TNFR2 and the resulting downstream pro-inflammatory cascade of events. The scientific literature indicates that this MOA is the primary MOA in RA, AS, PsA, PsO. The data provided by Celltrion showed similar TNF binding and potency to neutralize TNFα, supporting the demonstration of analytical similarity pertinent to this MOA.

Other issues considered in the scientific justification for extrapolation of data to support biosimilarity in PsO and PsA include:

- Clinical PK: No major differences in the PK of infliximab at a given dose are expected among the populations in which US-licensed Remicade is approved
- Immunogenicity/anti-product antibody formation with US-licensed Remicade was influenced by dose (lower likelihood with higher doses and more immunosuppression) and use of concomitant immunosuppressants (lower with concomitant use). In both the PsO and PsA indications, the recommended dose is 5 mg/kg. Infliximab is used without methotrexate in PsO and may be used with or without MTX in PsA. These usage scenarios were assessed in Celltrion's RA study (concomitant use of

[10] Guidance for Industry "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009", April 2015
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444661.pdf

Reference ID: 3775998

methotrexate) and Celltrion's AS study (use of the higher dose of 5 mg/kg, but without concomitant immunosuppressive therapy). No additional indication-specific concerns related to immunogenicity are expected.

- Because the RA and AS studies evaluate usage scenarios of concomitant methotrexate (common for RA and PsA) and 5 mg/kg dose (common for AS and PsA/PsO), and the primary MOA is believed to be the same in RA, AS, PsA, and PsO, it is reasonable to extrapolate conclusions regarding similar efficacy and safety of CT-P13 and US-licensed Remicade to PsA and PsO.

Extrapolation of Data to Support Biosimilarity in Inflammatory Bowel Disease (IBD) Indications

TNF plays a central role in the pathogenesis of IBD, and TNF inhibition is important in treating the disease, as evidenced by the efficacy of the approved TNF monoclonal antibodies, but the detailed cellular and molecular mechanisms involved remain unknown.[11] However, the scientific evidence suggests that for TNF inhibitors in IBD, in addition to binding and neutralization of sTNF, other MOA, listed in Table 3 may play a role.[12] Binding to sTNF and tmTNF involves the Fab region of the antibody, while the other mechanisms of action involve the Fc region of the molecule.

As outlined in CMC section above, Celltrion provided experimental data arguing in favor of similarity between CT-P13 and US-licensed Remicade and addressing each of the presumed mechanisms of action of US-licensed Remicade listed in Table 3.

As detailed in the CMC section above, CT-P13 showed ~25% lower FcγRIIIa/b binding affinity which was paralleled by ~20% lower activity in inducing ADCC in select assays (using NK cells expressing the high affinity V allele of FcγRIIIa), as compared with US-licensed Remicade and EU-licensed Remicade. At the time of this review, there is insufficient information on the consistency of the apparent FcγRIIIa binding/ADCC differences to determine whether these represent analytical differences that would preclude a determination that CT-P13 and US-licensed Remicade are highly similar. If the residual uncertainty in analytical similarity is resolved, then the remaining question is whether the apparent FcγRIII binding/ADCC differences translate into a clinically meaningful difference. The CMC review team has suggested that clinical data in IBD may be helpful in resolving this question. However, ADCC is only one possible mechanism among many in the IBD indications, as summarized in Table 3. It is noteworthy that products without ADCC have been approved for IBD (i.e. certolizumab) while other products with ADCC capability do not appear to be effective for IBD (i.e. etanercept). Therefore it is unclear whether IBD would have the assay sensitivity for exploring this question. If analytical structural characterization data are determined to support a conclusion of highly similar, and in light of the remaining functional data, including other ADCC assays, which support a conclusion of highly similar, and in the

[11] Oikonomopoulos A et. al, Anti-TNF Antibodies in Inflammatory Bowel Disease: Do We Finally Know How it Works?, Current Drug Targets, 2013, 14, 1421-1432
[12] Tracey D et al, Tumor necrosis factor antagonist mechanisms of action: A comprehensive review, Pharmacology & Therapeutics 117 (2008) 244–279

Reference ID: 3775998

absence of a clinical model where ADCC is known to be an important MOA for the molecule, I am of the opinion that the observed fractional difference in these particular assays should be considered not to be relevant to clinical activity. However, the applicant should consult with the Agency to discuss next steps to support a demonstration of biosimilarity and extrapolation of the data to support biosimilarity in IBD, after additional data is obtained on the consistency of the apparent FcγRIIIa binding/ADCC differences.

10. Advisory Committee Meeting

An Advisory Committee (AC) meeting was determined to be necessary to obtain independent expert advice on issues related to analytical similarity assessment and extrapolation to non-studied indications. The AC meeting was scheduled for March 17, 2015. However, due to questions regarding the adequacy of the data to determine whether CT-P13 is highly similar to US-licensed Remicade, as detailed in Section CMC, and the need for additional information, the AC was postponed.[13] As of the time of this review, a revised date for the AC has not been determined.

11. Pediatrics

- **PeRC Review Outcome-PMCs, deferrals, waivers, pediatric plan, pediatric assessment**

Under the Pediatric Research Equity Act (PREA), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable. Section 505B(m) of the FD&C Act added by section 7002(d)(2) of the Affordable Care Act, provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a new "active ingredient" for purposes of PREA, and a pediatric assessment is required unless waived or deferred. Thus, if CT-P13 requests licensure as a biosimilar product, its application would trigger PREA and Celltrion must address PREA requirements for every indication for which they are seeking licensure.

Following revisions to the initial pediatric study plan (iPSP), based on Agency's feedback, Celltrion submitted an agreed iPSP to address the PREA requirements for the following indications as detailed below:

- Rheumatoid Arthritis (RA): (b) (4)

[13] http://www.fda.gov/AdvisoryCommittees/Calendar/ucm433919 htm

(b) (4) The applicant has also submitted requests for waiver of the requirement to submit a pediatric assessment for (1) patients ages 2 to < 4 years old because CT-P13 does not represent a meaningful therapeutic benefit over existing therapies and is not likely to be used in a substantial number of pediatric patients with the condition and (2) patients < 2 years old because condition is rare in this age group and such studies would be impossible or highly impracticable.

- Ankylosing Spondylitis (AS), Psoriatic Arthritis (PsA): The applicant has submitted requests for waiver of the requirement to submit a pediatric assessment for juvenile AS and juvenile PsA because the studies would be impossible or highly impracticable due to the difficulty of making specific diagnoses of juvenile PsA or juvenile AS in the pediatric age range.

- Crohn's Disease (CD), Pediatric CD, Ulcerative Colitis (UC), (b) (4) With this BLA, Celltrion proposed that the pediatric assessment is fulfilled for pediatric CD patients 6 years of age and older by satisfying the statutory requirements for showing biosimilarity and providing an adequate scientific justification for extrapolating the pediatric information from the reference product to CT-P13. (b) (4) The applicant has also requested a waiver of the requirement to submit a pediatric assessment for pediatric CD (b) (4) patients younger than 6 years of age because such studies are impossible or highly impracticable. This request is not inconsistent with DGIEP's determination, based on recent epidemiologic data, that a pediatric assessment for pediatric CD (b) (4) patients should be conducted in patients 2 years and older, as opposed to previously recommended cut-off of 6 years of age and older. DGIEP however, acknowledges that in this case, dedicated pediatric studies in pediatric CD (b) (4) patients in only ages 2 to 5 years old would be impossible or highly impracticable due to the low incidence of the disease in this pediatric age group.

- Plaque Psoriasis: With this submission, Celltrion submitted a request for a waiver of the requirements for pediatric assessment in patients with pediatric chronic severe plaque psoriasis ages 0 to less than 17 years old due to safety concerns (b) (4) .

The CT-P13 pediatric study plan was discussed at the Pediatric Review Committee (PeRC) meeting on April 29, 2015. The PeRC agreed with the requested waivers (b) (4). PeRC also recommended granting the requested waiver of the requirement to submit a pediatric assessment for pediatric CD (b) (4) patients 2 to 5 years old because dedicated

Reference ID: 3775998

pediatric studies in this age group would be impossible or highly impracticable due to the low incidence of the disease in this pediatric age group.

12. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP)—**Not warranted, no issues.
- **Exclusivity or patent issues of concern**—The CDER Exclusivity Board has reviewed the application on October 03, 2014, and has determined that the dates that are 4 and 12 years after the date of first licensure of Remicade (infliximab) are August 24, 2002, and August 24, 2010, respectively. A licensure of a supplement does not trigger a separate period of exclusivity. Accordingly, section 351(k)(7) of the PHS Act does not prohibit the submission, or approval, of any 351(k) application for a proposed biosimilar to Remicade (infliximab). Celltrion's 351(k) BLA requests licensure for pediatric ulcerative colitis. However, this indication is protected by orphan drug exclusivity expiring on September 23, 2018 (see the Orphan Drug Designations and Approvals database at http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm).
- **Financial disclosures**—No issues.
- **Other GCP issues**—No issues.
- **OSI audits—**Four clinical sites covering the comparative clinical study 3.1 in RA and the supportive clinical study 1.1 in AS were selected for inspection. For three sites in Poland the conclusion was that no regulatory action was indicated. The site in Chile received a voluntary action indicated letter because of inadequate investigational drug accountability and preparations records for several subjects. In response, the investigator has taken appropriate preventive and corrective actions to address the deficiencies. Celltrion's site in The Republic of Korea underwent OSI inspection from April 6 to 10, 2015. The overall conclusion was that no regulatory action was indicated based on observations of adequate oversight of the clinical trials with adequate monitoring of the investigator sites and no evidence of under-reporting of adverse events. The inspection findings supported the acceptability of the clinical data submitted.
- **Other discipline consults**—Not applicable
- **Any other outstanding regulatory issues**—Not applicable

13. Labeling

- **Proprietary name**

The initially proposed proprietary name for CT-P13 was (b) (4). This name has been reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) and by the Office of Prescription Drug Promotion (OPDP, formerly the Division of Drug Marketing and Advertising) and was found to be conditionally acceptable. Subsequently, on November 27,

Reference ID: 3775998

2014, the applicant proposed a second proprietary name, Inflectra. The applicant clarified that in the US, CT-P13 will be marketed only as Inflectra to avoid medication errors. The proposed second proprietary name, Inflectra, was also found acceptable by DMEPA and OPDP. The applicant subsequently requested withdrawal of the proposed proprietary name (b) (4) in the US, and it was considered withdrawn as of February 10, 2015.

- **Address important issues raised by brief discussion of OPDP and OSE Division comments**

The reviewer from the Division of Medication Error Prevention and Analysis (DMEPA), Office of Surveillance and Epidemiology (OSE) noted that the proposed label and labeling reference the proprietary name (b) (4). As the applicant informed FDA on February 10, 2015 that they intend to market this product with the proprietary name Inflectra, DMEPA review team recommended replacing the originally proposed use of the proprietary name (b) (4)" with the proprietary name "Inflectra" throughout the label and labeling.

Labeling discussions however, have not been initiated with the applicant as a complete response action is recommended.

- **Physician labeling**

The applicant proposed a labeling closely mirroring the labeling of US-licensed Remicade. In addition, the applicant proposed inclusion in:

(1) Section 6.1, Adverse Reactions: (b) (4)

(2) Section 12.3, Pharmacokinetics:
- Study description and pharmacokinetic data from study 1.4 in healthy volunteers, and
- A summary statement on pharmacokinetic data from studies 3.1 in RA, (b) (4)

(3) Section 14, Clinical Studies:
- Study description and efficacy results, including clinical response, radiographic response, and physical function from study 3.1 in RA
- Study description (b) (4) and efficacy results from study 1.1 in AS in Section 14, Clinical Studies.

Labeling discussions however, have not been initiated with the applicant as a complete response action is recommended.

- **Highlight major issues that were discussed, resolved, or not resolved at the time of completion of the CDTL review**

As discussed above.

- **Carton and immediate container labels (if problems are noted)**

Reference ID: 3775998

As discussed above in the DMEPA review and recommendations.

- **Patient labeling/Medication guide (if considered or required)**

As discussed above in the DMEPA review and recommendations.

14. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

I recommend a complete response action on BLA 125,544 due to deficiencies detailed in the Recommended Comments to Applicant section below.

- **Totality of the Evidence**

Celltrion submitted comparative analytical data on the CT-P13 lots used in clinical studies intended to support a demonstration of biosimilarity ("clinical product lots") and on the proposed commercial product. Based on the review of the data provided, Celltrion's analytical data for CT-P13 does not provide sufficient information to conclude that CT-P13 is highly similar to the reference product (US-licensed Remicade). Specifically, apparent differences in functional activity, namely FcγRIII binding and some of the ADCC by NK cells, are not explained by consistent glycoform pattern differences between CT-P13, US-licensed Remicade and EU-approved Remicade.

The proposed commercial CT-P13 drug product used to support the original BLA submission also has slightly higher protein content than that of US-licensed Remicade. The higher protein content of the proposed commercial CT-P13 appeared to be a manufacturing issue; however, this was resolved by manufacturing, control, and validation strategies implemented during the review cycle.

Due to the fact that Celltrion used a non-US-licensed comparator (European Union-approved Remicade (EU-approved Remicade)) in its clinical program, Celltrion was required to scientifically justify the relevance of that data to a demonstration of biosimilarity to the US-licensed reference product. While the 3-way PK data support one aspect of the scientific bridge between EU-approved and US-licensed Remicade, as well as PK similarity of CT-P13 to both of these products, a final conclusion regarding the relevance of the comparative clinical data obtained using EU-approved Remicade to a determination of biosimilarity to US-licensed Remicade is pending the additional CMC information needed to confirm the 3-way analytical bridge between products to establish an adequate scientific bridge.

The nonclinical Pharmacology/Toxicology program demonstrated similar human tissue binding profile, off-target toxicity profiles, and PK/TK profiles between CT-P13 and EU-Remicade.

Reference ID: 3775998

The results of the clinical development program indicate that, assuming the bridge between EU-approved and US-licensed Remicade is confirmed, the applicant's data would meet the requirement for a demonstration of "no clinically meaningful differences" between CT-P13 and the US-licensed reference product in terms of safety, purity, and potency in the indications studied. Specifically, the results from the comparative clinical efficacy, safety, and PK studies, which included two different chronic dosing regimens of CT-P13 and EU-approved Remicade (3 mg/kg on the background of methotrexate, and 5 mg/kg as monotherapy) in two distinct patients populations (RA and AS), and a single dose of 5 mg/kg in healthy subjects of CT-P13, EU-approved Remicade, and US-licensed Remicade, adequately supported the determination that there are no clinically meaningful differences between CT-P13 and US-licensed Remicade in RA and AS. Further, the transition from EU-approved Remicade to CT-P13 during the long-term extension studies in RA and AS did not result in worsening safety or immunogenicity. This would support the safety of the clinical scenario where non-treatment naïve patients would transition to CT-P13.

The submitted clinical pharmacology studies are adequate to (1) support the demonstration of PK similarity between CT-P13 and US-licensed Remicade, (2) establish a PK bridge to justify the relevance of the data generated using EU-approved Remicade, (3) justify the relevance of the PK findings from the CT-P13 clinical program to all the indications for which the applicant is seeking licensure.

Although the clinical data do not suggest that there are clinically meaningful differences between CT-P13 and EU-approved Remicade; nor are there differences in PK between CT-P13, EU-approved Remicade and US-licensed Remicade, based on the currently available data, there is insufficient information to conclude that CT-P13 and US-licensed Remicade are highly similar, and to confirm the 3-way analytical bridge between products that would provide an essential element of the rationale for the applicability of comparative clinical data. Therefore, at this time, this application does not meet the requirements for licensure as a biosimilar product under section 351(k) of the PHS Act.

Extrapolation of Data to Support Biosimilarity in Non-studied Conditions of Use

Conclusions regarding the ability to extrapolate data to support biosimilarity in non-studied conditions of use are pending additional information to clarify the existence, extent, and consistency of FcγRIIIa binding and ADCC differences.

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies**

Not applicable.

- **Recommendation for other Postmarketing Requirements and Commitments**

Not applicable.

Reference ID: 3775998

- **Recommended Comments to Applicant**

Deficiencies precluding approval of BLA 125,544:

1. You provided data from a limited number of lots showing lower levels of subvisible particulates in the range of 1 to 5 microns in US-licensed Remicade compared to both CT-P13 and EU-approved Remicade. The observed differences may be due to the limited number of lots of CT-P13, US-licensed Remicade and EU-approved Remicade used to perform the analysis. However, these results suggest that analytical differences may exist between US-licensed Remicade and EU-approved Remicade, which, if confirmed, could impact the assessment of the adequacy of the analytical bridge between the three products. To address this concern, provide results of subvisible particulate analysis from an adequate number of additional CT-P13, US-licensed Remicade, and EU-approved Remicade lots.

2. You evaluated the analytical similarity of CT-P13 and US-licensed Remicade using a variety of functional assays. Your data generated using a standard NK-cell based killing ADCC assay suggest that CT-P13 has ~20% lower ADCC activity compared to the reference product US-licensed Remicade, which correlates with differences in FcγRIIIa binding. The difference in ADCC leads to residual uncertainty about whether CT-P13 is highly similar to US-licensed Remicade, as the role of ADCC remains uncertain in the clinical activity of the reference product (e.g., in the setting of inflammatory bowel disease). Furthermore, you did not adequately justify the impact of the difference in ADCC on the analytical similarity assessment and did not identify the structural basis underlying this difference. For example, you should determine whether the H2L1 variant that is present at relatively high levels in CT-P13 compared to US-licensed Remicade plays a role in decreasing NK-dependent ADCC activity. On the other hand, the Agency has not excluded the possibility that analysis of additional lots of CT-P13, US-licensed Remicade, and EU-approved Remicade lots could overcome a statistical anomaly due to the analysis of a limited number of lots. To this point, we note that prior differences in glycan patterns were reduced when additional lots of CT-P13, US-licensed Remicade and EU-approved Remicade were analyzed. To address the current deficiency with respect to differences in ADCC activity, we recommend that you repeat the evaluation of ADCC using additional lots to determine whether the ADCC difference you have reported was due to small sample size and decreases when additional lots are evaluated. If the difference in ADCC persists following analysis of additional lots, you should identify and demonstrate control of the product quality attributes that underlie ADCC activity in CT-P13 (e.g., glycan pattern, contribution of H2L1 variant, etc.) and provide an adequate justification, including an evaluation of the role of ADCC particularly in the setting of inflammatory bowel disease, that the observed difference in ADCC is not relevant to clinical activity.

Additional Comments:

3. You conducted comparative clinical study CT-P13 1.4 to assess the immunogenicity of CT-P13 and US-licensed Remicade, and differences were observed in immunogenicity

Reference ID: 3775998

incidence rates between these products. This single dose, healthy volunteer study suggests a potential trend towards increased neutralizing immunogenic responses in CT-P13-treated subjects compared to the pooled group of subjects receiving either U.S.-licensed Remicade or EU-approved Remicade [27% vs. 19%, respectively (90% confidence Interval: -2.5%, +20%)]. Differences are also observed in binding antibody titers (mean transformed titers 4.74 vs 3.63 in CT-P13 and US-Remicade samples, respectively) and neutralizing antibody titers (mean transformed titers 3.42 vs 2.63, respectively). To address these observations, provide a rationale for why the results from study CT-P13 1.4 are in alignment with the conclusion that the immunogenicity profiles of CT-P13 and US-licensed Remicade are similar.

4. The current drug product stability data using Process B batches of CT-P13 support an expiry date of 42, not (b) (4) months. To address this concern, adjust your proposed expiry dating to reflect existing data and provide a stability protocol to support post-approval expiry extension.

5. We acknowledge the plan outlined in your April 17, 2015, letter to develop and validate a revised version of the visible particle test for reconstituted drug product. The revised test will use (b) (4) and visual inspection of 20 reconstituted vials. Data supporting the assay revision have not been provided to the BLA. To address this concern, submit the assay SOP, validation report and revised specification to the Agency for review.

Reference ID: 3775998

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/s/

NIKOLAY P NIKOLOV
06/08/2015

Clinical Investigator Financial Disclosure
Review Template

Application Number: 125544

Submission Date(s): 08/08/2014

Applicant: Celltrion, Inc.

Product: CT-P13, a proposed biosimilar to US-licensed Remicade

Reviewer: Nikolay P. Nikolov, M.D.

Date of Review: 05/20/2015

Covered Clinical Study (Name and/or Number):

- CT-P13 3.1
- CT-P13 3.2
- CT-P13 1.1
- CT-P13 1.3
- CT-P13 1.4

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 486		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: N.A. Significant payments of other sorts: N.A. Proprietary interest in the product tested held by investigator: N.A. Significant equity interest held by investigator in sponsor of covered study: N.A.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to	Yes ☐	No ☐ (Request information

minimize potential bias provided:		from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Reviewer's Comment: The applicant has adequately disclosed financial interests and/or arrangements with clinical investigators by having submitted a signed Form FDA 3454 stating that none of the 116 principal investigators and the 370 sub-investigators in the covered clinical studies had a financial agreement with the sponsor or financial interest in the company.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NIKOLAY P NIKOLOV
05/21/2015

CLINICAL REVIEW

Application Type	351(k) BLA
Application Number(s)	125544
Priority or Standard	Standard
Submit Date(s)	August 8, 2014
Received Date(s)	August 8, 2014
PDUFA Goal Date	June 8, 2015
Division / Office	DPARP – lead division Collaborative review with DGIEP & DDDP
Reviewer Name(s)	Juwaria Waheed, MD
Review Completion Date	May 4, 2015
Nonproprietary Name	CT-P13
(Proposed) Trade Name	Inflectra
Therapeutic Class	TNF-inhibitor
Applicant	Celltrion, Inc.
Formulation	Intravenous (IV)
Dosing Regimens	• Rheumatoid Arthritis: In conjunction with methotrexate, 3mg/kg at 0, 2, and 6 weeks, then every 8 weeks increasing up to 10mg/kg or treating every 4 weeks • Ankylosing Spondylitis: 5mg/kg at 0, 2, and 6 weeks, then every 6 weeks • Psoriatic Arthritis, Plaque Psoriasis and Ulcerative Colitis: 5mg/kg at 0, 2, and 6 weeks, then every 8 weeks • Crohn's disease: 5mg/kg at 0, 2, and 6 weeks, then every 8 weeks increasing up to 10mg/kg in patients who initially respond but lose their response later

Reference ID: 3747317

Indications Sought

- Rheumatoid Arthritis in combination with methotrexate,
- Ankylosing Spondylitis
- Psoriatic Arthritis
- Plaque Psoriasis
- Crohn's Disease
- Pediatric Crohn's Disease
- Ulcerative Colitis
- Pediatric Ulcerative Colitis[1]

Intended Populations

- Rheumatoid Arthritis: moderate to severe disease
- Ankylosing Spondylitis: active disease
- Psoriatic Arthritis: active disease
- Plaque Psoriasis: chronic, severe disease
- Crohn's Disease: moderate to severe disease
- Pediatric Crohn's Disease: moderate to severe disease
- Ulcerative Colitis: moderate to severe disease
- Pediatric Ulcerative Colitis: moderate to severe disease[1]

1 This reflects information for Inflectra that Celltrion submitted on August 8, 2014. We note that the indication for pediatric ulcerative colitis is protected by orphan drug exclusivity expiring on September 23, 2018. See the Orphan Drug Designations and Approvals database at http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm.

Table of Contents

1 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT 9

1.1 Recommendation on Regulatory Action 9
1.2 Risk Benefit Assessment 9
1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies . 13
1.4 Recommendations for Postmarket Requirements and Commitments 13

2 INTRODUCTION AND REGULATORY BACKGROUND 13

2.1 Product Information 13
2.2 Tables of Currently Available Treatments for Proposed Indications 14
2.3 Availability of Proposed Active Ingredient in the United States 17
2.4 Important Safety Issues With Consideration to Related Drugs 17
2.5 Summary of Presubmission Regulatory Activity Related to Submission 17
2.6 Other Relevant Background Information 18

3 ETHICS AND GOOD CLINICAL PRACTICES 19

3.1 Submission Quality and Integrity 19
3.2 Compliance with Good Clinical Practices 20
3.3 Financial Disclosures 20

4 SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES 21

4.1 Chemistry Manufacturing and Controls 21
4.2 Clinical Microbiology 23
4.3 Preclinical Pharmacology/Toxicology 23
4.4 Clinical Pharmacology 24

5 SOURCES OF CLINICAL DATA 25

5.1 Tables of Studies/Clinical Trials 25
5.2 Review Strategy 27
5.3 Discussion of Individual Studies/Clinical Studies 28
Study 1.4: PK Similarity Study 28
Study 3.1: Comparative Clinical Study in RA 33
Study 1.1 PK Equivalence study in AS 40

6 REVIEW OF EFFICACY 43

Efficacy Summary 43
6.1 Indication 44
6.1.1 Methods 46
6.1.2 Demographics 46

Reference ID: 3747317

6.1.3 Subject Disposition 48
6.1.4 Analysis of Primary Endpoint(s) 49
6.1.5 Analysis of Key Secondary Endpoints(s) 51
6.1.6 Other Endpoints 60
6.1.7 Subpopulations 61
6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations 61
6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects 61
6.1.10 Additional Efficacy Issues/Analyses 61

7 REVIEW OF SAFETY 62

Safety Summary 62
7.1 Methods 63
7.1.1 Studies/Clinical Trials Used to Evaluate Safety 63
7.1.2 Categorization of Adverse Events 64
7.1.3 Pooling of Data Across Studies to Estimate and Compare Incidence 65
7.2 Adequacy of Safety Assessments 65
7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations 65
7.2.2 Explorations for Dose Response 66
7.2.3 Special Animal and/or In Vitro Testing 66
7.2.4 Routine Clinical Testing 66
7.2.5 Metabolic, Clearance, and Interaction Workup 66
7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class 66
7.3 Major Safety Results 67
7.3.1 Deaths 68
7.3.2 Nonfatal Serious Adverse Events 68
7.3.3 Dropouts and/or Discontinuations 69
7.3.4 Significant Adverse Events 72
7.3.5 Submission Specific Primary Safety Concerns 78
7.4 Supportive Safety Results 78
7.4.1 Common Adverse Events 78
7.4.2 Laboratory Findings, Vital Signs and Electrocardiograms (ECGs) 84
7.4.5 Special Safety Studies/Clinical Trials 84
7.4.6 Immunogenicity 85
7.5 Other Safety Explorations 88
7.5.1 Dose Dependency for Adverse Events 88
7.5.2 Time Dependency for Adverse Events 88
7.5.3 Drug-Demographic Interactions 88
7.5.4 Drug-Disease Interactions 88
7.5.5 Drug-Drug Interactions 88
7.6 Additional Safety Evaluations 88
7.6.1 Human Carcinogenicity 88
7.6.2 Human Reproduction and Pregnancy Data 88
7.6.3 Pediatrics and Assessment of Effects on Growth 89

Reference ID: 3747317

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound 89
7.7 Additional Submissions / Safety Issues 89

8 POSTMARKET EXPERIENCE 91

9 APPENDICES 92

9.1 Literature Review/References 92
9.2 Labeling Recommendations 92
9.3 Advisory Committee Meeting 92
9.4 Supportive Clinical Studies – Study Protocols 93
Study 1.2 (Pilot Study) 93
Study B1P13101 (Local Registration Study, Japan) 93
Study 3.3 (Local Registration Study, Russia) 94

Reference ID: 3747317

Table of Tables

Table 1. Small Molecule DMARDs Approved for RA in the United States..... 14
Table 2. Biologic DMARDs Approved for RA in the United States 15
Table 3. Biologics Approved for Psoriatic Arthritis in the United States..... 16
Table 4. Approved Products for the Treatment of AS in the United States..... 16
Table 5. Small Molecules Approved for Plaque Psoriasis in the United States..... 17
Table 6. Approved Biologic Therapies for Plaque Psoriasis in the United States..... 17
Table 7. Clinical Development - Controlled Studies 26
Table 8. Clinical Development - Extension Studies..... 27
Table 9 Baseline Demographic Characteristics in the Key Clinical Studies (Controlled Studies)..... 47
Table 10. Demographic Characteristics (Extension Studies) 48
Table 11. Patient Disposition..... 49
Table 12. Proportion of Patients Achieving ACR20 response at Week 30 - Study 3.1, All-randomized population 50
Table 13. Proportion of Patients Achieving ACR20 response at Week 30 - Study 3.1, Per-Protocol population 51
Table 14. Individual ACR components - Baseline Values and Change from Baseline at Weeks 14, 30 and 54 in Study 3.1 53
Table 15. DAS28 Disease Activity Scores in Study 3.1 (Per-protocol population) 55
Table 16. Proportion of Patients Achieving ACR20, ACR50 and ACR 70 at Weeks 30 and 54 (using Exact Binomial Method) in Study 3.1 - Per-Protocol Population 56
Table 17. SDAI and CDAI, Change from Baseline at Weeks 30 and 54 in Study 3.1 - Per-protocol Population 57
Table 18. Study 1.1 - Proportion of patients achieving ASAS20 and ASAS40 response - All randomized population..... 58
Table 19. Study 1.1 - BASDAI, BASFI, BASMI, and Chest Expansion Baseline And Change from Baseline Values - All Randomized Population 59
Table 20. Japanese Study - Proportion of Patients Achieving ACR20, 50 and 70 at Week 30..... 62
Table 21. Exposure to CT-P13: Number of Subjects receiving at least 1 dose of CT-P13 in Controlled and Extension Studies 64
Table 22. Summary of TEAEs - Controlled Studies 67
Table 23. Adverse Events Leading to Discontinuation – Controlled Studies..... 70
Table 24. Adverse Events Leading to Discontinuation – Extension Studies..... 71
Table 25. Adverse Events of Special Interest - Controlled Studies 73
Table 26. Adverse Events of Special Interest - Extension Studies..... 74
Table 27. Summary of Common Adverse Events (Reported in ≥3% of Subjects) - Controlled Studies..... 80
Table 28. Summary of Common Adverse Events (Reported in ≥3% of Subjects) - Extension Studies 83

Reference ID: 3747317

Table 29. Proportion of ADA Positive Patients - Controlled & Extension Studies (Safety Population) 85
Table 30. Incidence of Infusion-related Reactions and Anaphylaxis by ADA Status-Controlled Studies (All-Randomized Population) 86
Table 31. ACR20 Responder Rates by ADA Status in Study 3.1 (All-Randomized Population) 87
Table 32. Summary of TEAEs - Supportive Studies 90

Table of Figures

Figure 1. Study Design for Study 3.1 34
Figure 2. Study Design for Study 1.1 42

Reference ID: 3747317

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This biologic licensing application (BLA 125544) seeks approval of the product CT-P13 (proposed trade name: Inflectra) which is a proposed biosimilar to US-licensed Remicade (active ingredient infliximab, a TNFα-inhibitor). The biosimilar licensure pathway under section 351(k) of the Public Health Service Act (PHS Act) requires that the proposed biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between the proposed biosimilar and reference products in terms of safety, purity and potency. Both parts of the statutory definition need to be met to demonstrate biosimilarity, but the foundation of the data demonstrating biosimilarity is extensive structural and functional characterization to support a demonstration that the products are highly similar.

