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APPLICATION NUMBER:

125544Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

BLA	125544
Submission Date:	10/05/2015
Proposed Brand Name:	Inflectra
Nonproprietary Name	Infliximab-dyyb
Clinical Pharmacology Reviewer:	Lei He, Ph.D.
Clinical Pharmacology Team Leader (Acting):	Ping Ji, Ph.D.
OCP Division:	Division of Clinical Pharmacology II
OND Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Sponsor:	Celltrion
Submission Type; Code:	351(k); resubmission
Formulation; Strength(s)	Lyophilized powder for intravenous infusion; 100 mg/vial
Proposed Indications:	Rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PA), plaque psoriasis (Ps), ulcerative colitis (UC), pediatric UC ¹ , Crohn's disease (CD), pediatric CD ¹
Proposed Dosage Regimens:	RA: 3-10 mg/kg at 0, 2, 6 weeks, and then every 4-8 weeks. AS: 5 mg/kg at 0, 2, 6 weeks, and then every 6 weeks. Ps, PA, CD, UC, Pediatric UC, Pediatric CD: 5 mg/kg at 0, 2, 6 weeks, and then every 8 weeks.

Executive Summary

On October 5, 2015, Celltrion submitted an amendment of the 351(k) Biologics License Application (BLA) 125544 for CT-P13, a proposed biosimilar to US-licensed Remicade (infliximab), to address the deficiencies outlined in the Complete Response (CR) Letter from FDA on June 8, 2015. In the amendment, there is no change of the PK similarity

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>.

data assessment. For detailed information on the clinical pharmacology review, please refer to the Clinical Pharmacology Review (Reference ID: 3747351 in DARRTS) authored by the clinical pharmacology reviewer, Dr. Lei He.

On February 9, 2015, an Arthritis Advisory Committee (AAC) meeting was held to discuss BLA 125544 for CT-P13. Refer to the Clinical Review by the clinical reviewer, Dr. Juwaria Waheed, for details and the official AC transcript for detailed information of the committee discussion.

In the CR letter, the Agency stated in the Additional Comment 1: “You conducted comparative clinical study CT-P13 1.4 to assess the immunogenicity of CT-P13 and US-licensed Remicade, and differences were observed in immunogenicity incidence rates between these products. This single dose, healthy volunteer study suggests a potential trend towards increased neutralizing immunogenic responses in CT-P13-treated subjects compared to the pooled group of subjects receiving either US-licensed Remicade or EU-approved Remicade [27% vs. 19%, respectively (90% confidence Interval: -2.5%, +20%)]. Differences are also observed in binding antibody titers (mean transformed titers 4.74 vs 3.63 in CT-P13 and US Remicade samples, respectively) and neutralizing antibody titers (mean transformed titers 3.42 vs 2.63, respectively). To address these observations, provide a rationale for why the results from study CT-P13 1.4 are in alignment with the conclusion that the immunogenicity profiles of CT-P13 and US-licensed Remicade are similar.” In response to this comment, Celltrion submitted additional analysis including analyzing the sub-visible particle content of CT-P13 drug product, US-licensed Remicade and EU-approved Remicade using additional lots. For detailed information on the analytical updates, refer to the Product Quality Review. In addition, Celltrion submitted an interim report of Study CT-P13 3.4 containing the interim immunogenicity data analysis on December 10, 2015.

Study CT-P13 3.4 is an ongoing randomized, double-blind, controlled, post-marketing study in patients with active CD, comparing efficacy, safety, and immunogenicity of CT-P13 with US-licensed Remicade and EU-approved Remicade. Eligible patients were randomized in a 1:1:1:1 ratio to 1 of 4 treatment groups receiving a 2-hour IV infusion of 5 mg/kg of either CT-P13, US-licensed Remicade, or EU-approved Remicade at Weeks 0, 2, 6, and 14 and then every 8-weeks through Week 54 (Figure 1) ^{(b) (4)}

The immunogenicity assessment was planned at Weeks 0, 14, 30, 54, and end-of-study visit.

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

Figure 1. Study Design of Study CT-P13 3.4

(Source: Figure 1, Interim Immunogenicity Data from Study CT-P13 3.4 Report)

As of September 14, 2015, a total of 109 patients were randomized and received at least 1 dose of study drug and had immunogenicity results both at Week 0 (Dose 1) and Week 14 (Dose 4), of which 54 patients received CT-P13, 43 patients received US-licensed Remicade, and 12 patients received EU-approved Remicade.

