CLINICAL REVIEW

Application Type	351(k) BLA
Application Number(s)	125544
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Division / Office	DPARP – lead division Collaborative review with DGIEP & DDDP
Reviewer Name(s)	Juwaria Waheed, MD
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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

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.

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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

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

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.

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.

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.

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

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

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

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

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

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

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

- 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

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_{τ}) 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.

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 $C_{max,ss}$ 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.

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

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

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.

- 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

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

- 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

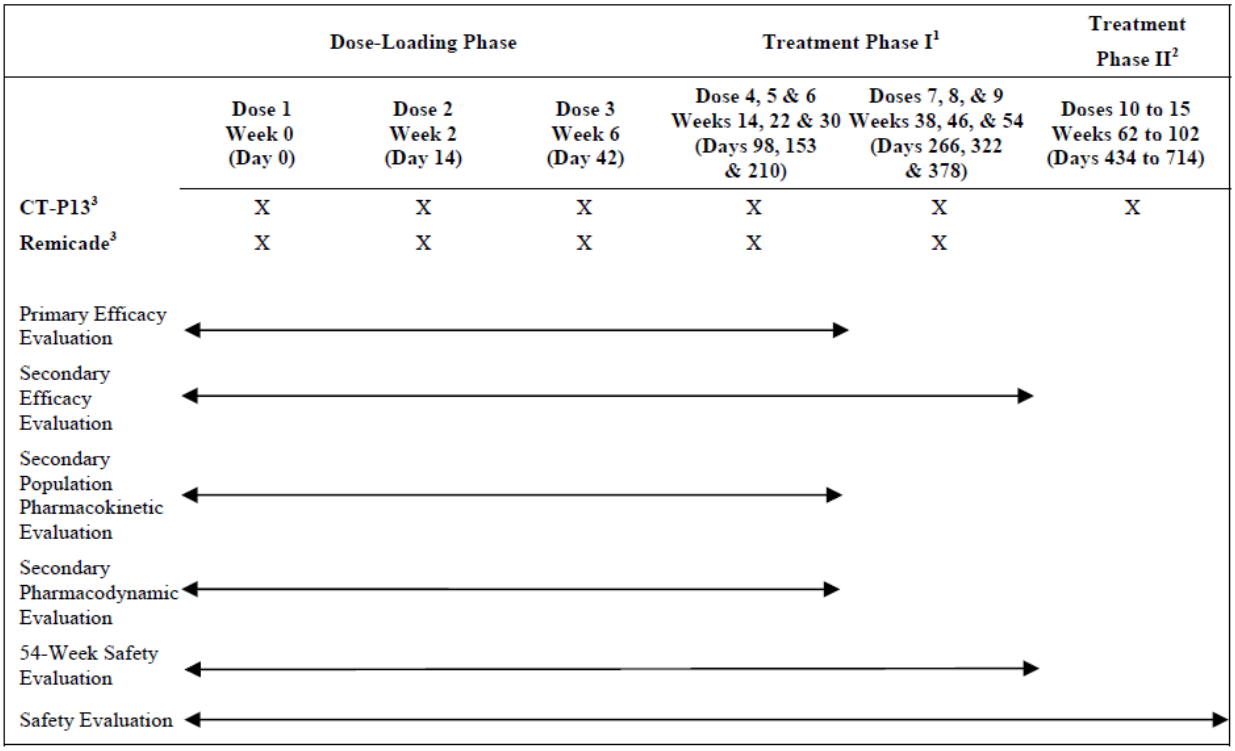
Primary objective: The primary objective of this study was to demonstrate that CT-P13 is therapeutically equivalent to EU-approved Remicade up to Week 30 in RA patients, in terms of efficacy as determined by clinical response according to the American College of Rheumatology (ACR) definition of a 20%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

Figure 1. Study Design for Study 3.1



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.

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.

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.