From a clinical standpoint, the data submitted to the 351(k) BLA from the clinical development program of CT-P13, support a demonstration of no clinically meaningful differences between CT-P13 and US-licensed Remicade in pharmacokinetic parameters and in the indications studied, i.e., rheumatoid arthritis (RA) and ankylosing spondylitis (AS). However, because of residual uncertainty in the analytical characterization data, specifically with respect to antibody-dependent cellular cytotoxicity (ADCC), it is not clear what clinical impact differences in ADCC may have on other indications for which Celltrion is seeking licensure and for which US-licensed Remicade is licensed. At the time of this review, there is insufficient information to determine the potential impact of these observed differences in ADCC and whether there are clinically meaningful differences between CT-P13 and US-licensed Remicade. As such, a conclusion of no clinically meaningful differences cannot be made based on the data and information provided to date. Therefore, based on the currently available data, this application does not meet the requirements for licensure as a biosimilar product under section 351(k) of the PHS Act.

1.2 Risk Benefit Assessment

Brief Overview of the Clinical Program

The following three controlled studies provide the primary evidence to support the determination of no clinically meaningful differences between CT-P13 and the reference product, US-licensed Remicade:

- Study 1.4 is a single-dose, 3-way pharmacokinetics (PK) study establishing the bridge between CT-P13, US-licensed Remicade and EU-approved Remicade. This bridge is necessary because the reference product of interest for this

Reference ID: 3747317

application is US-licensed Remicade, but the majority of the clinical program utilized EU-Remicade as the comparator. This study therefore provides justification for the relevance of EU-Remicade to the comparison of interest, which is US-licensed Remicade. Study 1.4 also provides the only data on immunogenicity allowing for a comparison between CT-P13 and US-licensed Remicade following single dose administration.

- Study 3.1 is the comparative clinical study that provides the efficacy data for CT-P13 in rheumatoid arthritis (RA). It was designed as a randomized, double-blind, parallel-group study.
- Study 1.1, although designed as a primary PK study between CT-P13 and EU-approved Remicade in ankylosing spondylitis (AS) patients, the study also captures safety and efficacy in AS as secondary endpoints. This was also a randomized, double-blind, parallel-group study.

Additional long-term safety and immunogenicity data for patients who had a single transition at week 54 from EU-approved Remicade to CT-P13 or continued to receive CT-P13 came from studies 3.2, and 1.3, open-label, long-term extension studies in RA and AS, respectively. With the exception of Study 1.4, the majority of the clinical program was conducted with minimal FDA input.

Clinical Efficacy Overview and Conclusions

Study 3.1, the comparative clinical study (CCS) in RA patients, met its primary objective of demonstrating that the proportion of patients achieving ACR20 response at week 30 was similar between the CT-P13 and EU-approved Remicade treatment groups [184 (61%), and 179 (59%) patients, respectively]. The 95% confidence interval (CI) for the estimate of the treatment difference was contained within the applicant's prespecified similarity margin of -15% to 15% (95% CI: -0.06, 0.10). Of note, as discussed in detail in the FDA statistical review, the Agency has determined that a ±12% similarity margin would be generally expected, based on considerations of the clinical importance of different losses in effect against the feasibility of the comparative clinical study. The results from the primary analysis were supported by consistent sensitivity analyses and were also within the margin preferred by the Agency. These results support the conclusion of no clinically meaningful differences between CT-P13 and EU-approved Remicade in the RA indication.

Analysis of key secondary efficacy endpoints in Study 3.1 including disease activity score-28 joints (DAS28), individual components of the ACR20 criteria, ACR50 and ACR70 responses showed similar results between CT-P13 and EU-approved Remicade treatment groups.

Study 1.1 in AS patients also met its key secondary efficacy endpoints by demonstrating that the proportion of patients achieving ASAS20 and ASAS40 responses at week 30 was similar between the CT-P13 and EU-approved Remicade treatment groups. These

Reference ID: 3747317

results provide further support of no clinically meaningful differences between CT-P13 and EU-approved Remicade in a different patient population and using a different dosing regimen, i.e. 5 mg/kg without background methotrexate immunosuppression.

Long-term extension studies 3.2 and 1.3 in RA and AS respectively demonstrated consistent efficacy up to week 102 with no difference between CT-P13 maintenance and CT-P13 transition groups.

Clinical Safety Overview and Conclusions

The safety evaluation plan of CT-P13 was based on the known safety profile of US-licensed Remicade as described in the USPI and other published data.

In summary, no new safety signals were identified in the CT-P13 group compared to the known adverse event profile of the reference product, US-licensed Remicade. Overall, there were no major differences in treatment-emergent adverse events, serious adverse events, adverse events leading to discontinuations, or deaths between the treatment groups. Infections were the most common adverse event in all treatment groups (CT-P13, US-licensed Remicade and EU-approved Remicade). Numerical differences in serious infections, driven by small number of cases of tuberculosis (TB), and pneumonia, were observed between CT-P13 and EU-approved Remicade in study 3.1. However, the differences are small and the types and overall incidence of the events are within what is expected from the US-licensed Remicade and do not indicate a clinically meaningful difference. Most frequent adverse events leading to discontinuation were hypersensitivity reactions, infusion-related reactions and infections. A total of four deaths occurred in the CT-P13 development program with 2 each in CT-P13 and EU-Remicade treatment groups. All deaths were assessed as unrelated to the treatment regimen. Cases of anaphylaxis were balanced between the two groups, with 7 cases in each group (CT-P13 and EU-Remicade). Rates of anaphylaxis did not increase following transition from EU-Remicade to CT-P13.

Immunogenicity Overview and Conclusions

In studies 3.1 and 1.1, comprised of RA and AS patients respectively, the rates of immunogenicity, assessed as the proportion of anti-drug antibody (ADA) positive patients, were similar between the CT-P13 and EU-licensed Remicade treatment groups for the duration of the study. Rates of ADA positivity were also similar between the two treatment groups, CT-P13 maintenance and CT-P13 transition groups, in the two extension studies 3.2 and 1.2. Further, the impact of immunogenicity on safety and efficacy in the controlled and extension studies was similar between the respective treatment groups.

In the extension studies, there was no appreciable difference in the proportion of ADA-positive patients following the single transition from EU-approved Remicade to CT-P13.

Reference ID: 3747317

Study 1.4 is the only study comparing immunogenicity of CT-P13 with US-licensed Remicade. This study enrolled 213 healthy volunteers with 71 subjects in each treatment group: CT-P13, EU-approved Remicade and US-licensed Remicade. While the study met its primary objective of demonstrating PK similarity between the three products, some numerical differences were seen in the incidence of immunogenicity. After a single dose administration of treatment drug at the start of the study, immunogenicity was measured at a single time point, Day 57, with the following results of patients testing positive for ADA by ELISA: CT-P13 19/71 patients (27%), EU-approved Remicade – 18/71 patients (25%) and US-Remicade – 8/71 patients (11%). Using ECLA assay (used in the rest of the clinical studies), which is more sensitive to circulating drug, ADAs to CT-P13 were higher (14% positive) versus US-licensed Remicade (3% positive) and EU-approved Remicade (7% positive). ADA titers were overlapping between US and EU Remicade, but trended higher (though still overlapping) with CT-P13. However, no assay-related or subject-related factors could be identified to explain the reported differences. In considering the clinical significance of these numerical imbalances, this reviewer considered the following:

- The immunogenicity imbalance seen in study 1.4 was not associated with a difference in PK.
- Published data (Udata et al 2014) comparing US-licensed Remicade and EU-approved Remicade showed similarly high immunogenicity after a single-dose (28% and 33% ADA positive, respectively) in healthy volunteers.
- Clinically significant differences in immunogenicity between CT-P13 and EU-approved Remicade were not observed in studies 3.1 and 1.1 where two distinct disease patients (RA and AS, respectively), were administered two different dosing regimens (either 3 mg/kg of study product on the background of methotrexate or a monotherapy of 5 mg/kg of study product, respectively).
- Immunogenicity and hypersensitivity reactions did not increase after a single transition from EU-approved Remicade to CT-P13 in studies 3.2 and 1.2.

Based on these considerations, the numerical imbalance in the incidence of immunogenicity following a single dose regimen in healthy volunteers seen in study 1.4, was not considered clinically relevant and does not preclude the conclusion of no clinically meaningful differences between CT-P13 and US-licensed Remicade.

Risk-Benefit Assessment

The clinical development program of CT-P13 provides evidence of no clinically meaningful differences in efficacy between CT-P13 and EU-approved Remicade in RA and AS. Safety analysis showed a similar assessment of adverse events, serious adverse events, adverse events leading to treatment discontinuations, and deaths between the two products. Small numerical differences in cases of tuberculosis and pneumonia were within the incidence rates expected for US-licensed Remicade and do not indicate a clinically meaningful difference.

Reference ID: 3747317

Extrapolation to Non-studied Indications

Celltrion is seeking licensure for the indications studied in the clinical program, i.e. RA and AS, as well as for psoriatic arthritis, plaque psoriasis, adult and pediatric Crohn's disease, or adult and pediatric ulcerative colitis[2] for which they have not submitted clinical data. To support the use of CT-P13 for the non-studied indications, Celltrion has provided a scientific justification relying on extrapolation of biosimilarity to those indications. The justification addresses issues for the testing and extrapolating conditions of use outlined in Guidance for Industry: "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009."

However, at this time we are unable to conclude there are no clinically meaningful differences in the indications that were not studied in the CT-P13 development program, specifically the inflammatory bowel disease (IBD) indications, due to residual uncertainty in the analytical data pertaining to ADCC, as a plausible mechanism of action in IBD, as discussed in Section 4.1 Chemistry Manufacturing and Controls. This impacts the determination of biosimilarity, as well as the justification for extrapolation.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No clinical postmarket risk evaluation and mitigation strategies are anticipated at this time.

1.4 Recommendations for Postmarket Requirements and Commitments

No postmarket requirements and commitments are anticipated at this time.

2 Introduction and Regulatory Background

2.1 Product Information

CT-P13 is a proposed biosimilar biological product to US-licensed Remicade (infliximab). CT-P13 is a chimeric human murine immunoglobulin G1 (IgG1) monoclonal antibody that binds to the human tumor necrosis factor alpha (TNFα). The active

2 This reflects information for Inflectra that Celltrion submitted on August 8, 2014. We note that the indication for pediatric ulcerative colitis is protected by orphan drug exclusivity expiring on September 23, 2018. See the Orphan Drug Designations and Approvals database at http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm.

Reference ID: 3747317

substance is a glycoprotein with 1 N-linked glycosylation site in the CH2 domain of each heavy chain. CT-P13 is comprised of two identical heavy chains of 450 amino acids and two identical light chains of 214 amino acids, all with a sequence identical to infliximab.

2.2 Tables of Currently Available Treatments for Proposed Indications

Rheumatoid Arthritis

Many effective therapies are approved for the treatment of patients with RA including nonsteroidal anti-inflammatory drugs (NSAIDs) and selective COX-2 inhibitors, corticosteroids, disease modifying anti rheumatic drugs (DMARDs) and biologics. Currently approved DMARDs and biologic therapies are listed in Table 1 and Table 2, respectively.

Table 1. Small Molecule DMARDs Approved for RA in the United States

Product Name (Trade Name) [Applicant]	Mechanism of Action in RA	Year of First Approval for RA
Sulfasalazine (AZULFIDINE) [Pfizer]	Anti-inflammatory and antimicrobial	1950
Methotrexate sodium (METHOTREXATE SODIUM) [Multiple]	Anti-metabolite	1953
Hydroxychloroquine (PLAQUENIL) [Sanofi-Aventis]	Interference with antigen processing (?)	1955
Azathioprine (IMURAN) [Prometheus Labs]	Cytostatic	1968
Penicillamine (CUPRIMINE) [Alton]	Unknown	1970
Auranofin (RIDAURA) [Prometheus Labs]	Unknown	1985
Cyclosporine (NEORAL) (SANDIMMUNE) [Novartis]	T-cell activation inhibitor	1995, 1990
Leflunomide (ARAVA) [Sanofi-Aventis]	Anti-metabolite	1998

Reference ID: 3747317

Table 2. Biologic DMARDs Approved for RA in the United States

Product Name (Trade Name) [Applicant] {year} *	Presentation and *ROA* †	Description and *MOA* §
Etanercept (ENBREL) [Immunex/Amgen] {1998}	Vial 25 mg Prefilled syringe 25 or 50 mg/mL SureClick Autoinjector 50 mg/mL *SC injection*	Fusion protein consisting of TNF-R and human IgG1 Fc *TNF inhibitor*
Infliximab (REMICADE) [Centocor] {1999}	Vial 10 mg/mL *IV infusion*	Chimeric IgG1 k mAb *TNF inhibitor*
Anakinra (KINERET) [Amgen] {2001}	Prefilled syringe 10 mg *SC injection*	Recombinant polypeptide *IL-1 receptor antagonist*
Adalimumab (HUMIRA) [Abbott] {2002}	Prefiled syringe 40 mg/0.8 mL Humira Pen 40 mg/0.8 mL *SC injection*	Human IgG1 k mAb *TNF inhibitor*
Abatacept (ORENCIA) [Bristol Myers Squibb] {2005}	Lyophilized powder 250 mg/vial *IV infusion*	Fusion protein consisting of CTLA-4 and human IGg1 Fc *T cell activation inhibitor*
Rituximab (RITUXAN) [Genentech and Biogen] {2006}	Vial 10 mg/mL *IV infusion*	Chimeric murine/human IgG1 k mAb *Anti CD20, B cell depletor*
Golimumab (SIMPONI) [Centocor] {2009}	Prefilled syringe 50 mg/0.5 mL SmartJect Autoinjector 50 mg/0.5 mL *SC injection*	Humanized IgG1 k mAb *TNF inhibitor*
Certolizumab Pegol (CIMZIA) [UCB Inc] {2009}	Lyophilized powder 200 mg/vial *SC injection*	Humanized Fab fragment *TNF inhibitor*
Tocilizumab (ACTEMRA) [Genentech/Roche] {2010}	Vial 20 mg/mL *IV infusion*	Humanized IgG1 k mAb *IL-6 receptor inhibitor*
Tofacitinib (XELJANZ) [Pfizer] (2012)	*5mg,* (b) (4) *immediate-release tablets*	*JAK kinase inhibitor*

Year = Year of first approval for RA †ROA = Route of administration §MOA= Mechanism of action

Psoriatic Arthritis

The first-line therapy for the treatment of psoriatic arthritis is typically the off-labeled use of small molecular immunomodulators (commonly referred to as disease modifying anti-rheumatic drugs [DMARDs]), e.g., methotrexate (MTX), sulfasalazine (SSZ), and leflunomide (LEF). Non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids are also frequently used. Currently approved biologic drugs for treatment of adult patients with psoriatic arthritis are listed in Table 3.

Table 3. Biologics Approved for Psoriatic Arthritis in the United States

Product Name (Trade Name) [Applicant]	Class
Infliximab (REMICADE)	TNFα-blocker
Etanercept (ENBREL)	TNFα-blocker
Adalimumab (HUMIRA)	TNFα-blocker
Golimumab (SIMPONI)	TNFα-blocker
Certolizumab (CIMZIA)	TNFα-blocker
Ustekinumab (STELARA)	interleukin-12 and -23 antagonist

Ankylosing Spondylitis

There are four biologic TNF-inhibitors that are approved in the United States for the treatment of AS as listed in Table 4

Table 4. Approved Products for the Treatment of AS in the United States

Product	BLA (Applicant)	Date of approval for AS‡	Characteristic	ROA
Etanercept (Enbrel®)	103795 (Immunex)	7/24/03	Fusion protein (TNF-inhibitor)	SC
Infliximab (Remicade®)	103772 (Centocor)	12/17/04	Monoclonal antibody (TNF-inhibitor)	IV
Adalimumab (Humira®)	125057 (Abbott)	8/28/06	Monoclonal antibody (TNF-inhibitor)	SC
Golimumab (Simponi®)	125289 (Centocor)	4/24/09	Monoclonal antibody (TNF-inhibitor)	SC

Abbreviations: BLA=Biologics License Applications; ROA=route of administration; SC=subcutaneous; IV=intravenous; RA=rheumatoid arthritis; PsA=psoriatic arthritis; AS=ankylosing spondylitis
† NSAIDs (e.g., celecoxib, diclofenac, indomethacin, naproxen, sulindac) and steroids (e.g., betamethasone, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisone, prednisolone, and triamcinolone) are also approved for the treatment of AS
‡ Etanercept was originally approved in 1998 for RA, infliximab was originally approved in 1998 for Crohn's Disease, adalimumab was originally approved in 2002 for RA, and golimumab was approved for RA, PsA, and AS concurrently

Plaque Psoriasis

The products in the tables below (Table 5 & Table 6) could be considered as therapeutic options for the applicant's target population. These include systemic small molecule therapies, biologics and phototherapy.

Table 5. Small Molecules Approved for Plaque Psoriasis in the United States

Product Name (Trade Name) [Applicant]	Class
Acitretin	retinoid
Methotrexate	folate antagonist
Cyclosporine	IL-2 inhibitor
Apremilast (OTEZLA)	phosphodiesterase 4 inhibitor

Table 6. Approved Biologic Therapies for Plaque Psoriasis in the United States

Product Name (Trade Name) [Applicant]	Class
Infliximab (REMICADE)	TNFα-blocker
Etanercept (ENBREL)	TNFα-blocker
Adalimumab (HUMIRA)	TNFα-blocker
Ustekinumab (STELARA)	Interleukin-12 and -23 antagonist

Phototherapy: This therapy involves exposures to UVB (including narrowband) or to UVA in combination with the photosensitizer, Psoralen, a photochemotherapy that goes by the acronym PUVA.

2.3 Availability of Proposed Active Ingredient in the United States

CT-P13 is available as globally marketed under the trade names Inflectra® and Remsima®. CT-P13 has been approved for all indications as the reference product US-licensed Remicade in several world regions including the EU, South Korea, Japan, and India. Canada's regulatory authorities approved CT-P13 for all indications except ulcerative colitis and Crohn's disease.

2.4 Important Safety Issues With Consideration to Related Drugs

The safety program for CT-P13 was designed based on the well-known safety profile of US-licensed Remicade. Potential risks based on class of drug (TNFα) and of the drug substance (foreign protein) were considered. Potential risks associated with immunomodulating biologic therapies may include infections, cardiovascular safety, malignancies and autoimmune disorders. Potential risks of a foreign protein may include administration or immune reactions, such as hypersensitivity, injection site/infusion reactions and immunogenicity.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The development of CT-P13 was conducted exclusively outside of the US and was geared towards meeting the requirements of non-US regulatory agencies. During the development of CT-P13, the applicant initially sought scientific and procedural advice

Reference ID: 3747317

from European National Competent Authorities and from the European Committee of Human Medicinal Products (CHMP) covering the quality, nonclinical and clinical programs. The advice received was implemented and the clinical development program was refined and amended accordingly.
The first interaction with the FDA occurred at a Biosimilar Biological Product Development (BPD) Type 3 meeting held on 10 July 2013 and further discussed at a BPD Type 4 meeting held on 28 April 2014. A teleconference was held on 11 June 2014 to discuss the initial Pediatric Study Plan (iPSP).

At the BPD Type 3 meeting, in addition to product quality and non-clinical comments, FDA recommendations to the applicant regarding clinical development included:

- Establish PK similarity between CT-P13, US-licensed Remicade and EU-approved Remicade using all three PK variables (AUCinf, Cmax and AUClast).
- Provide a detailed description of the methodology and plans for validation of the assays that will be used for the detection of anti-drug antibodies.
- Assess safety and immunogenicity in the setting of patients who undergo a single transition from EU-approved Remicade to CT-P13 to provide a descriptive comparison with patients who continue on EU-approved Remicade.

During the BPD Type 4 meeting, the FDA provided guidance on Agency's expectation of the information and needed to support a demonstration of biosimilarity and extrapolation of clinical data to support the demonstration of biosimilarity for each indication for which licensure is sought. The content and the format of the 351(k) BLA were discussed, including details on the safety and efficacy analyses. Celltrion agreed to facilitate FDA review by reporting all TEAEs, AEs leading to discontinuation and SAEs per individual study without integrating across studies and indications. For adverse events of special interest (AESIs), it was agreed that pooled analyses will be prepared to allow a review by individual studies and across all studies and indications. Celltrion also agreed to provide adequate justification for the selection of the equivalence margin used in the primary efficacy analysis of efficacy in the comparative clinical study 3.1.

2.6 Other Relevant Background Information

CT-P13 is available globally, marketed under the trade names Inflectra® and Remsima®. CT-P13 has been approved for all indications as the reference product US-licensed Remicade in several world regions including the EU, South Korea, Japan, and India. Canada's regulatory authorities approved CT-P13 for all indications except ulcerative colitis and Crohn's disease, citing a slight difference in mechanism of action between CT-P13 and the innovator product. Health Canada's 2014 Summary Basis of Decision on Inflectra indicated a reduced FcγRIIIa binding of CT-P13 and reduced ability of CT-P13 to mediate antibody-dependent cell-mediated cytotoxicity (ADCC) compared to infliximab. Because the exact mechanism of action of infliximab is unknown in the

Reference ID: 3747317

treatment of inflammatory bowel diseases (IBD), and ADCC could not be ruled out as an important mechanism of action in IBD, Health Canada concluded that extrapolation from the settings of rheumatoid arthritis and ankylosing spondylitis to IBD cannot be recommended due to the absence of clinical studies in IBD.

The applicant has ongoing observational studies to assess the safety and efficacy of CT-P13 in patients with ulcerative colitis and Crohn's disease. The applicant also intends to conduct a phase 3 randomized, double-blind, parallel-group, prospective study to demonstrate that CT-P13 is non-inferior to Remicade at week 6 (Dose 3) in terms of efficacy as determined by the Crohn's Disease Activity Index (CDAI)-70 response rate.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

In general, the data quality and integrity of the studies were good. The amount of missing data was small and did not interfere with reaching conclusions on safety and efficacy.

OSI Inspection

The BLA submission was in electronic common technical document (eCTD) format and was adequately organized. The Office of Scientific Investigations (OSI) was consulted to conduct routine applicant/monitor inspection for CT-P13, a proposed biosimilar to US-licensed Remicade.

The inspection audited both clinical studies 3.1 and 1.1. Four clinical sites (one in Chile, and three in Poland), which were among the highest enrollers of patients were selected for inspection.

OSI inspection found minor and sporadic regulatory deficiencies and deficiencies in documentation at one of the study sites, site 2007 in Chile with Dr. Miranda as the site investigator, who received a Form 483. In response to the Form 483 findings, Dr. Miranda has taken appropriate preventive and corrective actions. There was one specific infusion center providing the infusions at site 2007 with missing drug accountability documentation for the period of January to June 2011. This deficiency was identified by Dr. Miranda who, as a proactive corrective measure at the time, switched the infusions to a different infusion center where all cGMP practices were followed. FDA sensitivity efficacy analyses excluding the data from patients infused at this site during the abovementioned time frame , were consistent with the primary analysis and did not change the overall conclusion of the efficacy similarity seen in study 3.1 (see Section 6.1.4 Analysis of Primary Endpoint(s). Overall, the studies

Reference ID: 3747317

appear to have been conducted adequately and the nature of the deficiencies is unlikely to significantly impact data integrity and reliability.

OSI inspection of the applicant did not identify major deficiencies in data quality and integrity. Based on review of inspectional findings for the clinical investigators and the applicant, the study data collected appear generally reliable in support of the BLA.

3.2 Compliance with Good Clinical Practices

All studies were conducted by Good Clinical Practice as described in International Conference on Harmonization (ICH) Guideline E6 and in accordance with the ethical principles outlined in the Declaration of Helsinki. The studies were conducted in compliance with the protocols. Informed consent, protocol, amendments, and administrative letters form for each study received Institutional Review Board/Independent Ethics Committee approval prior to implementation. The investigators conducted all aspects of these studies in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

Written informed consent was obtained prior to the subject entering the studies (before initiation of protocol-specified procedures). The investigators explained the nature, purpose, and risks of the study to each subject. Each subject was informed that he/she could withdraw from the study at any time and for any reason. Each subject was given sufficient time to consider the implications of the study before deciding whether to participate. Subjects who chose to participate signed an informed consent document.

3.3 Financial Disclosures

The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators*. The applicant submitted FDA Form 3454 certifying investigators and their spouses/dependents were in compliance with 21 CFR part 54. No potentially conflicting financial interests were identified.

In accordance with 21 CFR part 54 Financial Disclosures by Clinical Investigators, CELLTRION requested statements of financial interests from a total of 116 Principal Investigators and 370 sub-investigators for the following studies:

- CT-P13 3.1
- CT-P13 3.2
- CT-P13 1.1
- CT-P13 1.3
- CT-P13 1.4

As of 30 Jun 2014, a total of 486 financial disclosures for the investigators who participated in these trials were received. There were no principal or sub-investigators

Reference ID: 3747317

with financial information to disclose, and there were no principal or sub-investigators who did not return the financial disclosure information.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

CT-P13 is a proposed similar biological product to US-licensed Remicade (infliximab). It is a chimeric human-murine immunoglobulin G1 (IgG1) monoclonal antibody that binds with high affinity to human tumor necrosis factor alpha (TNFα). The active substance is a glycoprotein with 1 N-linked glycosylation site in the CH2 domain of each heavy chain. Each heavy chain consists of 450 amino acids with 11 cysteine residues, and each light chain consists of 214 amino acids with 5 cysteine residues.

Drug Substance

CT-P13 drug substance is a chimeric monoclonal antibody of the IgG1 subclass with identical primary amino-acid structure to US-licensed Remicade. CT-P13 drug substance includes (b) (4) mg/mL of active pharmaceutical ingredient and excipients such as sucrose, sodium dihydrogen phosphate monohydrate, di-sodium hydrogen phosphate dihydrate and polysorbate 80. The CT-P13 cell substrate was generated using Sp2/0 cell line, similar to the one for the manufacturing of US-licensed Remicade.