The previously developed ELISA method, which was validated by [REDACTED] (b) (4) for the ADA analysis of Study CT-P13 1.4, has been further optimized and validated by [REDACTED] (b) (4) for the immunogenicity sample analysis of Study CT-P13 3.4. Celltrion stated that the ELISA assay has been validated, but did not provide the validation report. Refer to the OBP review by Dr. William Hallett for more detailed information regarding the immunogenicity assay.
<http://panorama.fda.gov/task/view?ID=56b22cbe008c0a72b664ac5b6cadb942>.

The ADA assay followed a 3-tiered approach consisting of (i) a screening assay, (ii) confirmatory assay and (iii) titration. Samples that were positive in the screening assay were spiked with excess study drug to determine if patients were a true positive. The results of the confirmatory assay have been summarized by visit. For further characterization, the antibody level was assessed by titration in confirmed positive samples. The ADA titer values were transformed using a $[\log_2(x)] + 1$ transformation (where x is the reported titer result). The results of ADA titer values are only summarized for patients where the confirmatory assay was positive using descriptive statistics: n, mean, standard deviation (SD), median, minimum and maximum.

The interim analysis of immunogenicity data from Study CT-P13 3.4 is shown in Table 1. At baseline, all patients were ADA negative except 1 patients in CT-P13 group. At Week

14, the number of patients with positive ADA was 8/54 (14.8 %), 5/43 (11.6 %) and 4/12 (33.3 %) at Week 14 in the CT-P13 group, US-licensed Remicade group, and EU-approved Remicade group, respectively. The mean (and median) titers between CT-P13 and US-Remicade at this interim analysis are similar. One patient who was ADA positive at Week 0 (baseline) could not be further analyzed for titration at baseline due to insufficient sample volume. The data on neutralizing antibodies (Nab) are currently not available and will be reported at later stage. This interim analysis shows the incidence of ADA formation was similar between CT-P13 and US-licensed Remicade in patients with IBD treated with 5 mg/kg dosing regimen. In this interim analysis, the ADA incidence was numerically higher in patients treated with the EU-approved Remicade, likely due to the small sample size of this subgroup.

Table 1. Interim Analysis of Immunogenicity Data in Study CT-P13 3.4

	CT-P13 (N=54)	US-licensed Remicade® (N=43)	EU-approved Remicade® (N=12)	Total (N=109)
Week 0 (Baseline)				
Number of patient with ADA positive (%)	1(1.9) ²	0	0	-
Mean ADA Titer (± SD)	2	-	-	-
Median ADA Titer (Min, Max)	2	-	-	-
Week 14				
Number of patient with ADA positive (%)	8 (14.8%)	5 (11.6%)	4 (33.3%)	17 (15.6%)
		9 ¹		
Mean ADA Titer (± SD)	2.3 (±1.49)	2.4 (±0.89)	3.5 (±2.08)	2.6 (± 1.50)
		2.9 (±1.54) ¹		
Median ADA Titer (Min, Max)	2.0 (1.5)	3.0 (1,3)	3.5 (1,6)	2.0 (1,6)
		3.0 (1,6) ¹		

Source: Table 2

¹ US-licensed Remicade® and EU-approved Remicade® were combined.

² one patient had a positive baseline ADA result but cannot be further analyzed for titration due to insufficient sample volume

Note: The ADA titer values were transformed using a $[\log_2(x)] + 1$ transformation (where x is the reported titer result)

(Source: Table 8, Interim Immunogenicity Data from Study CT-P13 3.4 Report

¹ US-licensed Remicade and EU-approved Remicade were combined)

Recommendation

The Office of Clinical Pharmacology has reviewed the submission and found that BLA125544 for CT-P13 is acceptable from a clinical pharmacology perspective.

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/s/

LEI HE
03/11/2016

PING JI
03/11/2016

CLINICAL PHARMACOLOGY REVIEW

BLA	125544
Submission Date:	08/08/2014
Proposed Brand Name:	Inflectra
Nonproprietary Name:	TBD
Clinical Pharmacology Reviewer:	Lei He, Ph.D.
Clinical Pharmacology Team Leader (Acting):	Ping Ji, Ph.D.
OCP Division:	Division of Clinical Pharmacology II
OND Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Sponsor:	Celltrion
Submission Type; Code:	351(k); standard review
Formulation; Strength(s)	Lyophilized powder for intravenous infusion; 100 mg/vial
Proposed Indications:	Rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PA), plaque psoriasis (Ps), ulcerative colitis (UC), pediatric UC ¹ , Crohn's disease (CD), pediatric CD ¹
Proposed Dosage Regimens:	RA: 3-10 mg/kg at 0, 2, 6 weeks, and then every 4-8 weeks. AS: 5 mg/kg at 0, 2, 6 weeks, and then every 6 weeks. Ps, PA, CD, UC, Pediatric UC, Pediatric CD: 5 mg/kg at 0, 2, 6 weeks, and then every 8 weeks.