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

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

- 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

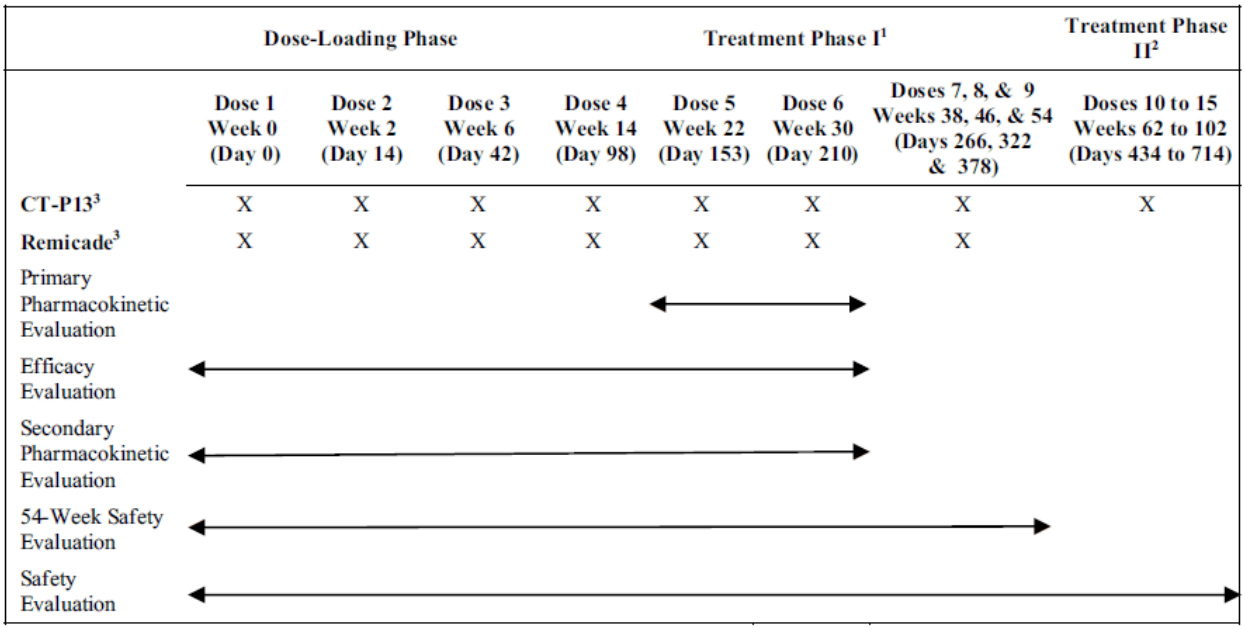
Additionally, ASAS20 responders should not have deterioration (worsening of ≥20% and an absolute worsening of at least 1 unit on a 0 to 10 scale) of the remaining assessment domain compared to baseline.

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



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-

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:

Rheumatoid Arthritis (RA):
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

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:

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.

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 Male	245(81) 57(19)	252(84) 48(16)	26(20) 102(80)	22(18) 100(82)	10(14) 61(86)	10(14) 61(86)	10(14) 61(86)
Race, (%) White Black Asian Other	220(73) 2(<1) 34(11) 46(15)	219(73) 1(<1) 36(12) 44(15)	98(77) 16(13) 14(11)	91(75) 13(11) 18(15)	71(100) 0 0 0	69(97) 1 (1) 0 0	70(99) 0 0 1(1)
Region(n%) Eastern Europe Western Europe Latin America Asia	179(59) 16(5) 72(24) 34(11)	180(60) 17(6) 66(22) 37(12)	81(63) 7(6) 24(19) 16(13)	82(67) 3(3) 25(21) 12(10)	71(100)	71(100)	71(100)
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

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.

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

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

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.

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.

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.

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

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

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.

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%).

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 Anaphylactic reaction Drug hypersensitivity	2(1) 2(1.3) -	1(0.7) - 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).

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

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

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.

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

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.

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.

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.

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.

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.

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.

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.

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

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/s/

JUWARIA F WAHEED
05/04/2015

NIKOLAY P NIKOLOV
05/04/2015
I concur.