Drug Product

CT-P13 is formulated as a sterile, lyophilized powder and each vial is designed to deliver 100 mg CT-P13 drug substance. No overfill is used in the CT-P13 drug product manufacture. The lyophilizate is reconstituted with 10 mL of sterile water for injection to yield a single dose formulation containing 10 mg/mL infliximab, at pH 7.2.

Studies to Support Biosimilarity

To support a determination that CT-P13 is highly similar to the reference product, Celltrion submitted extensive analytical similarity package consisting of multiple orthogonal physicochemical and biological assays.

Since CT-P13 was initially developed in support of marketing authorization application (MAA) to the European Medicines Agency (EMA), the initial similarity assessment was conducted using 2-way analytical similarity exercise comparing CT-P13 to EU-approved Remicade, a non-US-licensed reference product. Further, the clinical development program was conducted using EU-approved Remicade. To obtain licensure of CT-P13

Reference ID: 3747317

under section 351(k) of the PHS Act, the Celltrion had to demonstrate that CT-P13 is biosimilar to a single reference product that previously has been licensed by FDA, i.e. US-licensed Remicade. As outlined in the draft FDA Guidance for Industry "*Scientific Considerations in Demonstrating Biosimilarity to a Reference Product - February 2012*", Celltrion had to provide adequate data or information to scientifically justify the relevance of these comparative data to an assessment of biosimilarity and to establish an acceptable bridge to the US-licensed reference product. To that extent, Celltrion submitted a 3-way analytical similarity assessment comparing CT-P13 to both EU-approved and US-licensed Remicade to establish an acceptable bridge to US-licensed Remicade. These analyses were intended to demonstrate:

- Identical primary structure
- Highly similar secondary and higher order structure
- Highly similar disulfide bonding
- Highly similar glycosylation profile with very minor differences in core fucose content
- Highly similar critical quality attributes such as TNF binding and neutralization and other functional characteristics, including, Fc receptor binding, induction of cell-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), Induction of regulatory macrophages and mucosal healing.

The CMC review team has identified several areas of concern with the analytical similarity data. Specifically:

- TNF binding affinity: Submitted data on TNF binding did not meet equivalence margin expectations, possibly due to the limited number of lots tested
- Protein content: Inconsistencies in the amino acid analyses that lead to uncertainty in whether the protein content data represent true differences
- Glycan analysis and ADCC activity: CT-P13 showed ~25% lower FcγRIIIa/b binding affinity which was paralleled by ~20% lower activity in inducing ADCC in select assays (using NK cells expressing the high affinity V allele of FcγRIIIa) as compared with US-licensed and EU-approved Remicade. These differences appeared to be associated with shifts in glycan patterns on the Fc portions of CT-P13 and US-licensed and EU-approved Remicade. However, glycan data in the three-way analysis (CT-P13 vs. US-licensed Remicade vs. EU-approved Remicade) was inconsistent with observed pattern in functional assays (FcγRIII binding, ADCC).

To address these concerns, Celltrion provided additional data and clarification. Specifically:

- TNF binding affinity: Additional lots were tested of all 3 products (CT-P13, US-licensed Remicade, and EU-approved Remicade) and values for the 10 CT-P13 lots originally submitted were corrected due to calculation errors. Data for the TNF binding affinity ELISA and the in-vitro TNF neutralization tests now pass equivalence expectations

Reference ID: 3747317

- Protein content: Samples used in the three-way analysis were tested in sequence (delayed analysis) which caused apparent discrepancy
- Glycan analysis and ADCC activity: Celltrion explained the differences in the glycan data between the 2-way and the 3-way similarity exercise with different methods used and different number of lots tested. However, this suggests that glycan data are inconsistent with observations in the functional assays. Thus, there remain unresolved issues regarding whether there are structural differences that would explain the apparent differences in ADCC, which in turn may impact on the ability to conclude whether CT-P13 is highly similar to US-licensed Remicade.

For a detailed review and analysis of the CMC data, refer to the review by Peter Adams, Ph.D.

4.2 Clinical Microbiology

No issues have been identified by the CMC review team at the time of this review.

4.3 Preclinical Pharmacology/Toxicology

The non-clinical data submitted, demonstrate the similarity of CT-P13 to EU-approved Remicade in terms of pharmacokinetics. From the perspective of pharmacology and toxicology the results of these animal studies can be taken together with the data from the analytical bridging studies (see CMC section above for details) to demonstrate CT-P13 is also similar to the reference product US-licensed Remicade. No residual uncertainties have been identified by the discipline.

CT-P13 drug substance has an identical primary sequence to that of infliximab. The development of the innovator product Remicade had non-clinical challenges as there is no standard toxicological species that is relevant to assess its potential toxicological profile. The drug substance, infliximab, binds to TNFα from humans and chimpanzees, but no other species.

Due to the lack of standard relevant species used for toxicological assessments in which to compare CT-P13's toxicity profile to that of Remicade's, the similarity program was completed largely based on quality (CMC) *in vitro* similarity studies with several nonclinical *in vivo* similarity studies conducted to assess off-target toxicity using EU-approved Remicade as the comparator.

The nonclinical program included *in vitro* binding screening in various species, one human tissue cross reactivity study, one pharmacokinetic (PK) study, and two toxicology studies conducted in rats (one with both toxicokinetic (TK) and immunogenicity testing) In addition, a dose range finding rat study investigated the toxicity, TK and immunogenicity of EU-approved Remicade. The *in vivo* studies were

Reference ID: 3747317

completed to assay for potential off-target toxicities. The nonclinical studies demonstrated that CT-P13 does not bind to TNFα from standard toxicological species, has a similar human tissue binding profile to the EU-approved Remicade, and has a similar off-target toxicity profile and PK/TK profile as the EU-approved Remicade.

Please refer to the review by Dr. Whittaker, Ph.D. for detailed analysis of the pharmacology/toxicology findings.

4.4 Clinical Pharmacology

Pharmacokinetics

The clinical development program consisted of three randomized double-blind, parallel-group studies (Studies 1.4, 1.1 and 3.1) and in all of these studies PK parameters were evaluated. PK parameters were also assessed in the supportive studies (Studies 1.2, B1P13101 and 3.3).

Pharmacokinetic (PK) similarity of CT-P13 to US-licensed Remicade was evaluated in study 1.4, which was designed and conducted as a single-dose 3-arm PK study in healthy volunteers using CT-P13, US-licensed Remicade and EU-approved RemicadeThe study was required by the FDA to provide needed PK bridging data, in addition to the analytical bridging, to scientifically justify the relevance of the clinical comparative data from the clinical development program which used exclusively EU-approved Remicade to the assessment of biosimilarity to the US-licensed Remicade. .

Study 1.1, on the other hand, was designed to demonstrate PK similarity between CT-P13 and EU-approved Remicade using approved chronic dosing of 5 mg/kg doses as monotherapy in AS patients.

In Study 1.4, the primary endpoints were Cmax, AUClast and AUCinf The primary endpoints in Study 1.1 were area under the concentration-time curve for the dosing interval (AUC_T) and maximum serum concentration at steady state ($C_{max,ss}$). In both studies, secondary PK endpoints included but were not limited to time to Cmax (Tmax), mean residence time (MRT) and terminal half-life (T1/2).

In Study 1.4, healthy subjects were given a single 5 mg/kg dose of CT-P13, EU-approved Remicade or US-licensed Remicade. Analysis of the results revealed that PK parameters of Cmax, AUClast and AUCinf were similar among all three treatment groups of CT-P13, EU-approved Remicade and US-licensed Remicade, based on meeting the predefined bioequivalence criteria of 80% -125% around the ratio of geometric means. The PK study 1.4 met its primary endpoint supporting the conclusion that CT-P13, US-licensed Remicade and EU-approved Remicade are similar in regards to PK.

Reference ID: 3747317

In Study 1.1, patients with AS were given multiple doses (5 mg/kg) of CT-P13 or EU-approved Remicade. Primary PK parameters were assessed at steady state (between Week 22 [Dose 5] and Week 30 [Dose 6]). The study met its primary endpoint in that CT-P13 and EU-approved Remicade had similar results for the PK parameters AUC_T and Cmax,ss and met the predefined bioequivalence criteria of 80% - 125%.

Overall, the submitted clinical pharmacology studies data support the demonstration of PK similarity between CT-P13 and US-licensed Remicade.

Refer to the clinical-pharmacology review by Lei He, PhD, for a detailed analysis of the pharmacokinetic and pharmacodynamics aspects related to this application.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Key design features of the CT-P13 clinical studies are summarized in Table 7 and Table 8.

Reference ID: 3747317

Table 7. Clinical Development - Controlled Studies

Protocol	Patient Population	Design/Objectives	Duration	Sample size/ Randomization	Treatment arms
CT-P13 1.4	HV	R, DB, PG, SD 3-way PK bridging	Single dose	N=250 1:1:1	CT-P13 EU-Remicade[1] US-Remicade[2]
CT-P13 1.1	AS	R, DB, PG PK and Efficacy	54 weeks	N=250 1:1	CT-P13 EU-Remicade
CT-P13 3.1	RA,MTX-IR	R, DB, PG Comparative Clinical Study	54 weeks	N=606 1:1	CT-P13 + MTX EU-Remicade + MTX
B1P13101 (Japan)	RA,MTX-IR	R, DB, PG PK and Efficacy	54 weeks	N=108 1:1	CT-P13 + MTX EU-Remicade + MTX
CT-P13 1.2 (Philippines)	RA,MTX-IR	R, DB, PG Pilot Study	54 weeks	N=19 1:1	CT-P13 + MTX EU-Remicade + MTX
CT-P13 3.3 (Russia)	RA,MTX-IR	R, DB, PG Pilot Study	54 weeks	N=15 1:1	CT-P13 + MTX EU-Remicade + MTX

[1]EU-approved Remicade [2]US-licensed Remicade
R–Randomized, DB-Double blind, PG-Parallel-group, PK-Pharmacokinetics, SD-Single dose, MTX– Methotrexate, IR-Inadequate Responders

Table 8. Clinical Development - Extension Studies

Protocol	Patient Population	Design/Objectives	Duration	Sample size	Treatment (CT-P13)
CT-P13 3.2	RA, Enrolled from controlled study 3.1	OLE, Safety & Immunogenicity	Weeks 62-102 (~1year)	N=302	Maintenance (n=158) Transitioned from EU-Remicade[1] (n=144)
CT-P13 1.3	AS, Enrolled from controlled study 1.1	OLE, Safety & Immunogenicity	Weeks 62-102 (~1year)	N=174	Maintenance (n=88) Transitioned from EU-Remicade[1] (n=86)
[1]EU-approved Remicade; OLE-open label extension					

5.2 Review Strategy

The clinical development program for CT-P13 consists of six controlled clinical studies, listed in Table 7 and two long-term open label extension studies listed in Table 8. Of these, the following three studies provide the primary evidence to support the determination of no clinically meaningful differences between CT-P13 and the reference product, US-licensed Remicade:

- Study 1.4 is a single-dose, 3-way study in healthy volunteers providing a PK data to support the scientific bridging between CT-P13, US-licensed Remicade and EU-approved Remicade..
- Study 3.1 is the comparative clinical study that provides the comparative clinical efficacy data for CT-P13 in rheumatoid arthritis.
- Study 1.1, although designed as a primary PK study between CT-P13 and EU-infliximab in AS patients, the study also captures safety and efficacy in AS as secondary endpoints and provides supportive evidence for the determination of no clinically meaningful differences.

Additional long-term safety and immunogenicity data for patients who transitioned from EU-approved Remicade to CT-P13 or continued to receive CT-P13 were provided in studies 3.2, and 1.3, as listed in Table 8.

Assessment of comparative clinical efficacy to support the determination of no clinically meaningful differences between CT-P13 and Remicade is provided in the comparative

Reference ID: 3747317

clinical study 3.1 in patients with RA. Data from all clinical studies are included in the safety review.

Additional supportive clinical safety and efficacy data were derived from study 1.2 (pilot study in 19 RA patients in Philippines), study B1P13101 (PK study with secondary efficacy evaluated in 108 RA patients in Japan) and study 3.3 (another small, pilot study in 15 RA patients in Russia). The applicant conducted these studies as part of their global development program. Each study had a similar study design and similar inclusion and exclusion criteria compared with the larger controlled studies.

All endpoints used are validated endpoints used in the approval of other drugs in RA, AS and represent clinically meaningful endpoints.

Of note, the only study conducted based on discussions with FDA was Study 1.4 with the rest of the clinical development conducted primarily outside US with limited input from the Agency. Despite these limitations, the overall clinical program is adequate to provide the evidence to support the determination of no clinically meaningful differences in the studied indications of RA and AS. However, it is not clear whether this conclusion can be made overall, because of residual uncertainty in the analytical characterization data, specifically with respect to antibody-dependent cellular cytotoxicity (ADCC).

5.3 Discussion of Individual Studies/Clinical Studies

Study 1.4: PK Similarity Study

Title: A Randomized, Double-blind, Three-arm, Parallel Group, Single-dose Study to Compare the Pharmacokinetics, Safety, Tolerability, and Immunogenicity of Three Formulations of Infliximab (CT-P13, EU-approved Remicade and US-licensed Remicade) in Healthy Subjects

Study Objectives:

Primary objective

- To evaluate and compare the pharmacokinetic profiles of CT-P13, US-Remicade and EU-Remicade in healthy subjects (CT-P13 to US-Remicade, CT-P13 to EU-Remicade and EU-Remicade to US-Remicade)

Secondary objectives

- To assess the safety, tolerability, and immunogenicity data of CT-P13, US-Remicade and EU-Remicade in healthy subjects

Study Design: Study 1.4 was designed as a double-blind, three-arm, parallel group, single-dose study. A total of 213 subjects were to be enrolled; 71 subjects in each of the three arms of the clinical study. In each arm, all subjects received a single dose (5 mg/kg) of either CT-P13, EU-approved Remicade, or US-licensed Remicade by intravenous (IV) infusion for 120 min on Day 1 followed by 8 weeks during which the pharmacokinetic, safety, tolerability and immunogenicity measurements were made. To avoid infusion-related reactions, premedication with IV hydrocortisone (100 mg), oral paracetamol (1000 mg) and oral loratadine (10 mg) were administered 30 to 60 minutes prior to the infusion of CT-P13, EU-approved Remicade, or US-licensed Remicade.

Treatment Groups and Regimen:
A total of 213 patients were to be randomized (1:1:1) to receive 1 dose (IV infusion) at a dose of 5mg/kg of:

- CT-P13
- EU-approved Remicade
- US-licensed Remicade

Patient Population
Healthy male and female subjects. Subjects must be able to provide written informed consent and meet all the inclusion criteria and none of the exclusion criteria.

Key Inclusion Criteria

- Healthy male and female subjects between the ages of 18 and 55 years, inclusive (healthy is defined as no clinically relevant abnormalities identified by a detailed medical history, full physical examination, including blood pressure and pulse rate measurement, 12-lead ECG and clinical laboratory tests assessed at the screening visit).
- Body Mass Index (BMI) between 18.0 and 29.9 kg/m^2 (both inclusive) and a total body weight between 55 and 99.9 kg (both inclusive).
- Female subject is of non-childbearing potential defined as surgically sterile (i.e., documented bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or at least 12 months postmenopausal (defined as at least 12 months since last regular menses and follicle stimulating hormone [FSH] value showing evidence for the postmenopausal status).
- Male subject, unless surgically sterile for at least 3 months before the time of the administration of IMP, must be willing to engage in a highly effect form of contraception (defined in the protocol)

Key Exclusion Criteria

- Subject has a medical condition of disease including one or more of the following(s):
  − History and/or current presence of clinically significant atopic allergy (e.g., asthma, urticaria, angio-edema, eczematous dermatitis), hypersensitivity or

Reference ID: 3747317

allergic reactions (either spontaneous or following drug administration), also including known or suspected clinically relevant drug hypersensitivity to any components of the test and reference IMP formulation or comparable drugs.
− History of invasive systemic fungal infections (e.g., histoplasmosis) or other opportunistic infections judged relevant by the Investigator, including local fungal infections or a history of herpes zoster.
− History of and/or current cardiac, gastrointestinal, renal, hepatic, hematological (including pancytopenia, aplastic anemia or blood dyscrasia), metabolic (including known diabetes mellitus) or pulmonary disease classed as significant by the Investigator.
− History of any malignancy including but not limited to lymphoma, leukemia and skin cancer.
− History of and/or current immunodeficiency including those subjects with a positive test for human immunodeficiency virus (HIV)-1 or -2 antibodies at the screening visit.

- History of surgical intervention or operations within 4 weeks before administration of the IMP or plans a surgical procedure during the clinical trial.
- Evidence of latent, inadequately treated or active infection with tuberculosis (TB)
- Pregnancy or breastfeeding; females of childbearing potential.
- Male subjects planning to father a child or donating sperms within a 6 month period following study drug administration.
- Evidence of systemic or local infection, a known risk for developing sepsis and/or known active inflammatory process within 6 month prior to the administration of IMP. Subjects with C-reactive protein >1.5 times the upper limit of normal (ULN) at the screening period and/or baseline (Day –1) will not be enrolled in order to exclude those subjects with chronic inflammatory processes.
- History of infection (associated with hospitalization and/or which required intravenous antibiotics) within 6 months prior to the administration of IMP.
- Previous exposure to a monoclonal antibody or current use of a biologic (including but not limited to TNF-blockers).
- Treatment with an investigational drug or participation in another clinical trial within 30 days (or as determined by the local requirement, whichever is longer) or 5 half-lives preceding the first dose of study medication.
- Subject has impaired liver function as determined by one of the following:
  − Serum alanine transaminase and/or aspartate transaminase ≥1.5 times the ULN at the screening period and/or baseline (Day –1)
  − Gallbladder or bile duct disease (except for asymptomatic cholecystectomy)
  − Acute or chronic pancreatitis
  − A positive hepatitis C antibody test or hepatitis B surface antigen test
  − Hepatic disease (e.g., cirrhosis) classed as clinically significant by the Investigator
- History of illness within 4 weeks prior to randomization that is classed as clinically significant by the Investigator.

Reference ID: 3747317

- Live vaccine(s) within 30 days prior to randomization or who will require live vaccine(s) between randomization and the end-of-study visit.
- History of or presence of regular consumption exceeding an average weekly intake of >21 units of alcohol. One unit of alcohol is equivalent to a half-pint of beer/lager, 25 mL measure of spirits, or 125 mL of wine. Subject is unwilling to avoid use of alcohol or alcohol-containing foods, medications or beverages, within 24 hours prior to the screening visit, to Day –1 and to each study visit until completion of the study.
- Evidence (in the opinion of the Investigator) of drug abuse, including alcohol, as indicated by a positive urinary drug screening at the screening period and/or baseline (Day –1).
- Use of over-the-counter (OTC) medications (including vitamins), prescription medications, or herbal remedies that could affect the outcome of the study from 14 days (or 5 half-lives, whichever is longer) prior to Day –1 until End-of-Study.
- Donation or loss of 450 mL or more of blood within 8 weeks prior to the administration of MP.
- Inability to complete the study for whatever reason, in the opinion of the Investigator.
- Smoking i.e., consumes more than 10 cigarettes or equivalent per day and/or is unable to refrain from smoking during in-house stays
- Subject is vulnerable (e.g., employees of the clinical trial site or any other individuals involved with the conduct of the study, or immediate family members of such individuals, persons kept in prison or other institutionalized persons by law enforcement).
- Evidence of a condition (psychological, emotional problems, any disorders or resultant therapy) that is likely to invalidate informed consent, or limited the ability of the subject to comply with the protocol requirements in the opinion of the Investigator.
- Unable to understand the protocol requirements, instructions and study related restrictions, the nature, scope and possible consequences of the clinical study. Subject is unable to give written informed consent or to comply fully with the protocol

Concomitant Medications

Concomitant medications and doses include:

- Hydrocortisone 100 mg IV, oral paracetamol (1000 mg) and oral loratidine (10 mg)
  used as premedication
- Occasional use of 1000 mg paracetamol per single dose

Prohibited and restricted treatments

- Any medicinal product, prescribed or OTC drug, including herbal and other non-traditional remedies

Reference ID: 3747317

Endpoints/Outcome Measures

Primary Endpoint:
- PK parameters Cmax, AUC-infinity and AUClast

Key Secondary Endpoints:
- Pharmacokinetics
  - Time to Cmax (Tmax)
  - Volume of distribution during the terminal phase (Vz)
  - Terminal elimination rate constant (λz).
  - Terminal half-life (t1/2)
  - Total body clearance (CL)
  - Area under the concentration-time curve extrapolated from time zero to infinity as a percentage of total AUC (%AUCextrap)
  - Mean residence time (MRT)
- Safety and Tolerability
  - Vital signs (blood pressure [BP] and heart rate [HR], body temperature [BT], respiratory rate [RR])
  - Physical examination
  - Signs and symptoms of tuberculosis infection
  - Clinical laboratory tests including hematology, chemistry, and urinalysis
  - Twelve-lead electrocardiogram (ECG)
  - Adverse events (AEs) and concomitant medication
- Immunogenicity
  - Immunogenicity of infliximab

Statistical Analysis Plan:

Primary endpoint (PK) analysis
The PK similarity of CT-P13, US-licensed Remicade and EU-approved Remicade will be determined using the standard bioequivalence testing method. The statistical analysis of the log-transformed primary endpoints (Cmax, AUCinf and AUClast) will be based on an analysis of covariance (ANCOVA) model with treatment as a fixed effect and gender as covariate. The difference in least squares means between the CT-P13 and EU-approved Remicade, CT-P13 and US-licensed Remicade and EU-approved Remicade and US-licensed Remicade and the associated 90% confidence intervals (CIs) will be determined. Back transformation will provide the ratio of geometric means and 90% CIs for these ratios.

Equivalence of systemic exposure (Cmax, AUCinf and AUClast) will be determined if 90% CI for the ratio of geometric means is within the acceptance interval of 0.8 to 1.25 for the following comparisons:
- CT-P13 vs EU-approved Remicade

Reference ID: 3747317

- CT-P13 vs US–licensed Remicade
- EU-approved Remicade vs US-licensed Remicade

Secondary endpoint (safety) analyses:
Descriptive analyses of the secondary endpoints will be provided.

Protocol Amendments:
Minor amendments were made to the protocol which did not affect safety or efficacy results.

Study 3.1: Comparative Clinical Study in RA

Title: A Randomized, Double-Blind, Parallel-Group, Phase 3 Study to Demonstrate Equivalence in Efficacy and Safety of CT-P13 Compared With EU-Approved Remicade When Co-administered With Methotrexate in Patients With Active Rheumatoid Arthritis

Study Objectives

Primary objective: The primary objective of this study was to demonstrate that CT-P13 is therapeutically equivalent to EU-approved Remicade up to Week 30 in RA patients, in terms of efficacy as determined by clinical response according to the American College of Rheumatology (ACR) definition of a 20% improvement (ACR20).

Secondary objective: Secondary objectives of this study are to evaluate long-term efficacy, population pharmacokinetics and pharmacodynamics and overall safety of CT-P13 in comparison with EU-approved Remicade, up to Week 54.

Study Design: Study 3.1 was a randomized, double-blind, multicenter, parallel group, prospective Phase 3 study designed to assess efficacy equivalence, and to evaluate long-term efficacy, population pharmacokinetics, pharmacodynamics, and overall safety of multiple doses of either CT-P13 or EU-approved Remicade (3 mg/kg) administered by single 2-hour intravenous (IV) infusion per dose when co-administered with methotrexate between 12.5 to 25 mg/week, oral dose and folic acid (≥5 mg/week, oral dose) in patients with active RA who were not receiving adequate response to methotrexate alone over at least the last three months. Primary endpoint was assessed at week 30. The study remained blinded up to week 54 to patients and investigators. At week 54, consenting patients were enrolled into an open-label, extension study (study 3.3) in which patients receiving EU-approved Remicade were transitioned to CT-P13. The extension study continued up to week 102.

The study design is illustrated in Figure 1.

Reference ID: 3747317

Figure 1. Study Design for Study 3.1

	Dose-Loading Phase			Treatment Phase I[1]		Treatment Phase II[2]
	Dose 1 Week 0 (Day 0)	Dose 2 Week 2 (Day 14)	Dose 3 Week 6 (Day 42)	Dose 4, 5 & 6 Weeks 14, 22 & 30 (Days 98, 153 & 210)	Doses 7, 8, & 9 Weeks 38, 46, & 54 (Days 266, 322 & 378)	Doses 10 to 15 Weeks 62 to 102 (Days 434 to 714)
CT-P13[3]	X	X	X	X	X	X
Remicade[3]	X	X	X	X	X	
Primary Efficacy Evaluation	←				→	
Secondary Efficacy Evaluation	←					→
Secondary Population Pharmacokinetic Evaluation	←				→	
Secondary Pharmacodynamic Evaluation	←				→	
54-Week Safety Evaluation	←					→
Safety Evaluation	←					→

1. Following Dose 4, further doses may be administered every 8 weeks up to Week 54 maintaining treatment.
2. Following Dose 9, further doses may be administered every 8 weeks up to Week 102 after consenting patients switch from Remicade to CT-P13 or continuing with their CT-P13 treatment.
3. A dose visit window of ±3 days is allowed up to and including Dose 3; a dose visit window of ±5 days is allowed thereafter.

Patient Population

Approximately 584 male and female patients with active rheumatoid arthritis (RA) with inadequate response to methotrexate (MTX) were to be enrolled in a 1:1 ratio (approximately 292 patients per treatment group) into the CT-P13 plus methotrexate or EU-Remicade plus methotrexate reference product.

Inclusion Criteria

1. Males and females aged 18 to 75 years old, inclusive.
2. Patient was diagnosed RA according to the revised 1987 ACR classification criteria [Arnett et al 1987] for at least 1 year prior to Screening.
3. Patients have active disease as defined by the presence of 6 or more swollen joints, 6 or more tender joints, and at least two of the following: morning stiffness lasting at least 45 minutes, an ESR greater than 28 mm/h, and a serum CRP concentration greater than 2.0 mg/dL
4. Patients who have completed at least 3 months of treatment of oral dosing with methotrexate between 12.5 to 25 mg/week and on a stable oral dosing with methotrexate between 12.5 to 25 mg/week for at least 4 weeks prior to Screening.

5. Both male and female patients and their partners of childbearing potential must agree to use 2 medically accepted methods of contraception (eg, barrier contraceptives [male condom, female condom, or diaphragm with a spermicidal gel], hormonal contraceptives [implants, injectables, combination oral contraceptives, transdermal patches, or contraceptive rings], and intrauterine devices) during the course of the study and for 6 months following discontinuation of study treatments (excluding women who are not of childbearing potential and men who have been sterilized).
6. Male and female patients and their partners who have been surgically sterilized for less than 6 months prior to study entry must agree to use 2 medically accepted methods of contraception as per inclusion criterion 5.
7. Menopausal females must have experienced their last period more than 12 months prior to study entry to be classified as not of childbearing potential.
8. Patients have adequate renal and hepatic function at Screening as defined by the following clinical chemistry results:
    a. Serum creatinine <1.7 × upper limit of normal (ULN) or an estimated creatinine clearance level >75 mL per minute.
    b. Serum alanine aminotransferase <2 × ULN.
    c. Serum aspartate aminotransferase <2 × ULN.
9. Patients are permitted to receive both oral glucocorticoids equivalent to ≤10 mg daily prednisolone, NSAIDS, if they have received a stable dose for at least 4 weeks prior to Screening.
10. Patients have the ability to comprehend the full nature and purpose of the study, including possible risks and side effects, to cooperate with the investigator, to understand verbal and written instructions, and to comply with the requirements of the entire study.
11. Patient (or legal guardian, if applicable) is informed of the full nature and purpose of the study, including possible risks and side effects, and given ample time and opportunity to read and understand this information, signed and dated the written informed consent before inclusion in the study.

Exclusion Criteria

1. Patients who have previously been administered a biological agent for the treatment of RA.
2. Patients who have allergies to any of the excipients of infliximab or any other murine and human proteins.
3. Patients who have a current or past history of chronic infection with hepatitis B, hepatitis C or infection with human immunodeficiency virus -1 or-2 or who have a positive result to the screening test for those infections.
4. Patients who have a current diagnosis of tuberculosis (TB) or other severe or chronic infection (such as sepsis, abscess or opportunistic infections, or invasive fungal infection such as histoplasmosis) or a past diagnosis without sufficient documentation of complete resolution following treatment.

Reference ID: 3747317

5. Patients who have had recent exposure to persons with active TB, or who have a positive result to the screening test for latent TB determined by chest X-ray and interferon-γ release assay, and who have not received at least the first 30 days of country specific TB therapy and do not intend to complete the entire course of that therapy.
6. Patients who have had any other serious infection not already excluded in the 6 months before Screening or have a history of chronic infection.
7. Patients who have a current or past history of drug or alcohol abuse.
8. Patients who have a medical history including one or more of the following conditions:
    a. Bone marrow hypoplasia
    b. Diabetes mellitus according to the American Diabetes Association criteria
    c. Any other inflammatory rheumatic disease and other chronic painful musculoskeletal or neuropathic conditions such as fibromyalgia
    d. Any malignancy within the previous 5 years except completely excised and cured squamous carcinoma of the uterine cervix, cutaneous basal cell carcinoma, or squamous cell carcinoma
    e. Congestive heart failure (New York Heart Association [NYHA] Class III/IV) or unstable angina
    f. Organ transplantation
    g. Severe physical incapacitation
    h. Moderate, severe or very severe chronic obstructive pulmonary disease (COPD) according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria
    i. Previous diagnosis or symptoms suggestive of demyelinating disorders, including multiple sclerosis, and Guillain-Barre syndrome
    j. Any condition affecting the nervous system (i.e., nervous system injury) if it interferes with investigator assessment
    k. Patients with seizure disorder
9. Patients taking any of the following concomitant medications:
    a. Corticosteroids, except oral glucocorticoids of maximum equivalent daily dose of 10 mg of prednisolone within 4 weeks prior to Screening
    b. Disease-modifying antirheumatic drugs (DMARDs), other than sulfasalazine or methotrexate, within 6 months prior to Screening. Patients who discontinued leflunomide and have had successful chelation with 8 g of cholestyramine (3 times daily) for 11 days (levels documented as below 0.02 mg/L twice at least 14 days apart) must wait 4 weeks prior to Screening. Patients who discontinued leflunomide and did not have cholestyramine washout must wait 12 weeks after last dose of leflunomide before Screening
    c. Alkylating agents within 12 months prior to Screening
10. Patients who have participated in a study with an investigational drug within 6 months of Screening or who are currently receiving treatment with any other investigational drug or device.

Reference ID: 3747317

11. Female patients who are currently pregnant or breastfeeding, or are planning to become pregnant or breastfeed within 6 months of the last dose of CT-P13 or Remicade reference product.
12. Patients who have received a live or live-attenuated vaccination within 8 weeks of Screening or who are scheduled to receive a live or live-attenuated vaccination. Killed vaccines are acceptable during the study.
13. Patients who, in the opinion of their general practitioner or investigator, should not participate in the study.

Treatment Groups and Regimen
Patients were randomized (1:1) to the following treatment groups:

- CT-P13 + MTX
- EU-approved Remicade + MTX

Dosing regimen consisted of 3mg/kg of either CT-P13 or EU-approved Remicade administered via IV infusion every 8 weeks up to week 54. A dose visit window of ±3 days is allowed up to and including Dose 3; a dose visit window of ±5 days is allowed thereafter.

Concomitant Medications

Concomitant medications and doses include:

- Methotrexate 12.5 – 25mg weekly, oral dose
- Folic acid > 5mg weekly, oral dose
- Optional premedication with antihistamine (chlorpheniramine 2 to 4 mg or equivalent dose of equivalent antihistamine, or cetrazine 10mg) 30 to 60 minutes prior to the start of study infusion

The following concomitant medications were allowed if the patient had been administered a stable dose for at least 4 weeks prior to screening:
oral glucocorticoids up to a maximum equivalent dose of 10mg of prednisolone
NSAIDs

Tylenol (3000mg/day) and Tramadol (3g/day), and other analgesics should be maintained at the stable dose throughout the study except 24 hours prior to joint assessment at each study visit.

Study Medication, Dose and Treatment Duration
The study was comprised of 4 study treatment periods including Screening, Dose-Loading Phase, Maintenance Phase, and the End of Study (EOS) Period (8 weeks after the last dose). Both products were administered as a dose of 3 mg/kg via single 2-hour intravenous i.v.) infusion and co-administered with MTX (12.5 to 25 mg/week, oral or parenteral dose) and folic acid (≥5 mg/week, oral dose) in patients with active RA who were not achieving adequate response to MTX alone over at least 3 months.

Reference ID: 3747317

Screening was performed between Days –42 and –7, prior to the first study treatment infusion. On Day 0, Week 0, patients who met all inclusion criteria and none of the exclusion criteria were enrolled in the study and randomly assigned in a 1:1 ratio to receive either CTP13 or EU-approved Remicade. Patients were premedicated with an antihistamine (chlorpheniramine 2 to 4 mg or equivalent dose of equivalent antihistamine) 30 to 60 minutes prior to the start of study treatment infusion at the investigator's discretion. A non-sedating antihistamine such as 10 mg of cetirizine was also an acceptable premedication.

The Dose-Loading Phase of the study consisted of 3 doses of study treatment Day 0, Week 0; Day 14, Week 2; and Day 42, Week 6.

The Maintenance Phase of the study consisted of a further 6 doses of study treatment administered every 8 weeks (Weeks 14, 22, 30, 38, 46, and 54) with the last dose administered no later than Week 54. Each dosing period consisted of a single-dose administration of study treatment co-administered with methotrexate and folic acid, followed by an off-dose period of 8 weeks. At Week 30, the study was unblinded for reporting purposes and efficacy, PK, PD, and safety endpoints were evaluated. The study remained blinded to the investigators and patients. At Week 54, the secondary efficacy, PK, PD, and safety endpoints were evaluated.

An EOS Visit occurred 8 weeks after the last dose was received, either at the end of the Maintenance Phase or earlier if the patient withdrew from the study.

Endpoints/Outcome Measures

Primary Endpoint:

- Proportion of patients achieving clinical response (ACR20) at week 30

Key Secondary Endpoints

1) Efficacy

- Individual components of the ACR criteria comparison with Baseline at Weeks 14, 30, and 54
- ACR50 and ACR70 at Weeks 14, 30, and 54
- Mean decrease in disease activity measured by DAS28 comparison with Baseline at Week 30
- SDAI and CDAI at Weeks 14 and 30
- Joint damage progression based on radiographic evaluations, van der Heijde modification of the Sharp scoring system [van der Heijde 2000]) at Week 54
- SF-36 (Quality-of-Life Questionnaire (Medical Outcomes Study Short-Form Health Survey) at Weeks 14 and 30
- Fatigue

Reference ID: 3747317

2) Safety & Immunogenicity

Statistical Analysis Plans

Primary Efficacy Endpoint
The primary endpoint was defined as the proportion of patients achieving clinical response (according to the ACR20 criteria) at Week 30. A patient was defined as a responder according to ACR20 criteria if the following was fulfilled:

- A decrease of at least 20% in the number of tender joints
- A decrease of at least 20% in the number of swollen joints
- At least a 20% improvement in 3 of the following: Patient assessment of pain on VAS; patient global assessment of disease status (VAS); physician global assessment of disease status (VAS); health assessment questionnaire estimate of physical ability; serum CRP concentration or ESR.
-

For the derivation of ACR20 at Week 30 the following categories of patients were considered non-responders (this approach was also used for other time points where ACR20 was derived):

- Patients who did not meet the response criteria above
- Patients who discontinued the study prior to Week 30 except for any of the following safety reasons: life-threatening infusion-related anaphylactic reaction; deterioration of diabetes mellitus; malignancy; any adverse event which, in the opinion of the investigator, compromised the safety of the patient if he or she continued to participate in the study
- Patients with missing or incomplete data for the evaluation of ACR20 at Week 30
- Patients with protocol-prohibited changes in medication including initiation of therapy with a new DMARD, increase in dose of RA medication (MTX or corticosteroid) and administration of intra-articular corticosteroids in more than 1 joint
- Patients requiring a surgical joint procedure during the study

Primary Efficacy Analysis

The proportion of patients achieving clinical response according to ACR20 criteria at Week 30 were analyzed by the exact binomial approach, calculating a point estimate and 95% confidence interval (CI) for the difference in proportion between the 2 treatment groups.

Therapeutic equivalence of clinical response according to ACR20 criteria were concluded if the 95% CI for the treatment difference is entirely within −15% to 15% at Week 30.

As this method does not allow for stratification, a sensitivity analysis was performed on the primary endpoint, utilizing a logistic regression model, with treatment as a fixed effect and baseline DAS28 score, region, and CRP as covariates. The resulting odds ratio and 95% CI were converted into difference of proportions using the Delta method for the purpose of comparison.

Secondary Efficacy Analysis

The difference between CT-P13 and EU-approved Remicade was estimated with 95% CIs for specified secondary efficacy variables to quantify the treatment effect, but no formal assessment of equivalence was performed for any of the secondary efficacy variables. Descriptive statistics will be used to analyze secondary efficacy data.

Protocol Amendments:
Minor amendments were made to the protocol which did not affect safety or efficacy results.

Study 1.1 PK Equivalence study in AS

Title: Randomized Double-Blind, Parallel-Group, Phase 1 Study to Demonstrate the Equivalence With Respect to the Pharmacokinetic Profile of CT-P13 and EU-approved Remicade in Patients With Ankylosing Spondylitis

Study Objectives

Primary: To demonstrate comparable pharmacokinetics at steady state in terms of the area under the concentration-time curve over a dosing interval (AUC_T) and observed maximum serum concentration (Cmax) between CT-P13 and EU-approved Remicade in patients with active ankylosing spondylitis (AS) up to Week 30.

Secondary: To assess efficacy up to Week 30, and overall safety of CT-P13 up to Week 102 in comparison with EU-approved Remicade reference product.

Key Secondary Efficacy Endpoints:

- Proportion of patients achieving clinical response according to the Assessment of SpondyloArthritis International Society (ASAS) 20% criteria at Weeks 14, 30, and 54 (or at the EOS visit if not obtained at Week 54)
- Proportion of patients achieving clinical response according to ASAS40 criteria at Weeks 14, 30, and 54 (or at the EOS visit if not obtained at Week 54).
- BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) at Weeks 14, 30, and 54 (or at the EOS visit if not obtained at Week 54) compared with baseline
- BASFI (Bath Ankylosing Spondylitis Functional Index) at Weeks 14, 30, and 54 (or at the EOS visit if not obtained at Week 54) compared with baseline

Reference ID: 3747317

- BASMI (Bath Ankylosing Spondylitis Metrology Index) at Weeks 14, 30, and 54 (or at the EOS visit if not obtained at Week 54) compared with baseline
- Chest expansion at Weeks 14, 30, and 54 (or at the EOS visit if not obtained at Week 54) compared with baseline
- SF-36 at Weeks 14, 30, and 54 (or at the EOS visit if not obtained at Week 54)

The ASAS20 response is defined as an improvement of at least 20% and an absolute improvement of at least 1 unit on a 0 to 10 scale from baseline in at least 3 of the following domains:

- Patient global assessment of disease status
- Patient assessment of spinal pain
- Function according to BASFI
- Morning stiffness determined using the last 2 questions of BASDAI

Additionally, ASAS20 responders should not have deterioration (worsening of ≥20% and an absolute worsening of at least 1 unit on a 0 to 10 scale) of the remaining assessment domain compared to baseline.

ASAS40 responder are defined as an improvement of at least 40% and an absolute improvement of at least 2 units on a 0 to 10 scale from baseline in at least 3 of the 4 domains of the ASAS20, with no deterioration from baseline in the remaining domain.

Study Design

The study was designed as a randomized, double-blind, multicenter, parallel group, prospective Phase 1 study designed to assess the pharmacokinetic equivalence and safety of multiple doses of CT-P13 or EU-approved Remicade reference product (5 mg/kg) administered by a 2-hour IV infusion per dose in patients with active AS up to Week 30. The study was unblinded thereafter and continued for 54 weeks. At week 54, consenting patients were enrolled into an open-label, extension study (study 1.3) in which patients receiving EU-approved Remicade were transitioned to CT-P13 at week 54; the extension study continued up to week 102. Study design is shown in Figure 2.

Figure 2. Study Design for Study 1.1

	Dose-Loading Phase				Treatment Phase I[1]			Treatment Phase II[2]
	Dose 1 Week 0 (Day 0)	Dose 2 Week 2 (Day 14)	Dose 3 Week 6 (Day 42)	Dose 4 Week 14 (Day 98)	Dose 5 Week 22 (Day 153)	Dose 6 Week 30 (Day 210)	Doses 7, 8, & 9 Weeks 38, 46, & 54 (Days 266, 322 & 378)	Doses 10 to 15 Weeks 62 to 102 (Days 434 to 714)
CT-P13[3]	X	X	X	X	X	X	X	X
Remicade[3]	X	X	X	X	X	X	X	
Primary Pharmacokinetic Evaluation					←	→		
Efficacy Evaluation	←	→	→	→	→	→		
Secondary Pharmacokinetic Evaluation	←	→	→	→	→	→		
54-Week Safety Evaluation	←	→	→	→	→	→	→	
Safety Evaluation	←	→	→	→	→	→	→	→

1. Following Dose 4, further doses may be administered every 8 weeks up to Week 54 continuing with assigned treatment.
2. Following Dose 9, further doses may be administered every 8 weeks up to Week 102 after consenting patients switch from Remicade to CT-P13 or continuing with their CT-P13 treatment.
3. A dose visit window of ±3 days is allowed up to and including Dose 6; a dose visit window of ±5 days is allowed thereafter.

Study population and main inclusion and exclusion criteria

The study population consisted of male or female patients aged 18 to 75 years old, inclusive, who had been diagnosed with AS according to the 1984 modified New York classification criteria for at least 3 months prior to Screening.

- 250 patients were randomized 1:1 to:,
  - CT-P13 treatment group (n=125)
  - EU-approved Remicade treatment group (n=125)
-

Study Medication, Dose and Treatment Duration
CT-P13 or EU-approved Remicade was administered at 5 mg/kg by body weight by a 2 hour. i.v. infusion at Weeks 0, 2, and 6, and then every 8 weeks up to Week 54.

Statistical Analysis Plan

Pharmacokinetic Analysis
Serum concentrations were summarized using quantitative descriptive statistics (including geometric mean) by treatment, study visit, and time point. Pharmacokinetic parameter data was also summarized using descriptive statistics (including geometric mean, where appropriate) by treatment and study visit.

The primary pharmacokinetic endpoint of the observed AUC_T and Cmax between patients treated with CT-P13 and EU-approved Remicade at steady state between Dose 5 and Dose 6 were analyzed using an analysis of variance model with treatment as a fixed effect and region and baseline BASDAI score fitted as covariates. Point estimates (geometric means and ratio of geometric means) was calculated from back-transforming the least squares means of the log-transformed values of AUC_T and Cmax. Both AUC_T and Cmax were log-transformed prior to analysis, and 90% confidence intervals were also produced.

The equivalence of pharmacokinetics between CT-P13 and Remicade was concluded if the 90% confidence intervals for the test product to reference product ratios of geometric means were entirely contained within 80% to 125% for both AUC_T and Cmax.

Efficacy analysis
The proportion of patients achieving clinical response (ASAS20 and ASAS40) was analyzed by a logistic regression model, with treatment as a fixed effect and the stratification factors (region, baseline BASDAI score) as covariates. Treatment effect was estimated by calculating the odds ratio and 95% confidence interval.

Descriptive statistics for actual and change from Baseline were calculated for the following quantitative parameters: BASDAI, BASFI, BASMI, chest expansion, and SF 36. These will be presented in summary tables by treatment and study visit.

Protocol Amendments:
Minor amendments were made to the protocol which did not affect safety or efficacy results.

6 Review of Efficacy

Efficacy Summary

Efficacy of CT-P13 was primarily assessed in Study 3.1, the clinical comparative study (CCS), comparing CT-P13 with EU-approved Remicade in patients with RA. Study 1.1, the PK study in AS patients, was a supportive study in assessing efficacy of CT-P13 compared to EU-approved Remicade as a secondary objective. The FDA evaluation of efficacy focused on the two large, randomized, double-blind controlled studies 3.1 and 1.1 in RA and AS patients, respectively. Long-term extension studies 3.2 (extension to study 3.1 in RA) and 1.3 (extension to study 1.1 in AS) with a single transition from EU-approved Remicade to CT-P13 provided descriptive assessment of efficacy with longer administration of CT-P13.

Study 3.1 met its primary objective of demonstrating that the proportion of patients achieving ACR20 response at week 30 was similar between the CT-P13 and EU-

Reference ID: 3747317

approved Remicade treatment groups (184 (61%), and 179 (59%) patients, respectively. The 95% CI for the estimate of treatment difference was contained within applicant-prespecified similarity margin of -15% to 15% (95% CI: -0.06, 0.10). Of note, as discussed in detail in the FDA statistical review, the Agency has determined that a ±12% similarity margin would be generally expected, based on considerations of the clinical importance of different losses in effect against the feasibility of the comparative clinical study. The results from the primary analysis were supported by consistent sensitivity analyses and were also within the margin preferred by the Agency. These results support the conclusion of no clinically meaningful differences between CT-P13 and EU-approved Remicade in RA.

Analysis of key secondary efficacy endpoints in Study 3.1 including disease activity score DAS28, individual component of the ACR20 criteria, ACR50 and ACR70 responses showed similar results between CT-P13 and EU-approved Remicade treatment groups.

The supportive study, Study 1.1 also met its key secondary efficacy endpoints by demonstrating that the proportion of patients achieving ASAS20 and ASAS40 responses at week 30 was similar between the CT-P13 and EU-approved Remicade treatment groups. These results provide further support of no clinically meaningful differences between CT-P13 and EU-approved Remicade in a different patient population and using a different dosing regimen, i.e. 5 mg/kg without background methotrexate immunosuppression.

The two long-term extension studies, study 3.2 (extension to study 3.1) and study 1.3 (extension to study 1.1) had a single transition from EU-approved Remicade to CT-P13 at week 54. Efficacy endpoint analysis demonstrated consistent efficacy up to week 102 in each treatment group, CT-P13 maintenance and CT-P13 transition groups across both studies 3.2 and 1.2.

FDA's analysis of the key primary and secondary endpoints was in agreement with the Applicant's.

6.1 Indication

The proposed therapeutic indications, dosage and route of administration (intravenous infusion over a period of not less than 2 hours) for CT-P13 are identical to those of the reference product, US-licensed Remicade; listed below:

<u>Rheumatoid Arthritis (RA):</u>
Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis. To be administered in conjunction with methotrexate (MTX) at doses of 3 mg/kg at 0, 2 and 6 weeks, then every 8 weeks; for patients who have an incomplete

Reference ID: 3747317

response, consideration may be given to adjusting the dose up to 10 mg/kg or treating as often as every 4 weeks.

Ankylosing Spondylitis (AS):
Reducing signs and symptoms in patients with active ankylosing spondylitis. Recommended dosing is 5 mg/kg at 0, 2 and 6 weeks, then every 6 weeks.

Psoriatic Arthritis (PsA):
Reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in patients with psoriatic arthritis. Recommended dosing is 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks with or without MTX.

Plaque Psoriasis(Ps):
Treatment of adult patients with chronic severe (i.e., extensive and /or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate. Recommended dosing is 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.

Crohn's Disease (CD):

- Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely Crohn's active disease who have had an inadequate response to conventional therapy.
- Reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing Crohn's disease.
- Recommended dosing is 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. Some adult patients who initially respond to treatment may benefit from increasing the dose to 10 mg/kg if they later lose their response. Patients who do not respond by Week 14 are unlikely to respond with continued dosing and consideration should be given to discontinue.

Pediatric Crohn's Disease:
Reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. Recommended dosing is 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.

Ulcerative Colitis (UC):
Reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy. Recommended dosing is 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.

Pediatric Ulcerative Colitis:

Reference ID: 3747317

Reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy. Recommended dosing is 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.

6.1.1 Methods

In the context of a biosimilar development program, the objective of the clinical development program of a proposed biosimilar is to help resolve any residual uncertainties that arise after a robust analytical similarity is established between the proposed biosimilar and the reference product. As such, the clinical development program of CT-P13 was designed to assess efficacy and safety of CT-P13 in a limited number of clinical studies.

Efficacy of CT-P13 was primarily assessed in Study 3.1, the clinical comparative study (CCS), comparing CT-P13 with EU-approved Remicade in patients with RA. Study 1.1, the PK study in AS patients, also assessed efficacy of CT-P13 compared to EU-approved Remicade as a secondary objective. Long-term extension studies 3.2 (extension to study 3.1 in RA) and 1.3 (extension to study 1.1 in AS) further contributed to evaluation of CT-P13's efficacy. Our evaluation of efficacy focuses on the two large, randomized, double-blind controlled studies 3.1 and 1.1 in RA and AS patients, respectively, with study 3.1 as the primary focus.

To demonstrate therapeutic similarity between CT-P13 and US-licensed Remicade, the applicant chose the indication of RA in the efficacy study (study 3.1) as RA has been well-studied among the anti-TNF indications. Further, use of infliximab has been well-characterized including PK & PD profiles, safety and efficacy in the RA population. The Agency agrees with the applicant's rationale that the study population is a sensitive population to use in the assessment of no clinically meaningful differences in the context of a proposed biosimilar development.

6.1.2 Demographics

As shown in Table 9, subjects' baseline demographics between the CT-P13 and EU-approved Remicade treatment groups in both controlled (Studies 3.1 and 1.1) studies were comparable.

In the RA controlled studies, the majority of patients were women with an age range between 18 and 75 years old. In study 3.1, majority of patients were white and from the Eastern European region. In study 3.3 (Russia), all patients were white. And in studies 1.2 (Philippines) and B1P13101, all patients were Asian.

Reference ID: 3747317

In the AS controlled study, as expected, there were more male patients than female patients with a median age of 39 years. The majority of patients were white and from the Eastern European region.

Demographic characteristics were also similar between the treatment groups in the extension studies 3.2 and 1.3 as shown in Table 10.

Table 9 Baseline Demographic Characteristics in the Key Clinical Studies (Controlled Studies)

	Rheumatoid Arthritis		Ankylosing Spondylitis		Healthy Volunteers		
Study Number	Study 3.1		Study 1.1		1.4		
	CT-P13 3mg/kg (n=302)	EU-approved Remicade 3mg/kg (n=300)	CT-P13 5mg/kg (n=128)	EU-approved Remicade 5mg/kg n=122)	CT-P13 5mg/kg (n=71)	EU-approved Remicade 5mg/kg (n=71)	US-licensed Remicade 5mg/kg (n=71)
Age, years Mean (SD)	49(12)	49(12)	39(12)	39(10)	40.5(10)	42.6(9)	39(11)
Gender,n(%)							
Female	245(81)	252(84)	26(20)	22(18)	10(14)	10(14)	10(14)
Male	57(19)	48(16)	102(80)	100(82)	61(86)	61(86)	61(86)
Race, (%)							
White	220(73)	219(73)	98(77)	91(75)	71(100)	69(97)	70(99)
Black	2(<1)	1(<1)			0	1 (1)	0
Asian	34(11)	36(12)	16(13)	13(11)	0	0	0
Other	46(15)	44(15)	14(11)	18(15)	0	0	1(1)
Region(n%)							
Eastern Europe	179(59)	180(60)	81(63)	82(67)			
Western Europe	16(5)	17(6)	7(6)	3(3)	71(100)	71(100)	71(100)
Latin America	72(24)	66(22)	24(19)	25(21)			
Asia	34(11)	37(12)	16(13)	12(10)			
Height, cm mean (SD)	163 (9)	163(9)	172(10)	171(9)	179(8)	178(8)	178(9)
Weight, kg mean (SD)	71(16)	70 (16)	75(16)	76(14)	80(10)	79(11)	78(11)
Methotrexate use mg/week (SD)	15(3)	15(3)	1	0	-	-	-

Source: Summary of Clinical safety, section 2.7.4.1.4; CSR 3.1, Table 14.1.4

Table 10. Demographic Characteristics (Extension Studies)

	Rheumatoid Arthritis		Ankylosing Spondylitis	
Study Number	Study 3.2		Study 1.3	
	CT-P13 Maintenance (n=159) n (%)	CT-P13 Transition (n=143) n (%)	CT-P13 Maintenance (n=90) n (%)	CT-P13 Transition n=84) n (%)
Age, years Mean (SD)	49(10)	49(11)	38(12)	39(10)
Gender,n(%)				
Female	126(79)	121(84)	20(22)	12(14)
Male	33(21)	22(15)	70(78)	72(86)
Race, (%)				
White	120(76)	104(73)	70(78)	61(73)
Black	1(<1)	1(<1)		
Asian	17(11)	10(7)	10(11)	11(13)
Other	21(13)	28(20)	10(11)	12(14)
Region(n%)				
Eastern Europe	179(59)	180(60)	81(63)	82(67)
Western Europe	16(5)	17(6)	7(6)	3(3)
Latin America	72(24)	66(22)	24(19)	25(21)
Asia	34(11)	37(12)	16(13)	12(10)

Source: Summary of clinical safety, section 2.7.4.1.4

Concomitant Medication: co-administration of methotrexate and folic acid only in study 3.1.

For both the initial dose of MTX (taken at the date of first infusion) and the most recent dose of MTX, the mean (SD) dose taken was similar in the CT-P13 and EU-approved Remicade treatment groups. For the initial dose of MTX, the mean (SD) dose was 15.60 (3.08) mg/week and 15.61 (3.16) mg/week in the CT-P13 and EU-approved Remicade treatment groups, respectively. For the most recent dose of MTX, the mean (SD) dose was 15.41 (2.92) mg/week and 15.54 (3.19) mg/week in the CT-P13 and EU-approved Remicade treatment groups, respectively.

6.1.3 Subject Disposition

Subject disposition was similar between treatment groups in each study. The proportion of subjects discontinuing the study due to an adverse event or lack of efficacy was also similar between treatment groups.

Table 11. Patient Disposition

	Rheumatoid Arthritis		Ankylosing Spondylitis		Healthy Volunteers		
Study Number	Study 3.1		Study 1.1		1.4		
	CT-P13 3mg/kg (n=302) n(%)	EU-approved Remicade 3mg/kg (n=304) n(%)	CT-P13 5mg/kg (n=125) n(%)	EU-approved Remicade 5mg/kg n=125) n(%)	CT-P13 5mg/kg (n=71) n(%)	EU-approved Remicade 5mg/kg (n=71) n(%)	US-licensed Remicade 5mg/kg (n=71) n(%)
ITT Population							
• Screened	302(100)	304(100)					
• Randomized	300(99)	302(99)	125(100)	125(100)	71(100)	71(100)	71(100)
• Completed entire study	233(77)	222(73)	106(85)	104(83)	70(99)	71(100)	70(99)
• Total Discontinued	69(23)	82(27)	19(15)	21(17)			
Primary reason for Discontinuations							
• Lack of efficacy	10(3)	6(2)	2(2)	0			
• Adverse event	31(10)	41(14)	10(8)	8(6)			
• Death	0	1(<1)	0	2(2)			
Other withdrawals							
• Protocol violation	2(<1)	2(<1)	0	1(<1)	1(1)		
• Withdrew consent	16(5)	21(7)	3(2)	6(5)			1(1)

Source: Summary of Clinical Efficacy, Tables 2.7.3-6, 2.7.3-30. CSR 1.4, Table 10-1

6.1.4 Analysis of Primary Endpoint(s)

6.1.4.1 General discussion of choice of major endpoints

Primary Endpoint: ACR20 response

In Study 3.1, the key clinical comparative study, the proportion of subjects achieving an ACR 20 at Week 30 was used as the primary endpoint for improvement in signs and symptoms. The American College of Rheumatology's response in RA (ACR20) is calculated as a ≥20% improvement in:

- tender joint count (68) and
- swollen joint counts (66) and
- 3 of the 5 remaining ACR-core set measures:
  - patient global assessments of arthritis on a visual analog scale (VAS),
  - physician global assessment of arthritis on a VAS,
  - patient reported pain on a VAS,
  - patient assessment of physical function (e.g., Health Assessment Questionnaire-Disability Index [HAQ-DI], and

- acute-phase reactant (e.g., CRP).

Similarly, ACR50, and 70 are calculated with the respective percent improvement and were assessed as major secondary endpoints.

The primary efficacy analysis was performed on both the all-randomized and the PP population. All other efficacy analyses were performed on the PP population only.

Study 3.1 (CCS study)

The primary efficacy endpoint was the proportion of patients achieving ACR20 response at Week 30, i.e., a 20% improvement by ACR criteria.

Study 3.1 met its primary endpoint. In the all-randomized population (302 patients in the CT-P13 group and 304 patients in the EU-approved Remicade group), the proportion of patients achieving ACR20 clinical response at Week 30 was similar in the CT-P13 and EU-approved Remicade treatment groups (184 (61%), and 179 (59%) patients, respectively. The 95% CI for the estimate of treatment difference was contained within the applicant-prsepecified safety margin of -15% to 15% (95% CI: -0.06, 0.10) indicating therapeutic equivalence between the treatment groups. Applicant's analysis is presented in Table 12. The FDA statistical review of efficacy was in agreement with the applicant's analyses.

Table 12. Proportion of Patients Achieving ACR20 response at Week 30 - Study 3.1, All-randomized population

	CT-P13 (5mg/kg) n=302 (%)	EU-approved Remicade (5mg/kg) n=304 (%)	Estimate of Treatment Difference	95% CI of Treatment Difference
Week 30	184/302 (61)	179/304 (59)	0.02	(-0.06, 0.10)

CI, confidence interval.
Source: Summary of Clinical Efficacy, Table 2.7.3-8

Of note, as discussed in detail in the FDA statistical review, the Agency has determined that a ±12% similarity margin would be generally expected, based on considerations of the clinical importance of different losses in effect against the feasibility of the comparative clinical study. In study 3.1, the 90% CI (-4.6%, +8.7%) ruled out the margin of ±13% proposed by the applicant in addition to the margin of ±12% that the Agency has determined reasonable. The lower 90% CI bound of -4.6% also corresponds to the preservation of approximately 80% of conservative estimates of the effect of infliximab from historical trials, as detailed in the FDA statistical review.

Results for the per-protocol (PP) population supported the results for the all-randomized population as shown in Table 13. The per-protocol population consisted of all randomly assigned patients who did not have any major protocol deviations, received all doses of

Reference ID: 3747317

study treatment up to Week 30, had an ACR assessment at Week 30, and did not discontinue or reduce their methotrexate dose for more than 2 consecutive weeks up to Week 30.

At Week 30, the PP population comprised a total of 499 patients; 248/302 (82.1%) randomized to CT-P13 and 251/304 (82.6%) randomized to EU-approved Remicade as shown in Table 13.

Table 13. Proportion of Patients Achieving ACR20 response at Week 30 - Study 3.1, Per-Protocol population

	CT-P13 (5mg/kg) n=248 (%)	EU-approved Remicade (5mg/kg) n=251 (%)	Estimate of Treatment Difference	95% CI of Treatment Difference
Week 30	182/248 (73)	176/251 (70)	0.03	(-0.05, 0.11)

Source: Summary of Clinical Efficacy, Table 2.7.3-8

As noted in Section 3.1 Submission Quality and Integrity, drug accountability data were missing from an infusion center at site 2007 between January and June 2011. To account for the uncertainty of which product was administered to which subject, FDA conducted additional sensitivity analysis of the primary endpoint, excluding the data from all subjects in question. In the intention-to-treat population from study 3.1, a total of 18 patients received product infusions at site 2007 during the abovementioned time frame. FDA's efficacy analysis after removing the 18 subjects did not change the overall conclusion of the primary endpoint. The estimated difference in ACR20 response at Week 30 between CT-P13 and EU-approved Remicade, rounded to the nearest whole number, stayed the same at +2% (90% CI: -5%, +9%). Efficacy results did not change in FDA's sensitivity analysis after removing data from this site.

In summary, the primary analysis of study 3.1 in patients with RA, met its objective and supports the conclusion of no clinically meaningful differences between CT-P13 and EU-approved Remicade in RA.

Study 1.1 (PK study in AS patients)

Efficacy in AS patients was evaluated as a secondary endpoint. For efficacy endpoint analyses from study 1.1, see Section 6.1.5.2 Ankylosing Spondylitis patients

6.1.5 Analysis of Key Secondary Endpoints(s)

6.1.5.1 Rheumatoid Arthritis patients

1. Individual components of the ACR Criteria

In the all-randomized population, mean decreases from baseline to Week 14, 30, and 54 were similar in the CT-P13 and EU-approved Remicade treatment groups for the individual ACR components as shown in Table 14. The results of the PP population supported the results for the all-randomized population for each of the individual parameters of the ACR criteria.

Table 14. Individual ACR components - Baseline Values and Change from Baseline at Weeks 14, 30 and 54 in Study 3.1

ACR Component	CT-P13 3mg/kg N=302 Mean(SD)	EU-approved Remicade 3mg/kg N=304 Mean(SD)
Number of Tender Joints		
Baseline	26(14)	24(13)
Week 14	-14(12)	14(12)
Week 30	-16(12)	-16(13)
Week 54	-17(12)	-15(12)
Number of Swollen Joints		
Baseline	16(9)	15(8)
Week 14	-11(8)	-10(8)
Week 30	-12(9)	-12(9)
Week 54	-12(9)	-12(9)
Patient assessment of Pain (VAS, 0-100)		
Baseline	66(17)	66(17)
Week 14	-29(24)	-27(24)
Week 30	-29(26)	-28(25)
Week 54	-31(24)	-29(27)
Physician global assessment of disease activity (VAS, 0-100)		
Baseline	65(14)	65(13)
Week 14	-34(21)	-33(20)
Week 30	-36(20)	-35(21)
Week 54	-37(22)	-36(22)
HAQ Physical Ability (scale 0-3)		
Baseline	2(0.6)	2(0.6)
Week 14	-0.6(0.6)	-0.5(0.5)
Week 30	-0.6(0.6)	-0.5(0.6)
Week 54	-0.6(0.6)	-0.5(0.6)
CRP(mg/dL)		
Baseline	1.9(2)	1.9(2)
Week 14	-0.6(3)	-0.8(2)
Week 30	-0.7(2)	-0.7(2)
Week 54	-0.7(2)	-0.7(3)
ESR(mm/h)		
Baseline	47(22)	49(23)
Week 14	-14(21)	-17(20)
Week 30	-15(21)	-16(22)
Week 54	-12(22)	-16(22)

Source: Summary of clinical efficacy, Table 2.7.3.-9

2. DAS28, measure of disease activity

Disease Activity Score (DAS)28<2.6

In addition to assessing ACR criteria for response to treatment, disease activity was also measured in the RA studies using Disease Activity Score (DAS) which is a composite endpoint with differential weighting given to each component. The components of the DAS28 arthritis assessment include:

- tender joint count (28 joints to include bilateral shoulders, elbows, wrists, metacarpophalangeal joints, proximal interphalangeal joints, and knees.),
- swollen joint count (28),
- an acute phase reactant (ESR or CRP)
- patient's global assessment of arthritis.

There is a fair amount of overlap with the ACR response criteria, as DAS also uses tender and swollen joint counts, along with an inflammatory marker (ESR or CRP), and a physician's global assessment to calculate a disease activity score. However there are a number of important differences: 1) DAS describes disease activity at a given point in time, whereas ACR responses describe relative improvement; 2) DAS28 uses an abbreviated joint count that does not include the joints of the feet; 3) ACR responses incorporate patient-reported pain and an assessment of physical function as part of the core variables whereas the DAS does not.

The DAS components are summed mathematically into a single numerical value ranging from 0 to 10. A DAS28 score >5.1 is indicative of high disease activity, and <2.6 of low disease activity. A change of ≥1.2 in DAS28 score is considered clinically significant. DAS28-4(ESR) uses all 4 components listed above and ESR as the acute-phase reactant. DAS28-3(CRP) uses CRP as the acute-phase reactant but does not include the Patient's Global Assessment of Arthritis.

Results from Study 3.1: Consistent with the primary endpoint of the study, the mean scores for disease activity score, DAS28, and number of tender and swollen joints measured by DAS28 decreased in a similar manner in both treatment groups, CT-P13 and EU-approved Remicade from baseline to weeks 14, 30 and 54, as shown in Table 15.

Reference ID: 3747317

Table 15. DAS28 Disease Activity Scores in Study 3.1 (Per-protocol population)

	CT-P13 3mg/kg Mean (SD)	EU-approved Remicade 3mg/kg Mean(SD)
Disease activity: DAS28 (ESR)		
Baseline	7(0.8)	7(0.8)
Week 14	-2(1)	-2(1)
Week 30	-2(1)	-2(1)
Week 54	-2(1)	-2(1)
Disease activity: DAS28 (CRP)		
Baseline	6(0.9)	6(0.9)
Week 14	-2(1)	-2(1)
Week 30	-2(1)	-2(1)
Week 54	-2(1)	-2(1)
Number of tender joints		
Baseline	16(6)	15(6)
Week 14	-9(6)	-8(6)
Week 30	-10(6)	-10(6)
Week 54	-10(7)	-9(6)
Number of swollen joints		
Baseline	12(5)	12(5)
Week 14	-8(5)	-7(5)
Week 30	-9(5)	-8(6)
Week 54	-9(6)	-8(5)

Source: Summary of Clinical Efficacy, Table 2.7.3-12

3. ACR50 and ACR70

Similar to ACR20, the ACR50 and ACR70 are calculated as the respective percent improvement and were assessed as major secondary endpoints. Consistent with the primary endpoint of the study, the proportion of patients achieving ACR50 and 70 at weeks 30 and 54 in study 3.1 was similar between the two treatment groups, CT-P13 and EU-approved Remicade, as shown in Table 16. Statistically, there was no difference between the treatment groups.

Table 16. Proportion of Patients Achieving ACR20, ACR50 and ACR 70 at Weeks 30 and 54 (using Exact Binomial Method) in Study 3.1 - Per-Protocol Population

	Efficacy Parameter	Treatment Group	n/N(%)	Estimate of Treatment Difference	95% CI of Treatment Difference
Week 30	ACR20	CT-P13	182/248 (73)	0.03	(-0.05, 0.11)
		EU-approved Remicade	176/251 (70)		
	ACR50	CT-P13	106/248 (43)	0.03	(-0.06, 0.11)
		EU-approved Remicade	101/251 (40)		
	ACR70	CT-P13	50/248 (20)	0.02	(-0.05, 0.09)
		EU-approved Remicade	45/251 (18)		
Week 54	ACR20	CT-P13	168/225 (75)	0.03	(-0.05, 0.12)
		EU-approved Remicade	154/216 (71)		
	ACR50	CT-P13	98/225 (43)	0.00	(-0.09, 0.10)
		EU-approved Remicade	93/216 (43)		
	ACR70	CT-P13	48/225 (21)	0.01	(-0.06, 0.09)
		EU-approved Remicade	43/216 (20)		

Source: Summary of Clinical Efficacy, Table 2.7.3-15

4. SDAI and CDAI

SDAI (simplified disease activity index) and CDAI (Clinical Disease Activity Index (CDAI) were calculated using the following equations:
CDAI = SJC28+TJC28+PGA+EGA
SDAI = SJC28+TJC28+PGA+EGA+CRP
Where,

TJC28 = number of tender joints (0 to 28): tender joint count (TJC)
SJC28 = number of swollen joints (0 to 28): swollen joint count (SJC)
PGA = patient global assessment of disease activity (0 to 10 cm)
EGA = evaluator/physician global assessment of disease activity (0 to 10 cm)
CRP = C-reactive protein (mg/dL)

In study 3.1, the mean decreases from baseline in SDAI and CDAI scores were similar in the CT-P13 and EU-approved Remicade treatment groups at Weeks 30 and 54 as shown in Table 17.

Table 17. SDAI and CDAI, Change from Baseline at Weeks 30 and 54 in Study 3.1 - Per-protocol Population

	SDAI		CDAI	
	CT-P13	EU-approved Remicade	CT-P13	EU-approved Remicade
Baseline Mean (SD)	42 (12)	41 (12)	41 (11)	40 (11)
Week 14 Change from Baseline Mean (SD)	-24 (13)	-22 (12)	-24 (12)	-22 (12)
Week 30 Change from Baseline Mean (SD)	-26 (14)	-25 (14)	-25 (13)	-24 (13)
Week 54 Change from Baseline Mean (SD)	-26 (14)	-25 (14)	-26 (13)	-24 (13)

Source: Summary of Clinical Efficacy, Table 2.7.3-17

6.1.5.2 Ankylosing Spondylitis patients

Study 1.1,was designed to assess pharmacokinetic similarity of CT-P13 compared with EU-approved Remicade using a different dosing regimen (5 mg/kg without background methotrexate or other immunosuppression) in a different distinct patient population with active AS up to Week 30. The secondary objectives of this study were to assess long-term efficacy, safety and PK up to Week 54.

Efficacy Endpoints:

1. Proportion of patients achieving ASAS20 and ASAS40 responses at weeks 14, 30 and 54

The ASAS20 (Assessment of SpondyloArthritis International Society(ASAS)) response is defined as an improvement of at least 20% and an absolute improvement of at least 1 unit on a 0 to 10 scale from baseline in at least 3 of the following domains:

- Patient global assessment of disease status
- Patient assessment of spinal pain
- Function according to BASFI
- Morning stiffness determined using the last 2 questions of BASDAI

Additionally, ASAS20 responders should not have deterioration (worsening of ≥20% and an absolute worsening of at least 1 unit on a 0 to 10 scale) of the remaining assessment domain compared to baseline.

ASAS40 responders are defined as an improvement of at least 40% and an absolute improvement of at least 2 units on a 0 to 10 scale from baseline in at least 3 of the 4 domains of the ASAS20, with no deterioration from baseline in the remaining domain.

Results from Study 1.1:

The proportion of patients achieving clinical response according to the ASAS20 and ASAS40 criteria at Weeks 14, 30, and 54 was similar in the CT-P13 and EU-approved Remicade treatment groups, as shown in Table 18.

Table 18. Study 1.1 - Proportion of patients achieving ASAS20 and ASAS40 response - All randomized population

	Efficacy Parameter	Treatment Group	n/N(%)	Odds Ratio	95% CI of the Odds Ratio
Week 14	ASAS20	CT-P13	72/115 (63)	0.9	0.5, 1.5
		EU-approved Remicade	79/122 (65)		
	ASAS40	CT-P13	48/115 (42)	0.9	0.5, 1.4
		EU-approved Remicade	56/122 (46)		
Week 30	ASAS20	CT-P13	79/112 (71)	0.9	0.5, 1.6
		EU-approved Remicade	84/116 (72)		
	ASAS40	CT-P13	58/112 (52)	1.2	0.7, 2.0
		EU-approved Remicade	55/116 (47)		
Week 54	ASAS20	CT-P13	71/106 (67)	0.9	0.5, 1.6
		EU-approved Remicade	75/108 (69)		
	ASAS40	CT-P13	58/106 (55)	1.3	0.7, 2.1
		EU-approved Remicade	53/108 (49)		

Source: Summary of Clinical Efficacy, Table 2.7.3.-32

2. BASDAI, BASFI, BASMI and Chest expansion

Mean BASDAI, BASFI and BASMI scores, all decreased from baseline to Weeks 14, 30 and 54 in both treatment groups, CT-P13 and EU-approved Remicade. The mean decrease from baseline was similar in both treatment groups at Weeks 14, 30 and 54.

The mean chest expansion increased from baseline to Weeks 14, 30 and 54 within each treatment group and the mean increase was similar between both treatment groups. Results for Weeks 30 and 54 are shown in Table 19.

Table 19. Study 1.1 - BASDAI, BASFI, BASMI, and Chest Expansion Baseline And Change from Baseline Values - All Randomized Population

	CT-P13 3mg/kg N=125 Mean (SD)	EU-approved Remicade 3mg/kg N = 125 Mean(SD)
BASDAI Score		
Baseline	6.7 (1.4)	6.6 (1.6)
Change from Baseline		
Week 30	-3.0 (2.2)	-2.7 (2.2)
Week 54	-3.0 (2.3)	-2.8 (2.2)
BASFI Score		
Baseline	6.2 (1.9)	6.2 (2.2)
Change from Baseline		
Week 30	-2.6 (2.2)	-2.5 (2.2)
Week 54	-2.9 (2.3)	-2.7 (2.1)
BASMI Score		
Baseline	4.0 (2)	4.1 (2)
Change from Baseline		
Week 30	-1.0 (1.4)	-0.9 (1.4)
Week 54	-1.1 (1.5)	-0.9 (1.6)
Chest Expansion (cm)		
Baseline	3.1 (1.3)	2.9 (1.3)
Change from Baseline		
Week 30	0.6 (1.4)	0.8 (1.2)
Week 54	0.7 (1.4)	0.9 (1.2)

Source: Summary of Clinical Efficacy, Table 2.7.3-33

Overall, the results from study 1.1 provide further support for the conclusion of no clinically meaningful differences between CT-P13 and EU-approved Remicade providing data from a different dosing regimen (5 mg/kg monotherapy) in a different patient population (ankylosing spondylitis).

6..1.5.2 Efficacy Endpoints in Extension Studies

1. Study 3.2 (RA patients)

Study 3.2 was an open-label extension of Study 3.1, in which 302 patients from Study 3.1 were enrolled; 158 patients and 144 patients in the CT-P13 maintenance and CT-P13 transition groups, respectively. A total of 261 (96%) patients completed the study

(133 (84%) patients and 128 (89)% patients in the CT-P13 maintenance and transition groups, respectively).

Key efficacy endpoints

1. Proportion of patients achieving ACR20, 50 and 70 response at Weeks 54, 78 and 102 were similar between the CT-P13 maintenance and transition groups.

2. The mean scores for DAS28 (ESR) and DAS28 (CRP), measuring disease activity, decreased from baseline at weeks 54, 78 and 102 in each treatment group and were similar between the two treatment groups, CT-P13 maintenance and transition groups.

2. Study 1.3 (AS patients)

Study 1.3 was an open-label extension of Study 1.1 in which 175 patients from Study 1.1 were enrolled; 88 patients and 86 patients in the CT-P13 maintenance and transition groups, respectively. A total of 158 (91%) patients completed the study (81 (92%) patients and 77 (90%) patients in the CT-P13 maintenance and transition groups, respectively).

Key efficacy endpoints

1. The proportion of patients achieving ASAS20 and ASAS40 responses at weeks 54, 78 and 102 were similar at each time point between the CT-P13 maintenance and transition groups.

The results from the open-label extension studies 3.2 and 1.3, suggest that the overall efficacy is consistent with efficacy at earlier time points and is comparable between patients who transition from EU-approved Remicade to CT-P13 and those who continue CT-P13. However, methodological limitations, such as the open label nature of the studies and associated biases, and the missing data, preclude definitive conclusions.

6.1.6 Other Endpoints

1 Radiographic Progression

While radiographic endpoints are generally not expected for comparative clinical studies in RA, the applicant has included radiographic assessment in study 3.1 using the change from baseline in total van der Heijde radiographic joint score at Week 54. Original analysis of joint damage progression showed a similar decrease in the modified sharp score at Week 54 for CT-P13 compared to EU-approved Remicade in study 3.1 (difference: 2.6; 95% CI: -2.7, 7.9) but the within-group mean changes on the two arms (-28.5 and -31.9) was significantly larger compared to historical studies with infliximab (where the change was closer to zero). The Applicant, therefore, conducted a post-hoc

Reference ID: 3747317

re-evaluation of the radiographs from baseline and Week 54 using a similar approach as used in the historical studies with Infliximab. In the original assessment, a single reader evaluated a patient's radiographs with knowledge of the chronological order of the images. The re-evaluation utilized two independent readers without knowledge of the order of the radiographs, evaluating paired, rather than individual radiographs of the patient. Based on that re-evaluation, the average changes on the two arms remained similar, and the within-group changes from baseline were more in line with those of historical trials. However, the fact that a post hoc reassessment was needed precludes definitive conclusion regarding the radiographic data.

2. Quality-of-Life Questionnaire (SF-36) at Weeks 30 and 54

Mean increases from baseline at Weeks 30 and 54 were similar in both treatment groups, CT-P13 and EU-approved Remicade for SF-36 components in Study 3.1 (clinical comparative study in RA patients). Additionally in study 1.1 (PK trial in AS patients), the mean increases in SF-36 components from baseline at weeks 30 and 54 were also similar between the two treatment groups.

6.1.7 Subpopulations

Refer to Dr. Gregory Levin's detailed statistical review.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable to this application.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Refer to Dr. Gregory Levin's detailed statistical review.

6.1.10 Additional Efficacy Issues/Analyses

The applicant's sensitivity analysis for key primary and secondary efficacy endpoints to account for missing data demonstrated results consistent with primary analysis. FDA's analysis of key primary and secondary efficacy endpoints was consistent with the applicant's analysis. Refer to Dr. Gregory Levin's detailed statistical review.

Study B1P13101 (Supportive study in Japanese patients with RA)

Study B1P13101, a supportive study in Japan, was a double-blind, parallel-group, comparative study of CT-P13 and EU-approved Remicade for treatment of patients with RA. The study enrolled 108 patients, of which 104 patients, 51 patients in the CT-P13 and 53 patients in EU-approved Remicade treatment groups, respectively, were included in the efficacy analysis set defined as patients who received at least one dose

Reference ID: 3747317

of either CT-P13 or EU-approved Remicade. This was a primarily PK study with efficacy and safety as secondary objectives.

Demographic and baseline characteristics were similar between the treatment groups with an average age of 54 +/-13 years in the CT-P13 group and 54 +/-13 years in the EU-Remicade group. Both groups enrolled more women than men (80% in the CT-P13 group and 79% in the EU-Remicade group). Disease duration was similar with 6 +/-5 years in the CT-P13 group and 6 +/-6 years in the EU-Remicade group.

Efficacy Endpoints:
The proportion of patients achieving a clinical response according to ACR20 at Week 30 was comparable between the CT-P13 and EU-approved Remicade treatment groups. Results for ACR50 and ACR70 at Week 30 were also comparable, as shown in Table 20. These results are overall consistent with the efficacy seen in the comparative clinical study 3.1 and supportive of no clinically meaningful differences observed between CT-P13 and EU-approved Remicade in RA.

Table 20. Japanese Study - Proportion of Patients Achieving ACR20, 50 and 70 at Week 30

	Efficacy Parameter	Treatment Group	n/N(%)	Estimate of Treatment Difference	95% CI of Treatment Difference
Week 30	ACR20	CT-P13	38/50 (76)	13.3	(-6, 33)
		EU-approved Remicade	32/51 (63)		
	ACR50	CT-P13	26/50 (52)	4.9	(-15, 25)
		EU-approved Remicade	24/51 (47)		
	ACR70	CT-P13	15/50 (30)	2.5	(-17, 21)
		EU-approved Remicade	14/51 (28)		

Source: Summary of Clinical Efficacy, Section 2.7.3, CSR B1P13101 Section 11, Table 11-14

7 Review of Safety

Safety Summary

The clinical development program for CT-P13 was designed with the objective of assessing for clinically meaningful differences between CT-P13 and the reference product, US-Remicade by comparing PK, efficacy and safety. As such, the safety evaluation plan of CT-P13 was based on the known safety profile of US-licensed Remicade as presented in the USPI and other published data.

The safety population for CT-P13 is comprised of 803 patients including patients from the comparative clinical study in RA (Study 3.1), PK studies in AS (Study 1.1) and healthy volunteers (Study 1.4) as well as extension studies to the RA study (Study 3.2)) and the AS study (Study 1.3).

In summary, no new safety signals were identified in the CT-P13 group compared to the known adverse event profile of the reference product, US-licensed Remicade. Overall, there were no major differences in treatment-emergent adverse events, serious adverse events, and adverse events leading to discontinuations, and deaths between the treatment groups. Infections were the most common adverse event in all treatment groups (CT-P13, US-licensed Remicade and EU-approved Remicade). Numerical differences in serious infections, driven by small number of cases of TB, and pneumonia, were observed between CT-P13 and EU-approved Remicade in study 3.1. However, the differences are small and the types and overall incidence of the events are within what is expected from the US-licensed Remicade and do not indicate a clinically meaningful difference in the populations studies. Most frequent adverse events leading to discontinuation were hypersensitivity reactions, infusion-related reactions and infections. A total of four deaths occurred in the CT-P13 development program with 2 each in CT-P13 and EU-Remicade treatment groups. All deaths were assessed as unrelated to the treatment regimen. Cases of anaphylaxis were balanced between the two groups, with 7 cases in each group (CT-P13 and EU-Remicade). Rates of anaphylaxis did not increase following transition from EU-Remicade to CT-P13.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Studies 3.1 (comparative clinical study (CCS) in RA), 1.4 (PK study in healthy volunteers) , 1.1 (PK study in AS) and extension studies to the RA study (study 3.1) and to the AS study (study 1.3) make up the key studies used to evaluate safety in the CT-P13 clinical development program. Supportive safety information was also provided from studies B1P13101 (Japan), 1.2 (Philippines), 3.3 (Russia) in patients with RA.

Majority of the safety data comes from studies comparing CT-P13 and EU-approved Remicade. US-licensed Remicade was used only in study 1.4. The objectives of the study were to establish a, 3-way PK bridge between CT-P13, EU-approved Remicade and the reference product, US-licensed Remicade to further support the applicability of the data generated using EU-approved Remicade as discussed in detail in Section 4.4. And consequently study 1.4 justifies the use of safety and efficacy data from studies comparing CT-P13 to EU-Remicade in this biosimilar application.

Reference ID: 3747317

The safety population, defined as patients exposed to at-least one dose of study treatment, is comprised of 803 patients who were exposed to at least one dose of CT-P13, summarized in Table 21 below.

Table 21. Exposure to CT-P13: Number of Subjects receiving at least 1 dose of CT-P13 in Controlled and Extension Studies

Subjects	Study	Safety Population CT-P13 group
RA	CT-P13 3.1 Extension Study 3.2	302 CT-P13 transition group (study 3.2): 143
AS	CT-P13 1.1 Extension Study 1.3	128 CT-P13 transition group (study 1.3): 84
RA	CT-P13 1.2	10 CT-P13 transition group: 8
RA	CT-P13 3.3	6
RA	B1P13101	51
Healthy Subjects	CT-P13 1.4	71
Total	-	803

Source: Summary of clinical safety Table 2.7.4-2

7.1.2 Categorization of Adverse Events

Safety was evaluated by monitoring of adverse events (AEs), serious adverse events (SAEs), treatment-emergent adverse events (TEAEs), death, hypersensitivity via vital signs, electrocardiogram (ECG), physical examination, clinical laboratory tests, concomitant medications and pregnancy. Adverse events of special interest (AESI) for US-licensed Remicade including infections, infusion-related reactions, and signs and symptoms of tuberculosis (TB) were also closely monitored. Safety parameters were selected based on the known safety profile of the reference product, US-licensed Remicade.

AE was defined as any untoward medical occurrence, including a clinically significant laboratory finding, symptom, or disease in a patient enrolled in the study regardless of its causal relationship to study drug. TEAE was defined as any event not present before exposure to study drug or any event already present that worsened in either severity or frequency after exposure to study drug. SAE was defined in accordance with ICH E2A (1994) as an event that resulted in death, was immediately life-threatening (including events which put patients at risk of death at the time of the event but not events which may have caused patient death if more severe), required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, or was a congenital anomaly/birth defect.

Reference ID: 3747317

The Medical Dictionary for Regulatory Activities (MedDRA) was used to code all AEs (MedDRA version 13.1 for Studies CT-P13 3.1 and CT-P13 1.1 and version 14.0 for Study CT P13 1.2, MedDRA version 15.1 for Studies CT-P13 1.3, CT-P13 3.2 and CT-P13 3.3, MedDRA version 16.1 for Study CT-P13 1.4 and MedDRA J version 16.0 for B1P13101).

7.1.3 Pooling of Data Across Studies to Estimate and Compare Incidence

All reported TEAEs, SAEs, AEs leading to discontinuation are presented per individual study without integrating data across studies and indications. Consistent with the BPD Type 4 meeting discussions, for AESI, the Applicant provided pooled analyses to allow review by individual studies and across all studies and indications. FDA conducted a supplementary integrated analysis of AESI.

Safety analyses include the following AESI:

- Vascular disorder
- Infections: all infection, serious infections, pneumonia, active TB, latent TB
- Infusion related reactions/Anaphylactic reaction using the Sampson's criteria (Sampson et all, 2006)
- Serious hepatobiliary events/Drug induced liver injury
- Malignancy and lymphoma

For the post hoc analyses and pooled analyses, the applicant recoded the safety data using MedDRA version 15.1. Further, the applicant retrospectively reviewed the safety database for anaphylactic reactions using the Sampson's' criteria (Sampson et al, 2006).

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The safety population across all CT-P13 clinical studies consists of 990 patients and 213 healthy subjects. And the safety population for CT-P13 is comprised of 803 subjects including patients and healthy subjects. Patients with RA received 3 mg/kg CT-P13 or EU-approved Remicade in combination with methotrexate and folic acid and patients with AS received 5 mg/kg CT P13 or EU-approved Remicade, respectively. Healthy subjects received single dose of 5mg/kg CT-P13, EU-approved Remicade or US-licensed Remicade.

Reference ID: 3747317

In Study 3.1 (CCS in RA), the total number of doses received by week 54 was similar in the CT-P13 and EU-approved Remicade groups, 8 vs. 7.9 doses respectively. The mean total doses (SD) administered were 1712.43 (608.32) mg in the CT-P13 group and 1672.77 (595.08) mg in the EU-approved Remicade group, respectively. The exposure to each drug was similar in both treatment groups throughout the study.

In Study 3.2 (Extension to study 3.1), the total number of doses of CT-P13 received up to and including week 102 were similar in the CT-P13 maintenance and the CT-P13 transition groups, 5.6 and 5.7 doses, respectively.

In Study 1.1 (PK study in AS), the total number of doses received by week 54 was 8.4 doses and 8.5 doses in the CT-P13 and EU-approved Remicade treatment groups, respectively. The mean (SD) total dose administered by week 54 was 3186.69 (969.08) mg and 3258.02 (861.51) mg in the CT-P13 and EU-approved Remicade treatment groups, respectively. The exposure to each drug was similar in both treatment groups throughout the study.

In Study 1.3 (Extension to study 1.1), the total number of doses of CT-P13 received up to and including week 102 were similar in the CT-P13 maintenance and the CT-P13 transition groups, 5.8 and 5.7 doses, respectively.

The overall exposure of patients was balanced for the two treatment groups (CT-P13 and EU-approved Remicade) throughout the controlled and extension studies.

7.2.2 Explorations for Dose Response

In this BLA, the dose and dosing regimen of CT-P13 is identical to the reference product, US-licensed Remicade. As such, dose-exploration studies were not conducted.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable to this BLA.

7.2.4 Routine Clinical Testing

Not applicable to this BLA.

7.2.5 Metabolic, Clearance, and Interaction Workup

No special metabolic, clearance and interaction workup studies were conducted for this application. For further details, please refer to Section Clinical Pharmacology.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Reference ID: 3747317

CT-P13 is under development as a proposed biosimilar to the reference product, US-licensed Remicade, a TNF inhibitor. The safety profile of CT-P13 was assessed in the context of known adverse event profile of US-licensed Remicade, other DMARDs and biologics.

7.3 Major Safety Results

A summary of treatment-emergent adverse events across the controlled studies is found in Table 22 below. Similar trends in safety were noted for the extension studies.

Table 22. Summary of TEAEs - Controlled Studies

	Rheumatoid Arthritis Study 3.1		**Ankylosing Spondylitis Study 1.1**		**Healthy Volunteers Study 1.4**		
	CT-P13 3mg/kg (n=302)	EU-Remi 3mg/kg (n=300)	CT-P13 5mg/kg (n=128)	EU-Remi 5mg/kg n=122)	CT-P13 5mg/kg (n=71)	EU-Remi 5mg/kg (n=71)	US-Remi 5mg/kg (n=71)
Total # of TEAEs # of pts with ≥1 TEAE, n (%)	732 213 (71)	738 211 (70)	362 95 (74)	375 82 (67)	67 37 (42)	28 21 (30)	54 33 (46)
Total # of SAEs # of pts with ≥1 SAE, n (%)	49 42 (14)	39 3 (10)	12 10 (8)	11 8 (7)	1 1 (1)	1 1 (1)	0 0
TEAEs leading to discontinuation # of pts (%)	40 33 (11)	52 47 (16)	12 11 (9)	9 9 (7)	0	0	0
Infections, n # of pts with ≥1 infection, n (%)	237 127 (42)	231 137 (46)	91 55 (43)	107 49 (40)	18 18 (25)	12 12 (17)	26 24 (34)
Serious Infections (SIE), n # of pts with ≥ 1SIE, n(%)	13 13(4)	8 7(2)	2 2 (2)	4 3(3)	0	0	0
Infusion-related reactions (IRR) # of pts with IRR, n(%)	12 10(3)	11 11(4)	0 0	4 4(3)	0	0	0
Anaphylaxis, n (%)	6 (2)	4 (1)	1 (<1)	3 (2)	0	0	0
Death, n	0	1	1	1	0	0	0

Source: CSR 3.1, table 12-2; CSR 1.1, table 12-2; CSR1.4, tables 12-2, 12-4 , 12-5. Summary of Clinical Safety Tables 2.7.4-57, 2.7.4-64, 2.7.4-27, 2.7.4-83, Integrated safety summary post hoc analysis, Table 2.17 SAEs: serious adverse events, TEAEs: treatment-emergent adverse events

No new safety signals were identified in the CT-P13 group compared to the known adverse event profile of infliximab. Overall, there were no major differences in treatment-emergent adverse events, serious adverse events, adverse events leading to discontinuations, and deaths between the treatment groups. Infections were the most common adverse event in all treatment groups (CT-P13, US-licensed Remicade and EU-approved Remicade). Most frequent adverse events leading to discontinuation were hypersensitivity reactions, infusion-related reactions and infections. A total of four deaths occurred in the CT-P13 development program with 2 each in CT-P13 and EU-approved Remicade treatment groups. All deaths were assessed as unrelated to the

Reference ID: 3747317

treatment regimen by the investigators. Cases of anaphylaxis were balanced between the two groups, with 7 cases in each group (CT-P13 and EU-approved Remicade). Rates of anaphylaxis did not increase following transition from EU-approved Remicade to CT-P13.

7.3.1 Deaths

A total of 4 deaths occurred in the CT-P13 development program, two each in the CT-P13 and EU-approved Remicade treatment groups. All four cases were determined to be unrelated to treatment by the investigators. Details of each case are summarized below by study and treatment group.

Study 3.1, EU-approved Remicade: A 59-year-old female patient with a long-standing history of hypertension and RA died of sudden death after 379 days on treatment. The cause of death was unknown.
Study 3.2, CT-P13 maintenance group: A 44-year-old male patient with RA died after 578 days of treatment following appendectomy with peritonitis. The cause of death was suspected peritonitis, and multiorgan failure. .
Study 1.1, EU-approved Remicade: A 38-year-old patient died in a car accident.
Study 1.1, CT-P13: A 25-year-old patient died in a car accident as a passenger.

7.3.2 Nonfatal Serious Adverse Events

In Study 3.1, 42 (14%) patients in the CT-P13 group and 31 (10%) patients in the EU-approved Remicade treatment groups experienced 49 SAEs and 39 SAEs, respectively. This numerical imbalance was primarily driven by more cases of infection (pneumonia and tuberculosis) in the CT-P13 group. For further discussion, see Section 7.3.4 Significant Adverse Events.

The most frequently reported SAEs for patients in the CT-P13 group were pneumonia and anaphylactic reaction (3 (1%) patients each), infusion-related reaction, and disseminated TB (2 (0.7%) patients each). The most frequently reported SAEs for patients in the EU-approved Remicade group were infusion-related reaction (3(1%) patients).

For all other studies, including the PK studies in AS and healthy subjects (Studies 1.1 and 1.4, respectively) and the extension studies to in RA and AS populations (studies 3.2 and 1.3, respectively), the proportion of patients who experienced at least 1 SAE and the type of SAEs was similar in the CT-P13 and EU-approved Remicade groups.

In study 3.2 (extension to study 3.1), 12(7.5%) patients in the CT-P13 maintenance group and 19 (9%) in the CT-P13 transition groups experienced at least one 1 SAE.

Reference ID: 3747317

In study 1.1, 10(8%) patients in the CT-P13 group experienced 12 SAEs and 8 (7%) patients in the EU-approved Remicade group experienced 11 SAEs. Four (3.1%) patients in the CT-P13 group reported drug-related SAEs: TB (moderate) and esophageal perforation (severe) in one patient, disseminated TB (moderate) in the second patient, demyelination (mild) in the third patient and dyspnea (moderate) in the fourth patient.

Five (4.1%) patients in the EU-approved Remicade® group reported drug-related SAEs: cellulitis (mild) and wound infection (mild) in one patient, infusion-related reaction (severe) in a second patient, pulmonary TB (severe) in a third patient and infusion related reaction (moderate) in a fourth and fifth patient, respectively.

In study 1.3 (extension to CT-P13 1.1), 4 patients (4%) in each, CT-P13 maintenance and CT-P13 transition, groups experienced SAEs. The 4 SAEs reported for patients in the CT-P13 maintenance group were atrial fibrillation, appendicitis, lymph node TB and prostate cancer. The 4 SAEs reported for patients in the CT-P13 transition group were inguinal hernia, disseminated TB, osteonecrosis and alcohol withdrawal syndrome.

In study 1.4, single –dose PK study in health subjects, a total of two SAEs were reported. One SAE of humerus fracture was reported in the CT-P13 group and one SAE of acute cholecystitis was reported in the EU-approved Remicade group. Both SAEs were determined to be unrelated to the study drug.

In summary, the proportion of patients who experienced at least one SAE was similar between the two treatment groups, CT-P13 and EU-approved Remicade. The most frequently reported SAEs were infections and infusion-related reactions and were similar between both treatment groups. SAEs across the system organ classes showed a similar distribution with minor numerical differences between each group. There was no notable difference in the incidence of SAEs following transition of RA and AS patients from EU-approved Remicade to CT-P13 in the extension studies. The different SOCs of SAEs or the pattern of SAEs in the studies comparing CT-P13 and EU-approved Remicade was consistent with the known safety profile of the reference product, US-licensed Remicade.

7.3.3 Dropouts and/or Discontinuations

Adverse events leading to treatment discontinuation were overall balanced between the two treatment groups in both controlled studies (3.1 and 1.1) and extension studies (3.2 and 1.3). These are summarized in Table 23 and Table 24. Infections, infusion-related reactions (also categorized under MedDRA SOC immune system disorders and general administration disorders), and drug hypersensitivity were the leading causes of treatment discontinuation. In study 3.1, the incidence of infections was twice as high in the EU-approved Remicade group compared to CT-P13 (6% vs. 3%).

Reference ID: 3747317

Table 23. Adverse Events Leading to Discontinuation – Controlled Studies

	Rheumatoid Arthritis		Ankylosing Spondylitis	
Study Number	Study 3.1		Study 1.1	
	CT-P13 3mg/kg (n=302) n (%)	Remicade 3mg/kg (n=300) n (%)	CT-P13 5mg/kg (n=128) n (%)	Remicade 5mg/kg n=122) n (%)
Total # of TEAEs leading to treatment discontinuation	40	52	12	9
# of subjects with at least one TEAE leading to treatment dc	33 (11)	47 (16)	11 (9)	9 (7)
MedDRA SOC AE Term n(%)	Incidence n(%)			
Blood and Lymphatic System Disorders	2(0.7)	1(0.3)	-	-
Cardiac Disorders	-	3(1.0)	-	1(0.8)
Ear and labyrinth disorders	1(0.3)	-	-	-
Eye disorders	1(0.3)	-	-	-
GI disorders	1(0.3)	-	1(0.8)	-
General disorders and Admin site conditions	5(1.7)	8(2.7)	-	-
Infusion related reaction	5(1.7)	8(2.7)	-	-
Immune system disorder	7(2.3)	6(2.0)	1(0.8)	4(3)
Anaphylactic reaction	3(1.0)	1(0.3)	1(0.8)	3(2)
Anaphylactic shock	1(0.3)	-	-	-
Drug hypersensitivity	3(1.0)	5(1.7)	-	1(0.8)
Infections and Infestations	9(3.0)	18(6.0)	3(2.4)	1(0.8)
Injury, Poisoning, procedural complications	-	1	-	-
Investigations	2(0.7)	1(0.3)	2(1.6)	1(0.8)
Nervous system disorders	1(0.3)	3(1.0)	3(2.4)	1(0.8)
Neoplasms, benign, malignant and unspecified	2(0.7)	3(1.0)	1(0.8)	-
Respiratory, thoracic and mediastinal disorders	-	1(0.3)	-	-
Skin and subcutaneous disorders	4(1.3)	3(1.0)	1(0.8)	1(0.8)

Source: Adapted from CSR 3.1, Table 14.3.1.6, CSR 1.1 Table 12-6, Data listing 14.3.2.4, and Summary of Clinical Safety, Table 2.7.4-118

Table 24. Adverse Events Leading to Discontinuation – Extension Studies

	Rheumatoid Arthritis		Ankylosing Spondylitis	
Study Number	Study 3.2 (Extension study to 3.1)		Study 1.1 (Extension study to 1.1)	
	CT-P13 maintenance 3mg/kg (n=159)	CT-P13 transition (EU-Remi --> CT-P13) 3mg/kg (n=143)	CT-P13 maintenance 5mg/kg (n=90)	CT-P13 transition (EU-Remi --> CT-P13) 5mg/kg n=84)
Total # of TEAEs leading to treatment discontinuation	25	11	4	4
# of subjects with at least one TEAE leading to treatment dc	16(10)	8(6)	3(3.3)	4(4.8)
MedDRA SOC AE Term n(%)	Incidence n(%)			
Hepatobiliary disorders	-	-	-	1(1.2)
GI disorders	3(2)	-	-	-
General disorders and Admin site conditions	2(1)	1(0.7)	-	-
Immune system disorder	2(1)	1(0.7)	-	-
Anaphylactic reaction	2(1.3)	-		
Drug hypersensitivity	-	1(0.7)		
Infections and Infestations	4(2.5)	1(0.7)	1(1.1)	2(2.4)
Injury, Poisoning, procedural complications	2(1.3)	-	-	-
Investigations	2 (1.3)	-	-	-
Nervous system disorders	-	-	-	-
Neoplasms, benign, malignant and unspecified	0	4(3)	-	-
Respiratory, thoracic and mediastinal disorders	2(1.3)	-	-	1(1.2)
Skin and subcutaneous disorders	1(0.6)	-	1(1.1)	-
Vascular disorders	1(0.6)	-	1(1.1)	-

Source: Summary of Clinical Safety, Tables CSR 3.2, Table 14.3.1.5, CSR 1.3, Table 14..3.1.5

7.3.4 Significant Adverse Events

Adverse events of special interest (AESI)

In the context of the known adverse-event profile of US-licensed Remicade, the following risks were characterized as adverse events of special interest. (AESI):

1. Infections
    a. All infections
    b. Serious infections
    c. Pneumonia
    d. Active tuberculosis
    e. Latent tuberculosis
2. Vascular disorder
3. Infusion-related reactions/drug hypersensitivity meeting the criteria of anaphylaxis as per Sampson's criteria (Sampson et.al, 2006)
4. Malignancy
5. Drug-induced liver injury

The Applicant provided an integrated safety summary with a pooled analysis of AESIs across the controlled and extension studies in RA (studies 3.1, 1.2, 3.3 and 3.2) and AS (studies 1.1 and 1.3) patients. FDA conducted a supplementary safety analysis of the AESIs which differed slightly from the applicant's in the following ways:

- FDA analysis of AESI did not include the pilot studies in RA (studies 1.2 in Philippines, n=19; and study 3.3 in Russia, n=15)
- In addition to the specified AESI, the FDA definition of AESI included opportunistic infections, and specified additional preferred terms in the category of pneumonia, malignancy and all infections to be more inclusive.
- Incidence rates were calculated based on time to first event per 100-person years.

The FDA safety analysis of the AESI was in general agreement with the applicant's safety analysis of these events. Summary of FDA's analysis of AESI, incidence rates and integrated relative risk is presented in Table 25 and Table 26, controlled and extension studies, respectively. In the controlled studies, the incidence rates of AESI were similar between the two treatment groups across both studies 3.1 and 1.1 with a few exceptions that were driven by small numerical imbalances in the following AESIs: Active TB, pneumonia, and vascular disorders. The safety results from studies 1.1 and 3.1 were overall consistent with the safety observed in the supportive clinical studies 1.2 3.3, and B1P13101 as summarized in Table 32).

Reference ID: 3747317

Table 25. Adverse Events of Special Interest - Controlled Studies

	Rheumatoid Arthritis Study 3.1				Ankylosing Spondylitis Study 1.1				Integrated RR (95% CI)[3]
	CT-P13 (N=302)		EU-approved Remicade (N=300)		CT-P13 (N=128)		EU-approved Remicade (N=122)		
	n (%)[1]	Rate[2]	n (%)[1]	Rate[2]	n (%)[1]	Rate[2]	n (%)[1]	Rate[2]	
Latent TB	28 (9)	9.3	26 (9)	8.6	10 (8)	7.3	6 (5)	4.6	1.2 (0.7, 1.8)
Active TB	3 (1)	0.9	0	0.0	2 (2)	1.4	1 (1)	0.7	3.2 (0.5, 20.4)
Infection	127 (42)	53.8	137 (46)	60.4	55 (43)	52.5	49 (40)	48.4	1.0 (0.8, 1.1)
Serious Infection	13 (4)	4.2	7 (2)	2.2	2 (2)	1.4	3 (3)	2.2	1.4 (0.6, 3.5)
Pneumonia	8 (3)	2.5	5 (2)	1.6	2 (2)	1.4	0	0.0	1.8 (0.6, 5.1)
Malignancy and Lymphoma	3 (1)	0.9	4 (1)	1.3	2 (2)	1.4	0	0.0	1.2 (0.2, 5.7)
Infusion-related Reaction	30 (10)	9.8	43 (14)	14.8	11 (9)	8.2	15 (12)	11.8	0.7 (0.5, 1.0)
Vascular disorder	25 (8)	8.3	16 (5)	5.3	4 (3)	2.9	1 (1)	0.7	1.7 (0.9, 3.0)
Cardiac disorder	5 (2)	1.6	12 (4)	3.9	5 (4)	3.6	6 (5)	4.6	0.6 (0.3, 1.2)
Opportunistic Infection	4 (1)	1.3	6 (2)	1.9	0	0.0	2 (2)	1.5	0.6 (0.2, 1.8)

[2] Incidence rate of first event per 100 person-years
[3] Relative risk of event (95% confidence interval) comparing CT-P13 with EU-approved Remicade based on DerSimonian-Laird random effects meta-analysis of results from Studies 1.1 and 3.1
[4] Definitions of Adverse Events of Special Interest:
Latent TB: All preferred terms with latent tuberculosis or Mycobacterium tuberculosis complex test
Active TB: All preferred terms with tuberculosis not classified as latent TB
Infection: All events in infections and infestations system organ class
Serious Infection: All events in infections and infestations system organ class classified as serious
Pneumonia: All preferred terms with pneumonia, bronchopneumonia, lobar pneumonia, or lower respiratory tract infection
Malignancy and Lymphoma: All preferred terms with cancer, carcinoma, lymphoma, neoplasm, or Myeloproliferative disorder
Infusion-related Reaction: See applicant's ISS SAP Appendix 2 for definition
Vascular Disorder: All events in vascular disorders system organ class
Cardiac Disorder: All events in cardiac disorders system organ class
Opportunistic Infection: All preferred terms with Herpes zoster, Oesophageal candidiasis, Oral candidiasis, or Varicella

Table 26. Adverse Events of Special Interest - Extension Studies

	Rheumatoid Arthritis Study 3.2				Ankylosing Spondylitis Study 1.3				Integrated RR (95% CI)[3]
	CT-P13 → CT-P13 (N=159)		EU-Remi →CT-P13 (N=143)		CT-P13 → CT-P13 (N=90)		EU-Remi → CT-P13 (N=84)		
	n (%)[1]	Rate[2]	n (%)[1]	Rate[2]	n (%)[1]	Rate[2]	n (%)[1]	Rate[2]	
Latent TB	11 (7)	5.0	7 (5)	3.4	5 (6)	4.1	7 (8)	5.3	1.0 (0.3, 3.2)
Active TB	0	0.0	0 (0.0)	0.0	1 (1)	0.8	1 (1)	0.7	1.1 (0.1, 16.9)
Infection	50 (31)	32.3	47 (33)	34.9	23 (26)	25.4	29 (35)	30.5	1.1 (0.9, 1.5)
Serious Infection	4 (3)	1.7	3 (2)	1.4	2 (2)	1.5	1 (1)	0.7	0.7 (0.2, 2.6)
Pneumonia	1 (1)	0.4	0	0.0	0	0.0	0	0.0	NA
Malignancy and Lymphoma	1 (1)	0.4	4 (3)	1.9	1 (1)	0.8	0	0.0	1.7 (0.1, 18.6)
Infusion-related Reaction	11 (7)	5.0	4 (3)	1.9	7 (8)	5.7	6 (7)	4.5	0.6 (0.3, 1.4)
Vascular disorder	4 (3)	1.7	3 (2)	1.4	3 (3)	2.3	2 (2)	1.4	0.8 (0.3, 2.4)
Cardiac disorder	1 (1)	0.4	1 (1)	0.5	4 (4)	3.2	3 (4)	2.1	0.9 (0.2, 3.2)
Opportunistic Infection	1 (1)	0.4	1 (1)	0.5	1 (1)	0.8	1 (1)	0.7	1.1 (0.2, 7.7)

[1] Number of patients with event (percent)
[2] Incidence rate of first event per 100 person-years
[3] Relative risk of event (95% confidence interval) comparing EU-approved Remicade to CT-P13 transition with CT-P13 maintenance based on DerSimonian-Laird random effects meta-analysis of results from Studies 1.3 and 3.2
[4] Definitions of Adverse Events of Special Interest:
Latent TB: All preferred terms with latent tuberculosis or Mycobacterium tuberculosis complex test
Active TB: All preferred terms with tuberculosis not classified as latent TB
Infection: All events in infections and infestations system organ class
Serious Infection: All events in infections and infestations system organ class classified as serious
Pneumonia: All preferred terms with pneumonia, bronchopneumonia, lobar pneumonia, or lower respiratory tract infection
Malignancy and Lymphoma: All preferred terms with cancer, carcinoma, lymphoma, neoplasm, or Myeloproliferative disorder
Infusion-related Reaction: See applicant's ISS SAP Appendix 2 for definition
Vascular Disorder: All events in vascular disorders system organ class
Cardiac Disorder: All events in cardiac disorders system organ class
Opportunistic Infection: All preferred terms with Herpes zoster, Oesophageal candidiasis, Oral candidiasis, or Varicella

Infections

In the CT-P13 controlled studies 1.1 and 3.1, 182/430 (42%) patients in the CT-P13 group and 186/422 (44%) patients in the EU-approved Remicade group experienced infections. The incidence rates of infection were similar between the treatment groups and the types of infections consistent with the known adverse event profile of infliximab.

Serious Infections

During the controlled periods of the CT-P13 clinical studies, 15/430 (3.4%) patients treated with CT-P13, compared to 10/422 (2.4%) patients treated with EU-approved Remicade experienced serious infection. This difference was driven by the higher number of cases of TB and pneumonia as discussed in the respective sections below.

Active Tuberculosis (TB)

In the CT-P13 group, 5 cases of active TB were reported compared to 1 case of active Tb in the EU-approved Remicade group. Among the 5 cases in the CT-P13 group, 3 were reported in the RA study and 2 in the AS study. The sole case of active TB in the EU-approved Remicade group was in the AS study 1.1. Applicant's analysis that included the pilot studies in RA reported a total of 7 cases of active TB in the CT-P13 treatment group and 1 case of active TB in the EU-approved Remicade group. The two additional cases of TB in the applicant's analysis were reported in the small, pilot study (Study 1.2) in RA patients conducted in the Philippines.

In the CT-P13 group, a cluster of three patients from Philippines (Study 3.1 – 1 patient; and study 1.2 – 2 patients) received a clinical diagnosis of TB based on judgment alone rather than confirmation of presence of M. tuberculosis in clinical samples (eg. sputum or biopsy).

In all, there were 5 confirmed cases of TB (4 in the CT-P13 and 1 in the EU-approved Remicade groups), respectively. Most of these patients were recruited from regions with higher TB rates.

In the extension study 3.2, there were no cases of active TB. In the extension study 1.3 in AS patients, one case of lymph node TB in the CT-P13 maintenance group and one case of disseminated TB in the CT-P13 transition group were reported.

Tuberculosis is a well-recognized safety risk with TNF inhibition, including with infliximab. The slight numerical imbalance in the incidence of TB between CT-P13 and EU-approved Remicade is likely to reflect a chance finding. Furthermore, the numerical imbalance in the cases of active TB between the two treatment groups cannot be explained by the known analytical or functional differences between the molecules.

Pneumonia

In the CT-P13 group, 10 cases of pneumonia (8 in RA and 2 in AS patients respectively) were reported compared to 5 cases of pneumonia (RA patients only) in the EU-approved Remicade group. Only one case of pneumonia was reported in the extension studies that occurred in the CT-P13 maintenance group in the RA study.

Baseline risk factors largely account for the imbalance between the two treatment groups. Larger proportion of patients with pneumonia in the CT-P13 group had underlying predisposing risk factors including COPD, congestive heart failure, diabetes, and smoking compared to pneumonia cases in the EU-approved Remicade group.

Serious infections, including pneumonia, are a well-recognized safety risk with TNF inhibition, including with infliximab. Further, this imbalance is not observed in the

Reference ID: 3747317

Japanese RA study B1P13101 with 2 (4) patients with pneumonia in the CT-P13 group and 4 (8%) patients in the EU-approved Remicade group.

Vascular disorders

In the SOC of vascular disorder, the most frequently reported preferred term (PT) was hypertension. Overall, 19 (4%) and 11 (3%) patients reported hypertension in the CT-P13 and EU-approved Remicade groups in the controlled studies CT-P13 1.1 and 3.1. Most AEs of hypertension were mild to moderate in severity. There was one case of SAE of hypertension in a patient in the CT-P13 group with an underling history of hypertension and diabetes. None of the patients discontinued treatment due to an AE of hypertension.

In the extension studies, 7(3%) patients in the CT-P13 maintenance group and 5 (2%) patients in the CT-P13 transition group reported hypertension.

Hypertension had a slightly higher incidence in the CT-P13 group vs. EU-approved Remicade. More patients experiencing hypertension in the CT-P13 group had an underlying medical history of hypertension or other predisposing factors compared to the EU-approved Remicade group. Similar number of hypertension cases was reported in both treatment groups across both studies in patients without an underlying history of hypertension.

Infusion-Related Reactions, Drug Hypersensitivity, Anaphylaxis

Infusion-related reactions were captured under the SOCs General disorders and administration site conditions using the PTs infusion-related reaction and under Immune system disorders using the PTs anaphylactic shock, anaphylactic reaction, drug hypersensitivity and hypersensitivity. In addition, Celltrion applied an expanded definition to capture all infusion-related reactions including those reported as mild and moderate using the following definitions:

- Infusion-related reactions:
    - Hypersensitivity, drug hypersensitivity, anaphylactic shock, anaphylactic reaction or Infusion-related reaction with a possible, probably or definite relationship to study medication, OR
    - TEAE term related to hypersensitivity or infusion-related reactions with a possible, probably or definite relationship to study medication, OR
    - Signs and/or symptoms related to hypersensitivity or infusion-related reactions for which the TEAE start date matches an infusion date and classified as ‘possible, probably or definite’ relationship to study drug.
- Anaphylactic reactions:
    - Anaphylaxis based on criteria described by Sampson et al.,(2006) in cases of severe or serious infusion related reactions

Reference ID: 3747317

Infusion-Related Reactions

In the CT-P13 controlled studies 1.1 and 3.1, 41/430 (10%) patients in the CT-P13 group and 58/422 (14%) patients in the EU-approved Remicade group experienced infusion-related reaction or drug hypersensitivity. Importantly, the incidence of such reactions did not increase after patients transitioned from EU-approved Remicade to CT-P13 (10/227 or 4%) compared to patients who continued on CT-P13 (18/249 or 7%) in studies 3.2 and 1.3.

Anaphylaxis

In the CT-P13 controlled studies 1.1 and 3.1, 7/430 (1.6%) patients in the CT-P13 group and 7/422 (1.7%) patients in the EU-approved Remicade group experienced anaphylaxis. Importantly, there were no cases of anaphylaxis in patients who transitioned from EU-approved Remicade to CT-P13 in the extension studies 3.2 and 1.3.

The analysis of the overall incidence of infusion-related reaction or drug hypersensitivity, including anaphylaxis, indicate that transitioning of non-treatment naïve patients to CT-P13 is not likely to result in clinically significant reactions. These results are also consistent with the similar incidence of anti-drug antibodies between patients who transitioned from EU-approved Remicade to CT-P13 compared to patients who continued on CT-P13 in the same extension studies 3.2 and 1.3 as detailed in Section 7.4.6 Immunogenicity below.

Malignancy

In the CT-P13 controlled studies 1.1 and 3.1, there were similar numbers of malignancies in the two treatment groups: five in the CT-P13 group and four in EU-approved Remicade group. The cases included ovarian, breast, colon cancer, basal cell carcinoma, cervical carcinoma. During the long-term extension studies, additional cases of malignancy accrued, including prostate cancer, breast cancer, ovarian cancer, one case of intestinal T-cell lymphoma and one case of B-cell lymphoma. The incidence and types of malignancies reported are generally expected for the study population,

Drug-Induced Liver Injury

Celltrion conducted safety database analysis to identify potential cases of severe DILI in accordance with Hy's Law (i.e., incidence of 3-fold or greater elevations above the ULN of ALT or AST accompanied by elevation of serum TBL >2xULN, with no other reason to explain the combination of increased AT and total bilirubin). These criteria are used during clinical development, to assess a drug's potential of inducing fulminant hepatic failure with larger/longer exposure, which is a rare and usually fatal event. No cases of Hy's law were reported in the CT-P13 clinical program.

Reference ID: 3747317

Summary of AESI

Overall, the incidence of AESI between the two treatments groups, CT-P13 and EU-approved Remicade is similar across both controlled and extension studies in the RA and AS populations. A non-clinically significant numerical imbalance was noted for AESI of Active TB, pneumonia and hypertension in the CT-P13 group compared to EU-approved Remicade. No cases of drug-induced liver injury was reported in CT-P13 clinical program.

FDA safety analysis of the adverse events of special interest was in agreement with the applicant. The FDA supplementary analysis of the AESI identified single additional cases that did not change the overall conclusion of no clinically meaningful differences between CT-P13 and EU-approved Remicade in the indications studied.

Evaluation and review of the safety data did not identify any new safety signals with CT-P13 use. The safety risks identified are well within the known adverse event profile of the reference product, US-licensed Remicade. Most common adverse events include infection, and infusion-related reactions. The safety data support the conclusion of no clinically meaningful differences between CT-P13 and US-licensed Remicade in the populations studied. In addition, transitioning of non-treatment naïve patients, i,e, patients previously treated with infliximab, to CT-P13 does not appear to result in clinically significant adverse reactions.

7.3.5 Submission Specific Primary Safety Concerns

Please refer to adverse events of special interest.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Common adverse events, reported by ≥3% of subjects in the controlled studies (studies 3.1, 1.1 and 1.4) and extension studies (studies 3.2 and 1.3) are summarized in Table 27 and Table 28 below. In the comparative clinical study 3.1 in RA and in the PK study 1.1 in AS, the incidence of treatment-emergent adverse events (TEAS) was similar across both treatment groups, CT-P13 and EU-approved Remicade. The proportion of patients reporting TEAEs was similar in both treatment groups across both studies. In study 1.4, single-dose, PK bridging study in healthy volunteers, the number of TEAEs was similar between CT-P13 and US-licensed Remicade with a trend towards a lower incidence of TEAEs with EU-approved Remicade (67, 28 and 54 TEAEs, respectively). In all studies, the pattern of common adverse events in each SOC was similar between

Reference ID: 3747317

the treatment groups and consistent with the known safety profile of infliximab. The majority of TEAEs were mild to moderate in severity. For further discussion of serious adverse events, see Section 7.3.2 Nonfatal Serious Adverse Events.

In patients with RA and AS, the most frequently reported adverse events in both CT-P13 and EU-approved Remicade groups include nasopharyngitis, upper respiratory tract infection, latent tuberculosis (latent TB), urinary tract infection, increased AST and ALT. The overall safety profile was similar between CT-P13 and EU-approved Remicade. There were no new safety concerns or signals that were identified. Single transition to CT-P13 from EU-approved Remicade also did not identify any new safety concerns.

Reference ID: 3747317

Table 27. Summary of Common Adverse Events (Reported in ≥3% of Subjects) - Controlled Studies

	Rheumatoid Arthritis		Ankylosing Spondylitis		Healthy Volunteers		
Study Number	Study 3.1		Study 1.1		1.4		
	CT-P13 3mg/kg (n=302)	Remicade 3mg/kg (n=300)	CT-P13 5mg/kg (n=128)	Remicade 5mg/kg n=122)	CT-P13 5mg/kg (n=71)	EU-approved Remicade 5mg/kg (n=71)	US-licensed Remicade 5mg/kg (n=71)
Total # of TEAEs	732	738	362	375	67	28	54
# of pts with at least 1 TEAE	213(71)	211(70)	95(74)	82(67)	37(42)	21(30)	33(46)
MedDRA SOC PT n(%)							
Blood and Lymphatic System Disorders	**19(6)**	**21(7)**	**7(6)**	**12(10)**	**1(1)**	**1(1)**	**1(1)**
Anemia	10(3)	12(4)	1(1)	4(3)	-	-	-
Cardiac Disorders	**5(2)**	**12(4)**	**5(4)**	**6(5)**	**-**	**-**	**-**
Ear and labyrinth disorders	**5(2)**	**2(1)**	**1(1)**	**-**	**-**	**-**	**-**
Eye disorders	**15(5)**	**7(2)**	**6(5)**	**8(7)**	**-**	**1(1)**	**-**
GI disorders	**36(12)**	**33(11)**	**24(19)**	**20(16)**	**8(11)**	**1(1)**	**4(6)**
Diarrhea	9(3)	9(3)	6(5)	1(1)	1(1)	-	2(3)
Abdominal pain	4(1)	3(1)	1(1)	4(3)	3(4)	-	1(1)
Nausea			4(3)	3(3)	2(3)	-	-
General disorders and Admin site conditions	**21(7)**	**27(9)**	**3(2)**	**10(8)**	**6(9)**	**1(1)**	**2(3)**
Fatigue	-	1(<1)	-	2(2)	4(6)	1(1)	2(3)
Infusion-related reaction	10(3)	11(4)	-	4(3)	-	-	-
Pyrexia	2(1)	11(4)	3(2)	2(2)	1(1)	-	-
Hepatobiliary Disorders	**5(2)**	**6(2)**	**4(3)**	**2(2)**	**-**	**1(1)**	**-**
Immune system disorders	**13(4)**	**16(5)**	**2(2)**	**4(3)**	**-**	**-**	**-**
Drug hypersensitivity	6(2)	11(4)	2(2)	3(3)	-	-	-
Anaphylactic reaction	3(1)	1<1)	-	-	-	-	-
Anaphylactic shock	1(<1)	-	-	-	-	-	-
Infections and infestations	**127(42)**	**137(46)**	**55(43)**	**49(40)**	**18(25)**	**12(17)**	**24(34)**
Nasopharyngitis	25(9)	17(6)	12(9)	10(8)	11(15)	11(15)	17(24)
Upper respiratory tract infection	27(9)	17(6)	10(8)	13(11)	-	-	-
Latent TB	27(9)	25(8)	10(8)	5(4)	-	-	-
Urinary tract	18(6)	21(7)	8(6)	1(1)	-	-	-

infection							
Bronchitis	13(4)	17(6)	2(2)	4(3)	-	-	-
Influenza	11(4)	5(2)	2(2)	6(5)	-	-	-
Pharyngitis	7(2)	9(3)	4(3)	7(6)	-	-	-
Oral herpes			1(1)	2(2)	-	-	3(4)
Rhinitis	4(1)	9(3)	1(1)	2(2)	5(7)	1(1)	4(6)
Injury, Poisoning, and procedural complications	**17(6)**	**9(3)**	**7(6)**	**8(7)**	**2(3)**	**1(1)**	**1(1)**
Investigations	**47(16)**	**48(16)**	**28(22)**	**29(24)**	**1(1)**	**-**	**3(4)**
ALT increased	15(5)	17(6)	19(15)	19(16)	1(1)	-	1(1)
AST increased	6(2)	9(3)	16(12)	13(11)	1(1)	-	1(1)
Musculoskeletal and connective tissue disorders	**42(14)**	**37(12)**	**20(16)**	**16(13)**	**7(10)**	**4(6)**	**3(4)**
Arthralgia	5(2)	4(1)	3(2)	3(3)	1(1)	1(1)	-
Nervous system disorders	**26(9)**	**36(12)**	**19(15)**	**13(11)**	**4(6)**	**5(7)**	**6(8)**
Headache	14(5)	17(6)	10(8)	7(6)	4(6)	5(7)	6(8)
Dizziness	3(1)	3(1)	4(3)	1(1)			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**5(2)**	**7(2)**	**2(2)**	**2(2)**	-	-	-
Psychiatric disorders	**8(3)**	**6(2)**	**4(3)**	**4(3)**	**2(3)**	**-**	**-**
Renal and urinary disorders	**16(5)**	**11(4)**	**4(3)**	**4(3)**	-	-	-
Dysuria	3(1)	3(1)	-	-			
Hematuria	3(1)	4(1)	-	2(2)			
Proteinuria	0	1(<1)	-	-			
Reproductive and breast disorders	**9(3)**	**10(3)**	**2(2)**	**0**	-	-	-
Respiratory, Thoracic and mediastinal disorders	**19(6)**	**12(4)**	**12(9)**	**12(10)**	**4(6)**	**1(1)**	**4(6)**
Skin and subcutaneous tissue disorders	**27(9)**	**27(9)**	**18(14)**	**18(15)**	**6(8)**	**-**	**1(2)**
Rash	5(2)	6(2)	1(1)	5(4)	1(2)	-	-
Vascular disorders	**25(8)**	**16(5)**	**4(3)**	**1(1)**	-	-	-
Hypertension	15(5)	10(3)	4(3)	1(1)			

Source: Adapted from Clinical Safety Summary, Tables 2.7.4-14, 2.7.4-15, 2.7.4-20; CSR CT-P13 3.1 post-text table 14.3.1.2, CSR CT-P13 1.1 Post-text Table 14.3.1.2, CSR CT-P13 1.4 Post-text Table 14.3.1.2

Study 3.1

The most frequently reported TEAEs in the CT-P13 group and the EU-approved Remicade group (in ≥5% patients) included latent tuberculosis (9% and 8% patients, respectively), upper respiratory tract infection (9% and 6%), nasopharyngitis (8% and

6%), urinary tract infection (6% and 7%), rheumatoid arthritis (5% and 4%), hypertension (5% and 3%), ALT increased (5% and 6%), headache (6% and 6%) and bronchitis (4% and 6%).

Study 1.1
The TEAEs most frequently reported (in ≥5% subjects) in the CT-P13 and EU-approved Remicade group included nasopharyngitis (9% and 8%), respectively, upper respiratory infection (8% and 11%), latent TB (8% and 4%), urinary tract infection (6% and 1%), pharyngitis (3% and 6%), ALT increased (15% and 15%), AST increased (12% and 11%) and headache (8% and 6%).

Study 1.4
The most frequently reported TEAEs in the CT-P13 group, EU-approved Remicade® group and the US-licensed Remicade® group (in ≥5% subjects) included nasopharyngitis (15%, 15% and 24%, respectively), headache (6%, 7% and 8%, respectively), rhinitis (7%, 1% and 5%, respectively), flatulence (6%, 1% and 1%, respectively) and fatigue (6%, 1% and 3%, respectively).

Extension Studies

Study 3.2 (Extension to study 3.1 in RA)
Most frequently reported TEAS in the CT-P13 maintenance group were latent TB (6%), upper respiratory tract infection (5%) and urinary tract infection (5%). In the CT-P13 transition group (patients transitioning from EU-approved Remicade to CT-P13), most frequently TEAEs were bronchitis (6%) and urinary tract infections (6%). There was no notable increase in a particular SOC after transition from EU-approved Remicade to CT-P13. Specifically, there was no increase in adverse events of special interest of infusion-related reaction, drug hypersensitivity and anaphylaxis.

Study 1.3 (Extension to study 1.1 in AS)
Most frequently reported TEAEs in the CT-P13 maintenance group were latent TB (4%), nasopharyngitis (4%), and ALT increase (4%). The most frequently reported TEAES in the CT-P13 transition group were latent TB (8%), ALT increase (8%), upper respiratory tract infection (6%) and back pain (6%). Overall, there was a slightly higher incidence in the proportion of patients with TEAEs in the CT-P13 transition group (72%) compared to the CT-P13 maintenance group (49%). These numerical differences were driven primarily by adverse events with mild to moderate severity. Further, study 1.3 is limited by size and it was primarily designed as a PK study. No new SOC safety signals were identified compared to the primary study 1.1. There was no notable increase in a particular SOC after transition from EU-approved Remicade to CT-P13.

Reference ID: 3747317

Table 28. Summary of Common Adverse Events (Reported in ≥3% of Subjects) - Extension Studies

	Rheumatoid Arthritis		Ankylosing Spondylitis	
Study Number	Study 3.2 (Extension to study 3.1)		Study 1.3 (Extension study to 1.1)	
	CT-P13 maintenance 3mg/kg (n=159)	CT-P13 transition (EU-Remi --> CT-P13) 3mg/kg (n=143)	CT-P13 maintenance 5mg/kg (n=90)	CT-P13 transition (EU-Remi --> CT-P13) 5mg/kg n=84)
Total # of TEAEs	226	180	103	162
# of pts with at least 1 TEAE	85(54)	77(54)	44(49)	60(71)
MedDRA SOC PT n(%)				
Blood and Lymphatic System Disorders	6(4)	9(6)	1(1)	6(7)
Anemia				
Cardiac Disorders	1(<1)	1(<1)	4(4)	3(4)
Ear and labyrinth disorders	-	-	-	1(1)
Eye disorders	7(4)	0	2(2)	2(2)
GI disorders	16(10)	12(8)	4(4)	12(14)
General disorders and Admin site conditions	9(6)	2(1)	3(3)	3(4)
Hepatobiliary Disorders	1(<1)	3(2)	-	3(4)
Immune system disorders	3(2)	3(2)	-	1(1)
Drug hypersensitivity	1(<1)	1(<1)	-	1(1)
Anaphylactic reaction	2(1)	-	-	-
Infections and infestations	50(31)	47(33)	23(26)	29(35)
Nasopharyngitis	7(4)	3(2)	4(4)	4(5)
Upper respiratory tract infection	8(5)	6(4)	2(2)	5(6)
Latent TB	10(6)	5(4)	4(4)	7(8)
Urinary tract infection	8(5)	8(6)	1(1)	3(4)
Bronchitis	5(3)	9(6)	2(2)	1(1)
Influenza	1(<1)	2(1)	1(1)	1(1)
Pharyngitis	4(3)	4(3)	-	1(1)
Oral herpes	1(<1)	1(<1)	-	1(1)
Rhinitis	1(<1)	1(<1)	1(1)	1(1)
Injury, Poisoning, and procedural complications	8(5)	6(4)	3(3)	3(4)
Investigations	12(8)	13(9)	10(11)	16 (19)

ALT increased	3(2)	6(4)	4(4)	7(8)
AST increased			2(2)	4(5)
Musculoskeletal and connective tissue disorders	15(9)	9(6)	5(6)	11(13)
Arthralgia	1(<1)	1(<1)	-	1(1)
Back pain	1(<1)	1(<1)	-	5(6)
AS	-	-	-	3(4)
RA	4(3)	1(<1)	-	-
Nervous system disorders	5(3)	4(3)	6(7)	4(5)
Headache	3(2)	1(<1)	3(3)	2(2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3(2)	6(4)	1(1)	-
Psychiatric disorders	1(<1)	-	-	5(6)
Renal and urinary disorders	5(3)	4(3)	2(2)	3(4)
Reproductive and breast disorders	2(1)	2(1)	2(2)	3(4)
Respiratory, Thoracic and mediastinal disorders	6(4)	-	2(2)	6(7)
Skin and subcutaneous tissue disorders	8(5)	9(6)	9(10)	-
Vascular disorders	4(3)	3(2)	3(3)	2(2)
Hypertension	4(3)	3(2)	3(3)	-

Source: Adapted from Clinical Safety Summary, Tables 2.7.4-16, 2.7.4-21

In summary, the incidence and types of common adverse events were similar between the products, were consistent with the known safety profile of infliximab and no new safety signals have been identified supporting the conclusion that there are no clinically meaningful differences between CT-P13 and US-licensed Remicade in the indications studied.

7.4.2 Laboratory Findings, Vital Signs and Electrocardiograms (ECGs)

The distribution of laboratory findings, vital signs and electrocardiogram (ECGs) findings was balanced between the CT-P13 and EU-approved Remicade groups. No new or unexpected laboratory findings were reported in CT-P13 clinical program.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies with CT-P13have been submitted in the BLA.

Reference ID: 3747317

7.4.6 Immunogenicity

Infliximab is known to be immunogenic and anti-infliximab antibodies have implications on both safety and efficacy. Thus, immunogenicity was prospectively studied in the CT-P13 clinical program and the immunogenicity data reviewed in this section.

Incidence of Immunogenicity

The determination of anti-drug antibodies consisted of three sequential steps: 1) screening, 2) confirmation, and 3) characterization.

In the controlled (studies 3.1 in RA and 1.1 in AS) and extension studies (studies 3.2 LTE in RA and 1.3 LTE in AS), anti-drug antibodies (ADA) was assessed at multiple time points. The proportion of patients testing positive for ADA was similar between CT-P13 and EU-approved Remicade. Consistent with the known immunogenic potential of infliximab, in both treatment groups, the proportion of ADA-positive patients increased over time; however, the incidence of ADA positivity was similar between CT-P13 and EU-approved Remicade. There was a trend towards increased antibody titers with the number of doses received in both treatment groups. In the extension studies, there was no appreciable difference in the proportion of ADA-positive patients following the transition from EU-approved Remicade to CT-P13 (Weeks 78 and 102). ADA positivity results are summarized in Table 29.

Table 29. Proportion of ADA Positive Patients - Controlled & Extension Studies (Safety Population)

	Rheumatoid Arthritis				Ankylosing Spondylitis			
	Study 3.1		LTE 3.2		Study 1.1		LTE 1.3	
	CT-P13 3mg/kg (n=302) n(%)	EU-Remi 3mg/kg (n=300) n(%)	CT-P13 → CT-P13 3mg/kg (n=159) n(%)	EU-Remi → CT-P13 3mg/kg (n=143) n(%)	CT-P13 5mg/kg (n=128) n(%)	Remicade 5mg/kg n=(122) n(%)	CT-P13 → CT-P13 5mg/kg (n=90) n(%)	EU-Remi → CT-P13 5mg/kg (n=84) n(%)
Screening	9 (3)	6(2)	7(4)	4(3)	2(2)	1(<1)	2(2)	1(1)
Week 14	69(23)	70(23)	-	-	11(9)	13(11)	-	-
Week 30	122(40)	122(40)	-	-	32(25)	25(20)	-	-
Week 54	124(41)	108(36)	-	-	25(20)	28(23)	-	-
Week 78	-	-	71(44)	66(46)	-	-	21(23)	25(30)
Week 102	-	-	64(40)	64(45)	-	-	21(23)	23(27)

Source: CSR 3.1 Post-text table 14.3.6.5, CSR 1.1. Post-text table 14.3.6.5, Summary of Clinical Pharmacology Tables 2.7.2-11, 2.7.2-14, 2.7.2-23, 2.7.2-24

Impact of Immunogenicity on Safety

The clinical relevance of immunogenicity was assessed using adverse events potentially associated with ADA formation such as infusion related reaction and anaphylaxis. As summarized in Table 30, in sub-group analysis evaluating these adverse events, the incidence of infusion related reactions was higher in ADA positive patients compared to ADA negative patients with similar rates in both treatment groups. A similar trend was noted for anaphylaxis, where ADA-positive patients had a higher rate of anaphylaxis compared to ADA-negative patients with similar rates between CT-P13 and EU-approved Remicade. These results indicate that ADA formation against CT-P13 or EU-approved Remicade had similar impact on clinically-relevant safety.

Table 30. Incidence of Infusion-related Reactions and Anaphylaxis by ADA Status-Controlled Studies (All-Randomized Population)

TEAE	Seroconversion Subgroup	Rheumatoid Arthritis Study 3.1		Ankylosing Spondylitis Study 1.1		Total	
		CT-P13 3mg/kg (n=302)	EU-Remi 3mg/kg (n=300)	CT-P13 5mg/kg (n=128)	EU-Remi 5mg/kg n=122)	CT-P13 (n=430)	EU-Remi (n=422)
Infusion Related Reaction	ADA +	23/169 (14)	35/164(21)	6/44(14)	11/39(28)	29/213(14)	46/203(23)
	ADA -	7/133(5)	8/135(6)	5/84(6)	4/83(5)	12/217(6)	12/218(6)
Anaphylaxis	ADA +	4/169 (2)	2/164 (1)	1/44(2)	3/39(8)	5/213(2)	5/203(3)
	ADA -	2/133(2)	2/135(2)	0/84	0/83	2/217(1)	2/218(1)

Source: Summary of Clinical Safety Section 2.7.4.2.7.6

Impact of Immunogenicity on Efficacy

Immunogenicity was assessed at the same time as efficacy endpoint (ACR20) assessment, i.e. at Weeks 14, 30, 54 in the controlled studies, and weeks 78 and 102 in the extension studies.

In Study 3.1, ACR20 response was observed in a majority of the patients despite ADA status. Approximately 60% of ADA positive patients achieved the primary endpoint (ACR20) at Week 30. Response was lower in ADA positive patients compared to ADA negative patients; however, it was consistent between the CT-P13 and EU-approved Remicade groups. Table 31 provides a summary of results from study 3.1. Similar trends were noted in the AS study (1.1) and extension studies (1.3 and 3.2).

These results indicate that ADA formation against CT-P13 or EU-approved Remicade had similar impact on clinical efficacy.

Reference ID: 3747317

Table 31. ACR20 Responder Rates by ADA Status in Study 3.1 (All-Randomized Population)

ADA	Treatment	ACR20 Response		
		Week 14	Week 30	Week 54
ADA positive	CT-P13 3mg/kg	38/69 (55)	74/121(61)	77/123(63)
	EU-Remi 3mg/kg	38/70(54)	75/123(61)	65/109(60)
ADA Negative	CT-P13 3mg/kg	148/202(73)	106/129(83)	95/112(85)
	EU-Remi 3mg/kg	135/202(67)	100/132(76)	90/111(81)

Source: Summary of Clinical Efficacy Section 2.7.3.5.1.1.2

Immunogenicity of CT-P13 Compared to US-licensed Remicade

Study 1.4 is the only study in CT-P13 clinical program, comparing immunogenicity of CT-P13 with US-licensed Remicade. This study enrolled 213 healthy volunteers with 71 subjects in each treatment group: CT-P13, EU-approved Remicade and US-licensed Remicade. While the study met its primary objective of demonstrating PK similarity between the three products, some numerical differences were seen in the incidence of immunogenicity. After a single dose administration of treatment drug at the start of the study, immunogenicity was measured at a single time point, Day 57, with the following results of patients testing positive for ADA by ELISA: CT-P13 19/71 patients (27%), EU-approved Remicade – 18/71 patients (25%) and US-Remicade – 8/71 patients (11%). Using ECLA assay (used in the rest of the clinical studies), which is more sensitive to circulating drug, ADAs to CT-P13 were higher (14% positive) versus US-licensed Remicade (3% positive) and EU-approved Remicade (7% positive). ADA titers were overlapping between US and EU Remicade, but trended higher (though still overlapping) with CT-P13. However, no assay-related or subject-related factors could be identified to explain the reported differences. In considering the clinical significance of these numerical imbalances, this reviewer considered the following:

- The immunogenicity imbalance seen in study 1.4 was not associated with a difference in PK.
- Published data (Udata et al 2014) comparing US-licensed Remicade and EU-approved Remicade showed similarly high immunogenicity after a single-dose (28% and 33% ADA positive, respectively) in healthy volunteers.
- Clinically significant differences in immunogenicity were not observed in studies 3.1 and 1.1 where two distinct disease patients (RA and AS, respectively), were administered two different dosing regimens (either 3 mg/kg of study product on the background of methotrexate or a monotherapy of 5 mg/kg of study product, respectively).
- Immunogenicity and hypersensitivity reactions did not increase after a single transition from EU-approved Remicade to CT-P13 in studies 3.2 and 1.2.

Based on these considerations, the numerical imbalance in the incidence of immunogenicity following a single dose regimen in healthy volunteers seen in study 1.4, was not considered clinically relevant and does not preclude the conclusion of no clinically meaningful differences between CT-P13 and US-licensed Remicade.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Not applicable.

7.5.2 Time Dependency for Adverse Events

Not applicable.

7.5.3 Drug-Demographic Interactions

No significant safety signals were identified based on drug-demographic interactions.

7.5.4 Drug-Disease Interactions

Not applicable.

7.5.5 Drug-Drug Interactions

Not applicable for this application.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Malignancies, including lymphoma, have been identified as potential risk with US-licensed Remicade and other TNF-inhibitors as described in the Warnings and Precautions section of US-licensed Remicade's USPI. There was a small number of malignancies reported in the CT-P13 which were balanced between the treatment arms as summarized in Table 25and Table 26 above. The incidence and types of these malignancies is expected for the study population and treatment.

7.6.2 Human Reproduction and Pregnancy Data

Not applicable.

Reference ID: 3747317

7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable.

7.7 Additional Submissions / Safety Issues

The Applicant's cutoff dates for studies submitted to the original BLA ranged from October 07, 2013 to January 21, 2014. The cutoff date for the 120-day safety update was July 19, 2014.

Supportive Safety Data

Additional supportive clinical safety data were derived from study 1.2 (pilot study in 19 RA patients in Philippines), study B1P13101 (PK study with secondary safety and efficacy evaluated in 108 RA patients in Japan) and study 3.3 (another small, pilot study in 15 RA patients in Russia). Refer to Section 9.4 Supportive Clinical Studies – Study Protocols for individual study descriptions. Each study had a similar study design (randomized, double-blind, parallel group comparing CT-P13 and EU-approved Remicade in RA patients) and similar inclusion and exclusion criteria compared with the larger controlled studies. The demographic profile of the RA patients assigned to the CT-P13 and EU-approved Remicade was similar in these studies. The majority of patients were women with an age range of 18-75 years. In studies 1.2 and B1P13101, all patients were Asian and in study 3.3, all patients were White.

The distribution of treatment-emergent adverse events (TEAEs) in terms of types of TEAE's and incidence was similar between the treatment groups, CT-P13 and EU-approved Remicade in each study. TEAEs are summarized in Table 32. The most frequently reported adverse events in each treatment group included infections, mainly nasopharyngitis, and hepatobiliary events (increase in AST or ALT).

Analysis of adverse events of special interest (as identified in 7.3.4 Significant Adverse Events) in studies 1.2 and 3.1 showed a similar distribution of adverse events in each treatment group. No deaths were reported in studies 1.2, 3.3 or B1P13101.

The pattern of adverse events in these small, controlled, supportive studies was consistent with the well-known safety profile of US-licensed Remicade. No new safety signals were identified supporting the conclusion of clinically meaningful differences in RA patients.

Reference ID: 3747317

Table 32. Summary of TEAEs - Supportive Studies

	Study 1.2*		Study 3.3		Study B1P13101	
	CT-P13 3mg/kg (n=9)	EU-Remi 3mg/kg (n=9)	CT-P13 3mg/kg (n=6)	EU-Remi 3mg/kg (n=9)	CT-P13 3mg/kg (n=51)	EU-Remi 3mg/kg (n=53)
Total # of TEAEs # of pts with ≥1 TEAE, n (%)	49 8(89)	38 6(67)	3 2(33)	15 2(22)	177 45(88)	199 46(87)
# of pts with ≥1 SAE, n (%)	1(11)	1(11)	-	-	8(16)	8(15)
# of pts (%) with TEAEs leading to discontinuation	3 (11)	2(16)	-	1	10(20)	6(11)
# of pts with ≥1 infection, n (%)	6(67)	5(56)	-	2(22)	29(57)	23(43)
# of pts with Infusion-related reactions, n(%)	-	1(11)	-	-	7(14)	6(11)
Anaphylaxis, n (%)	-	-	-	-	-	1(2)
Death, n	-	-	-	-	-	-

*Patient 1016 from study 1.2 was excluded from this table as the patient was randomized to Remicade but received both CT-P13 and Remicade
CSR 1.2, Tables 31 and 35, CSR 3.3 Section 14.3, Tables R14.3.1.1., R14.3.1.4, R14.3.1.6, R14.3.1.8, CSR B1P13101, Tables 12-3, 12-6, Summary of Clinical Safety Section 2.7.4

120-Date Safety Update

Safety data from clinical studies 3.3 and B2P13111 with RA subjects and study 4.1 with IBD subjects make up the 120-day safety update.

Study 3.3, a small supportive study in Russia enrolling 15 RA patients, had a similar study design to study 3.1. It is a prospective, randomized, double-blind, multiple-dose IV infusion, parallel-group study comparing CT-P13 or EU-approved Remicade when co-administered with methotrexate (MTX) (12.5 – 25 mg) and folic acid (>5mg /week). The primary objective was to demonstrate similar efficacy between the two products with proportion of patients achieving ACR20 clinical response as the primary endpoint. Secondary objectives included safety, efficacy and PK data.

Study B2P13111, is an open label, single-arm, multicenter, extension study of the Japanese study B1P13101 with the primary objective of evaluating long term safety and efficacy of CT-P13 in 71 patients (CT-P13 transition group:33 patients, CT-P13 maintenance group: 38 patients). In Study B2P13111, CT-P13 (3 mg/kg) is administered by single 2 hour i.v. infusion per dose and co-administered with oral MTX and folic acid every 8 weeks

Study 4.1 is the one clinical study in patients with inflammatory bowel disease (IBD), designed as an open-label, single-arm study evaluating safety and efficacy of CT-P13 in South Korean patients with IBD who have an inadequate response to conventional therapy. Subjects will be treated with 5mg/kg of CT-P13 every 8 weeks for up to 4 years. Ten patients have been enrolled as of November 14, 2014; 5 with Crohn's

disease and 5 with ulcerative colitis. The majority of patients were exposed to at least 12 doses of treatment which spanned approximately 1 year 6 months of treatment including 6 week induction period. Each 4 (80%) patients in CD and UC groups experienced at least 1 treatment-emergent adverse event. Two cases of infusion-related reaction occurred. A total 4 cases of serious adverse events were reported in 3 patients: one case of gastritis in a patient with CD, 2 cases of colitis ulcerative and fistula repair, were reported in 2 UC patients. No deaths, malignancies, serious infections or TB were reported.

The 120-day safety update review included an additional 87 patients who received at least one dose of CT-P13. No new safety signals were identified. No deaths were reported. Adverse events of special interest did not identify any new cases of tuberculosis, or vascular disorders. There were two cases of infusion-related reactions; one in study 3.3 and one in the Japanese extension study; neither of them met anaphylaxis criteria described by Sampson et.al.

8 Postmarket Experience

The postmarket experience with CT-P13 is limited to data from a post-marketing surveillance study (PMS) to evaluate CT-P13 safety and efficacy in Korea in patients with Crohn's disease, fistulizing Crohn's Disease and Ulcerative Colitis in adults. As of November 14, 2014, a total of 173 patients with moderate-to-severe IBD were enrolled. Of these, 113 were naïve to Remicade and 60 were previously exposed to Remicade. Over half of the patients were treated for at least 5 doses. A total of 51 treatment emergent adverse events were reported in 38 patients. Of these, five were serious, including a case of tuberculosis, severe abdominal pain, lung abscess, anaphylactic reaction, severe treatment-related infusion related reaction. The latter three events led to discontinuation from the study. There were no deaths, malignancy, or pneumonia reported in this cohort. In summary, the safety data from this limited postmarket experience have not identified new safety signals.

Reference ID: 3747317

9 Appendices

9.1 Literature Review/References

FDA Guidance for Industry: "*Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*."

FDA Guidance for Industry "*Scientific Considerations in Demonstrating Biosimilarity to a Reference Product.*"

Sampson HA et al., Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium *J Allergy Clin Immunol.* 2006 Feb;117(2):391-7

Udata C, Yin D, Cai C, et al. Immunogenicity assessment of PF-06438179, a potential biosimilar to infliximab, in healthy volunteers. American College of Rheumatology Annual Meeting Abstract 2014.

USPI Remicade (infliximab), January 2015

9.2 Labeling Recommendations

At the time of this review, the Agency is continuing to consider its approach to labeling and nonproprietary naming of CT-P13.

9.3 Advisory Committee Meeting

As the first 351(k) BLA filed for proposed biosimilar monoclonal antibody, an Advisory Committee (AC) meeting was deemed necessary to obtain public input on issues related to analytical similarity assessment and extrapolation to non-studied indications. The AC meeting was scheduled for March 17, 2015. However, due to questions regarding the adequacy of the data to determine whether CT-P13 is highly similar to US-licensed Remicade, as detailed in Section 4.1 Chemistry Manufacturing and Controls, and the need for additional information, the AC was postponed. As of the time of this review, a revised date for the AC has not been determined.

9.4 Supportive Clinical Studies – Study Protocols

Study 1.2 (Pilot Study)

Title: A Randomized, Double-Blind, Parallel-Group, Phase I Study to Evaluate the Initial Pharmacokinetics, Efficacy, and Safety of CT-P13 Compared With Remicade When Co-administered With Methotrexate in Patients With Active Rheumatoid Arthritis

Objective
Primary: to demonstrate comparable observed Cmax between CT-P13 and EU-approved Remicade reference product in patients with active RA at Weeks 0, 2 and 6.

Secondary: to assess the PK and PD profiles, efficacy, and overall safety of CT-P13 in comparison with EU-approved Remicade reference product.

Study Design
This was a randomized, double-blind, multicenter, parallel-group, Phase I study. The study was designed to determine the PK, PD, efficacy, and safety of multiple doses of either CT-P13 or EU-approved Remicade (3 mg/kg) administered by a 2-hour IV infusion per dose when co-administered with methotrexate (between 12.5 to 25 mg/week, oral dose) and folic acid (≥5 mg/week, oral dose) in patients with active RA.

Patients were randomized to double-blind study drug and received Doses 1, 2 and 3 (Weeks 0, 2, and 6). Loading dose phase was followed by patients receiving 6 doses of randomized study drug every 8 weeks (Weeks 14, 22, 30, 38, 46 and 54).

Number of Subjects: 19 (Of note, patient 1016 was assigned to EU-approved Remicade but received both CT-P13 and EU-approved Remicade)

Study B1P13101 (Local Registration Study, Japan)

Title: A Double-Blind, Parallel-Group, Comparative Study of CT-P13 and Remicade in Treatment of Patients with Rheumatoid Arthritis

Objective
To verify equivalence of pharmacokinetic parameters for intravenously administered CT-P13 and Remicade® in patients with active rheumatoid arthritis who are inadequately responsive to MTX. Secondarily, to make a comparative study of efficacy and safety.

Study Design

This study was a multi-center, randomized, double-blind, parallel-group, comparative study in Japan. After enrollment, subjects were randomized to a CT-P13 group or Remicade group and the investigational drugs were administered (3 mg/kg) under blinded conditions for 54 weeks.

Number of Subjects: 104

Study 3.3 (Local Registration Study, Russia)

Title: A Randomized, Double-Blind, Parallel-Group, Phase 3 Study to Demonstrate Equivalence in Efficacy and Safety of CT-P13 Compared with Remicade when Co-administered with Methotrexate in Patients with Active Rheumatoid Arthritis

Objective
Primary: to demonstrate that CT-P13 was equivalent to Remicade up to Week 30, in terms of efficacy as determined by clinical response according to the American College of Rheumatology (ACR) definition of a 20% improvement (ACR20).

Secondary: to evaluate long-term efficacy, pharmacokinetics, pharmacodynamics, and overall safety of CT-P13 in comparison with Remicade reference product up to Week 54.

Study Design
This was a randomized, double-blind, multicenter, parallel-group, prospective Phase 3 study in Russia. Both CT-P13 and Remicade were administered as a dose of 3 mg/kg via single 2-hour IV infusion and coadministered with methotrexate between 12.5 to 25 mg/week, oral or parenteral dose and folic acid (≥5 mg/week, oral dose) in patients with active RA who were not achieving adequate response to methotrexate alone up to Week 30.

Patients were randomly assigned (1:1) to receive either CT-P13 or Remicade at Weeks 0, 2, 6, and then every 8 weeks up to Week 54. At Week 30, the study was unblinded for reporting purposes and efficacy, PK, PD, and safety endpoints were evaluated. Additionally, the study was unblinded at Week 6 for reporting purposes. The study remained blinded to the investigators and patients. At Week 54, the secondary efficacy, PK, PD, and safety endpoints were evaluated.

Number of Subjects: 15

Reference ID: 3747317

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/s/

JUWARIA F WAHEED
05/04/2015

NIKOLAY P NIKOLOV
05/04/2015
I concur.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 125544 **Applicant: CELLTRION, Inc.** **Stamp Date: August 8, 2014**

Drug Name: CT-P13 **BLA Type: 351 (k)**

An initial overview of the BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD format
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			The summary portion of your ISS is in Module 2 and the appendices of tables, figures, and datasets in Module 5 as agreed at Pre-BLA meeting.
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			The summary portion of your ISE is in Module 2 and the appendices of tables, figures, and datasets in Module 5 as agreed at Pre-BLA meeting.
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).			X	This is a 351(k) BLA
505(b)(2) Applications					
13.	If appropriate, what is the reference drug?			X	This is a 351(k) BLA. The reference product is US-licensed Remicade.
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?			X	
15.	Describe the scientific bridge (e.g., BA/BE studies)			X	

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

Reference ID: 3640611

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	This is a 351(k) BLA. Dosing is the same as the US-licensed reference product.
EFFICACY					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 CT-P13 1.4: A Randomized, Double-blind, Three-arm, Parallel Group, Single-dose Study to Compare the Pharmacokinetics, Safety, Tolerability, and Immunogenicity of Three Formulations of Infliximab (CT-P13, EU Sourced Remicade and US Sourced Remicade) in Healthy Subjects Indication: A 3-way bridging study (bridging to the safety and efficacy of the US-licensed Remicade) Pivotal Study #2 CT-P13 3.1 A Randomized, Double-Blind, Parallel-Group, Phase 3 Study to Demonstrate Equivalence in Efficacy and Safety of CT-P13 Compared with Remicade when Co-administered with Methotrexate in Patients with Active Rheumatoid Arthritis Indication: Rheumatoid Arthritis Pivotal Study #3 CT-P13 1.1: A Randomized, Double-Blind, Parallel-Group Study to Demonstrate the Equivalence with Respect to the Pharmacokinetic Profile of CT-P13 and Remicade in Patients with Ankylosing Spondylitis Indication: Ankylosing Spondylitis (supportive of extrapolation of biosimilarity)			X	This is a 351(k) BLA.
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	See above comment.
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			

Reference ID: 3640611

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
22.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	This is a 351(k) BLA.
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
26.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			Submitted IR, response received & sufficient.
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	This is a 351(k) BLA.
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

Reference ID: 3640611

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	previously by the Division?				
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes, as 351(k) BLA

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None.

Juwaria Waheed, M.D. — October 8, 2014
Reviewing Medical Officer — Date

Nikolay P. Nikolov, M.D. — October 8, 2014
Clinical Team Leader — Date

Reference ID: 3640611

Received: August 8, 2014
Filing: October 7, 2014
PDUFA: June 8, 2015

BLA 125544
CT-P13, Proposed Biosimilar to US-Licensed Remicade

MO: Juwaria Waheed, M.D.
TL: Nikolay P. Nikolov, M.D.

Filing Meeting
DPARP/DGIEP/DDDP Collaborative Review
September 29, 2014

Overview

- Sponsor: CELLTRION, Inc.
- Product: CT-P13, proposed biosimilar to infliximab (RP US-licensed Remicade®)
- Dosing: Same as RP (3-5mg/kg IV)
- Proposed indications (same as RP):
  - Rheumatoid arthritis (RA)
  - Ankylosing spondylitis (AS)
  - Psoriatic arthritis (PsA)
  - Plaque psoriasis (PsO)
  - Adult and pediatric Crohn's disease (CD)
  - Adult and pediatric Ulcerative colitis (UC)
- Recommendation: Fileable as 351(k) BLA
- Key review issues:
  - Extrapolation of biosimilarity to CD and UC
  - Labeling

Regulatory history

United States

- July 10, 2013: Type 3 BPD meeting
- Nov 18, 2014: IND 118,135 safe to proceed
- April 28, 2014: Pre-BLA Meeting

Worldwide

- Sep 2013: Approved in EU for all indications
- Jan 2014: Approved in Canada for all except IBD indications

Clinical Development – Controlled Studies

Protocol	Patient Population	Design/Objectives	Duration	Sample size/ Randomization	Treatment arms
CT-P13 1.4	HV	R, DB, PG, SD 3-way PK bridging	Single dose	N=250 1:1:1	• CT-P13 • EU-infliximab • US-Remicade
CT-P13 1.1	AS	R, DB, PG PK and Efficacy	54 weeks	N=250 1:1	• CT-P13 • EU-infliximab
CT-P13 3.1	RA, MTX-IR	R, DB, PG Comparative Clinical Study	54 weeks	N=606 1:1	• CT-P13 + MTX • EU-infliximab + MTX
B1P13101 (Japan)	RA, MTX-IR	R, DB, PG PK and Efficacy	54 weeks	N=108 1:1	• CT-P13 + MTX • EU-infliximab + MTX
CT-P13 1.2 (Philippines)	RA, MTX-IR	R, DB, PG Pilot Study	54 weeks	N=19 1:1	• CT-P13 + MTX • EU-infliximab + MTX
CT-P13 3.3 (Russia)	RA, MTX-IR	R, DB, PG Pilot Study	54 weeks	N=15	• CT-P13 + MTX • EU-infliximab + MTX

Clinical Development – Extension Studies

Protocol	Patient Population	Design/ Objectives	Duration	Sample size	Treatment (CT-P13)
CT-P13 1.3	AS, Rolled Over from Study 1.1	OLE, Safety & Immunogenicity	Wks 62-102 (~1year)	N=174	• Maintenance (n=88) • Transitioned from EU-infliximab (n=86)
CT-P13 3.2	RA, Rolled Over from Study 3.1	OLE, Safety & Immunogenicity	Wks 62-102 (~1year)	N=302	• Maintenance (n=158) • Transitioned from EU-infliximab (n=144)

Clinical Program - Inflammatory Bowel Disease Program (UC & CD)

Protocol	Patient Population	Design/ Objectives	Duration	Sample size	Treatment (CT-P13)
CT-P13 4.1	IBD	Open-label Safety & Efficacy	Ongoing (planned 4 year period)	N=10	• CT-P13
CT-P13 PMS	IBD	PMS, Safety & Efficacy	Ongoing (Interim data up to week 30)	N=88	• CT-P13

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Study CT-P13 1.4: 3-way PK bridging study

- **Study Design**
  - R, DB, three arm, PG, single dose study in HVs
  - Establish bridging between CT-P13, US licensed Remicade and EU approved infliximab
- **Treatment:** Dose 5 mg/kg
  - CT-P13
  - EU-infliximab
  - US-licensed Remicade
- **Population:** 213 HV (71 subjects per arm)
- **Primary Objective:** PK profile in HV
- **Secondary Objectives:** Safety, tolerability and immunogenicity data in HV
- **Results:** Sponsor's high level summary indicates PK similarity (AUC_{inf}, AUC_{last} and C_{max}) between the three products
  - The 90% CIs of ratio of geometric means for the PK parameters were contained within the equivalence limits of 80% to 125%

6

Study CT-P13 1.4: 3 Way PK

- Sponsor's high level summary indicates PK similarity (AUC_{inf}, AUC_{last} and C_{max}) between the three products

Summary Statistics: % Ratio of Geometric Means (90% CI)			
AUC_{last}	CT-P13/US-Remicade	98.4	(93.16, 104.03)
	CT-P13/EU-infliximab	101.8	(96.36, 107.56)
	EU-infliximab/US-Remicade	96.7	(91.52, 102.16)
AUC_{inf}	CT-P13/US-Remicade	96.5	(90.36, 103.02)
	CT-P13/EU-infliximab	100.8	(94.37, 107.59)
	EU-infliximab/US-Remicade	95.8	(89.72, 102.19)
C_{max}	CT-P13/US-Remicade	106.3	(101.86, 110.99)
	CT-P13/EU-infliximab	105.0	(100.64, 109.62)
	EU-infliximab/US-Remicade	101.2	(96.99, 105.65)

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Study 3.1: CCS in RA

- **Study 3.1** – Comparative clinical study in RA
  - R, DB, MC, PG study in RA patients MTX-IR
- **Population**
  - 606 RA patients: CT-P13 (n=302), EU-infliximab(n=304)
- **Treatment**
  - Dose 3mg/kg – CT-P13 or EU-infliximab
  - IV infusion over 120 mins on Week 0, 2, and 6 and then every 8 weeks through Week 54
  - Co-administration of MTX (12.5-25mg PO/IV) and folic acid
- **Primary Objective:** ACR20 at Week 30
- **Secondary Objectives:** ACR50, ACR70, DAS28, PK, PD and safety up to Week 54
- **Statistical Analysis:** Equivalence for the primary EP
  - NI margin (+/- 15%)

Study 3.1 Results: ACR Responses

Proportion of Patients Achieving ACR20, ACR50 and ACR70 Criteria at Weeks 30 and 54 (All Randomized Population, ITT Analysis)

Week 30	ACR20	CT-P13	184/302 (60.9)	0.02	-0.06, 0.10
		EU-approved Remicade®	179/304 (58.9)		
	ACR50	CT-P13	107/302 (35.4)	0.02	-0.06, 0.09
		EU-approved Remicade®	103/304 (33.9)		
	ACR70	CT-P13	50/302 (16.6)	0.01	-0.05, 0.07
		EU-approved Remicade®	47/304 (15.5)		
Week 54	ACR20	CT-P13	172/302 (57.0)	0.05	-0.03, 0.13
		EU-approved Remicade®	158/304 (52.0)		
	ACR50	CT-P13	100/302 (33.1)	0.02	-0.06, 0.09
		EU-approved Remicade®	96/304 (31.6)		
	ACR70	CT-P13	49/302 (16.2)	0.01	-0.05, 0.07
		EU-approved Remicade®	46/304 (15.1)		

Study 3.1 Results: HAQ-DI

Baseline Values and Change from Baseline in HAQ-DI at Weeks 14, 30, and 54 (All-Randomized Population, ITT Analysis)

ACR Component	CT- P13 3 mg/kg (N=302) (Mean±SD)	EU-approved Remicade® 3 mg/kg (N=304) (Mean±SD)
HAQ Physical Ability (scale 0-3)		
Baseline	1.61±0.55	1.56±0.59
Week 14	-0.56±0.56	-0.50±0.52
Week 30	-0.60±0.59	-0.51±0.57
Week 54	-0.61±0.61	-0.53±0.60

Study 3.1 Results: Radiographic Changes

- Re-analyzed post-hoc using mTSS method

Table 2.7.3-19: Joint Damage Progression without Incomplete/Missing Data Imputation in Study CT-P13 3.1 – All-Randomized Population

Statistic	CT-P13 3 mg/kg (N=302)		EU-approved Remicade® 3 mg/kg (N=304)		Difference between means (95% CI)	P-value [1]
	Result at each visit	Change From Baseline	Result at each visit	Change From Baseline		
Total Combined Score						
Week 0						
n	232	-	238	-	-	-
Mean (SD)	68.3 (58.88)	-	64.8 (62.46)	-		
Median (Min, Max)	52.0 (0, 307)	-	46.8 (0, 328)	-		
Week 54						
n	206	168	201	168	0.39 (-0.88, 1.66)	0.5463
Mean (SD)	66.0 (58.38)	1.0 (6.25)	63.7 (59.93)	0.6 (5.56)		
Median (Min, Max)	49.0 (0, 258)	0 (-18, 28)	45.5 (0, 353)	0 (-23, 23)		

Study 1.1: PK in AS

- **Study Design:**
  - R, DB, PG, study comparing CT-P13 and EU-Remicade in patients with active AS
- **Treatment:** Dose 5 mg/kg IV at weeks 0, 2, and 6 followed by every 8 weeks through Week 54
- **Population:** 250 subjects; 125 in each arm
- **Primary Objective:** PK equivalence at steady state (between Week 22 and Week 30)
- **Secondary Objective:** Safety and efficacy
- **Results:**
  - 1º EP PK similarity met by bioequivalence criteria
  - Descriptive efficacy comparable (ASAS20, ASAS40, BASDAI, BASFI, BASMI, SF-36)

Overview of Safety

- Safety population
  - 803 subjects (patients and HV) exposed to at least one dose of CT-P13
- No new safety signals
  - Types and incidence of TEAEs, SAEs, AE leading to discontinuation were similar
  - Most common TEAEs were infections
  - Most frequent AEs leading to discontinuation: hypersensitivity reactions, infusion-related reactions and infections
- Four deaths occurred across the CT-P13 development program:
  - Two on CT-P13 and two on EU-infliximab, all assessed as unrelated
- Anaphylaxis
  - Similar between CT-P13 and EU-infliximab (7 vs. 7 across controlled studies)
  - Did not increase following transition from EU-infliximab to CT-P13 (1 vs 1)
- Immunogenicity
  - Incidence of ADA comparable between CT-P13 and EU-infliximab
  - ADA incidence remained unchanged following transitioning from EU-Infliximab to CT-P13

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CT-P13 Safety: Exposure

Number of subjects receiving at least 1 dose of CT-P13			
Subjects	# of Patients	CT-P13 Maintenance During OLE	CT-P13 Transitioned from EU-infliximab
RA	520	158	144
AS	212	88	86
HV	71	-	-
Total	**803**		

Source: Table 2.7.4-2 Summary of clinical safety

Duration of Exposure	No. of Patients
≥ 6 months	653
≥1 year	605
≥ 2 years	230

Source: Table 2.7.4-3 Summary of clinical safety

CT-P13 Safety: Safety Overview

Summary Of TEAEs, deaths and SAE (Safety Population - study 3.1 and 1.1)				
	Study 3.1 (RA)		Study 1.1 (AS)	
	CT-P13 3mg/kg	EU-infliximab	CT-P13 5mg/kg	EU-infliximab
N of patients	302	300	128	122
TEAEs	732	738	362	375
N (%) pts with atleast 1 TEAE	213 (70.5)	211 (70 3)	95(74.2)	82(67.2)
SAEs	49	39	12	11
N(%) pts with atleast 1 SAE	42 (13 9)	31 (10.3)	10 (7 8)	8 (6.6)
TEAEs leading to discontinuation	40	52	12	9
N (%) of pts discontinued due to atleast 1 TEAE	33 (10 9)	47 (15.7)	11 (9 6)	9 (7.4)
Deaths	0	1	1	1
Infection related TEAEs	237	231	91	107
N(%) with atleast 1 infection related TEAE	127 (42.1)	137 (45.7)	55 (43.0)	49 (40.2)
Infusion-related TEAE	38	71	16	20
N(%) with atleast 1 infusion-related reaction	30 (9.9)	43 (12.3)	11 (8 6)	15 (12.3)

Source: Table 2.5-12 Clinical Overview

15

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CT-P13 Safety: AESI (Infections)

System Organ Class Preferred Term	All reported cases			
	Controlled Studies (Studies CT-P13 1.1, 1.2, 3.1, 3.3)		Extension Studies (Studies CT-P13 1.3, 1.2 Phase II, 3.2)	
	CT-P13 (N=446) n/N (%)	Remicade® (N=440) n/N (%)	CT-P13 Maintenance (N=257) n/N (%)	CT-P13 Switch (N=235) n/N (%)
No. of patients with at least one TEAE with infections[1]	189/446 (42.4%)	193/440 (43.9%)	74/257 (28.8%)	78/235 (33.2)
No. of patients with at least one SAE with infections[1]	16/446 (3.6%)	10/440 (2.3%)	6/257 (2.3%)	5/235 (2.1%)
No. of SAE with infections (events)[1, 2]	19	12	6	5
Tuberculosis[3,4]	6/446 (1.3%)	1/440 (0.2%)	1/257 (0.4%)	1/235 (0.4%)
Pneumonia[3,5]	5/446 (1.1%)	0/440 (0%)	1/257 (0.4%)	0/235 (0%)
Sepsis[3]	1/446 (0.2%)	2/440 (0.5%)	0/257 (0%)	1/235 (0.4%)
Other infections[6]	6/446 (1.3%)	9/440 (2.0%)	4/257 (1.6%)	3/235 (1.3%)

Source: Table 2.7.4-42 Summary Clinical Safety

16

Brief Review of Labeling

- CT-P13 (b) (4) draft label copy of US-licensed Remicade® label
- Indication:
  (b) (4) is a tumor necrosis factor (TNF) blocker indicated for:
  - Crohn's Disease
  - Pediatric Crohn's Disease
  - Ulcerative Colitis
  (b) (4)
  - Rheumatoid Arthritis in combination with methotrexate
  - Ankylosing Spondylitis
  - Psoriatic Arthritis
  - Plaque Psoriasis
- Section 6, Adverse Reactions, Summary of (b) (4) safety
- Section 14, Clinical Studies, proposed text to include:
  - RA efficacy: ACR20, HAQ-DI, Radiographic data, SF-36 (PCS, MCS)
  - AS efficacy: Clinical ASAS responses

17

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Filing and Planning

- Clinical Filing Checklist:
  - Completed, no omissions
- Advisory Committee:
  - Scheduled for March 26-27 (tentatively)
- OSI Audit:
  - Recommended for a new BLA
- Pediatric Development Plan:
  - Pediatric assessment is provided in the BLA and reflects the FDA recommendations provided on the iPSP
  - No revised/agreed iPSP has been submitted

18

Conclusions and Mid-Cycle Deliverables

- Application is fileable, as 351(k) BLA
- Mid-cycle deliverables: Complete review of:
  1. Comparative Efficacy
  2. Comparative Safety:
     - Deaths, SAEs
     - Adverse Events of Special Interest
  3. Assess extrapolation of biosimilarity to other indications

Other Disciplines

Additional Slides

Patient Disposition in Study 3.1 – All Randomized Population

	CT-P13 3 mg/kg (N=302) n (%)	EU-approved Remicade® 3 mg/kg (N=304) n (%)	Total (N=606) n (%)
Screened	-	-	1,077
Randomized	302 (100)	304 (100)	606 (100)
Initiated Treatment	300 (99.3)	302 (99.3)	602 (99.3)
Completed the entire study	233 (77.2)	222 (73.0)	455 (75.1)
Discontinued	69 (22.8)	82 (27.0)	151 (24.9)
All-randomized population	302 (100)	304 (100)	606 (100)
Per-protocol population up to Week 30[1]	248 (82.1)	251 (82.6)	499 (82.3)
Per-protocol population at Week 54[1, 2]	246 (81.5)	250 (82.2)	496 (81.8)
Pharmacokinetic population	290 (96.0)	288 (94.7)	578 (95.4)
Safety population[3]	302 (100)	300 (98.7)	602 (99.3)

Source: 2.7.3 summary clinical efficacy. Table 2.7.3-6

Study 3.1 Results: DAS28

Table 2.7.3-13: Analysis of DAS28 (ANCOVA) in Study CT-P13 3.1 – Per-Protocol Population

Visit/ Treatment Group	N'	Adjusted Mean (SE)	Estimate of Treatment Difference	95% CI of Treatment Difference
DAS28 (ESR)				
Week 14				
CT-P13	246	4.42 (0.074)	-0.11	(-0.31, 0.10)
EU-approved Remicade®	249	4.53 (0.074)		
Week 30				
CT-P13	245	4.21 (0.084)	-0.10	(-0.33, 0.13)
EU-approved Remicade®	249	4.31 (0.083)		
Week 54				
CT-P13	222	4.22 (0.089)	-0.05	(-0.30, 0.19)
EU-approved Remicade®	218	4.27 (0.090)		

Source: 2.7.3 summary clinical efficacy. Table 2.7.3-13, pg 55

Study 3.1 Results: SF-36

- Mean increases from baseline at Weeks 14, 30, and 54 were comparable between the treatment groups for SF-36 components BACKUP

SF-36 Component	Increase from Baseline, Mean±SD	
	CT-P13 3 mg/kg	EU-approved Remicade® 3 mg/kg
Physical function		
Baseline	29.44±8.78	30.36±9.22
Week 14	7.49±9.42	5.90±8.22
Week 30	7.63±10.59	6.84±9.00
Week 54	7.78±10.70	6.49±10.46

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/s/

JUWARIA F WAHEED
10/08/2014

NIKOLAY P NIKOLOV
10/08/2014
I concur.