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1. Executive Summary

Celltrion submitted a Biologic License Application (BLA) for CT-P13, a chimeric human-murine immunoglobulin G1 (IgG1) monoclonal antibody that binds to human tumor necrosis factor alpha (TNF α), under Section 351(k) of the Public Health Service Act (42 U.S.C. 262(k)). The applicant is seeking approval for CT-P13 as a biosimilar to US-licensed Remicade (BLA 103772) and licensure for all the indications currently approved for US-licensed Remicade. CT-P13 drug product is supplied as a sterile, white, lyophilized powder for intravenous infusion (100 mg/vial).

The clinical development for CT-P13 relevant to US submission included three clinical studies. Pharmacokinetic (PK) similarity of CT-P13 to US-licensed Remicade was evaluated in a pivotal three-way PK similarity study to compare the PK, safety, tolerability, and immunogenicity of CT-P13, EU-approved Remicade and US-licensed Remicade in healthy subjects (Study CT-P13 1.4). PK and immunogenicity were also assessed for CT-P13 and EU-approved Remicade in patients with active ankylosing spondylitis (AS) (Study CT-P13 1.1) and in patients with active rheumatoid arthritis (RA) (Study CT-P13 3.1).

In Study CT-P13 1.4, the 90% CIs for the geometric mean ratios (GMR) of CT-P13 to EU-approved Remicade, CT-P13 to US-licensed Remicade, and EU-approved Remicade to US-licensed Remicade for the tested PK parameters (i.e., AUC_{0-inf}, AUC_{0-t}, and C_{max}) were all within the biosimilarity acceptance interval of 80-125%. These pairwise comparisons met the pre-specified criteria for PK similarity between CT-P13, US-licensed Remicade and EU-approved Remicade, thus a scientific PK bridge was established to support the relevance of the data generated using EU-approved Remicade in the comparative clinical efficacy trial (Study CT-P13 3.1). In Study CT-P13 1.1, the steady-state AUC_τ and C_{max,ss} of CT-P13 were similar to those of EU-approved Remicade. In Study CT-P13 3.1, serum trough concentrations and peak concentrations assessed at Weeks 0, 2, 6, 14, 22, 30, 38, 46 and 54 were also similar between CT-P13 and EU-approved Remicade treatment groups.

The incidence of anti-drug antibody (ADA) formation on Day 57 in healthy subjects was 26.7%, 25.3%, and 11.4% for CT-P13, EU-approved Remicade, and US-licensed Remicade, respectively. Although the study had limited number of patients, the numerical ADA formation rate differences did not appear to impact the PK similarity between these three treatment groups. After multiple doses of i.v. infusions, the ADA formation rate was similar between CT-P13 and EU-approved Remicade in patients with RA (Study CT-P13 3.1) and patients with AS (Study CT-P13 1.1), respectively.

Overall, PK similarity has been demonstrated between CT-P13 and US-licensed Remicade, and the PK results add to the totality of evidence to support a demonstration of biosimilarity of CT-P13 and US-licensed Remicade.

1.1 Recommendations

The Office of Clinical Pharmacology has determined that PK similarity has been demonstrated between CT-P13 and US-licensed Remicade, and the PK results support a demonstration of no clinically meaningful differences between CT-P13 and US-licensed Remicade.

Labeling Recommendations

Please refer to Section 3 – Detailed Labeling Recommendations.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Celltrion submitted a Biologic License Application (BLA) for CT-P13, a chimeric human-murine immunoglobulin G1 (IgG1) monoclonal antibody that binds to human tumor necrosis factor alpha (TNF α), under Section 351(k) of the Public Health Service Act (42 U.S.C. 262(k)). The applicant is seeking approval for CT-P13 as a biosimilar to US-licensed Remicade (BLA 103772) and licensure for all the indications currently approved for US-licensed Remicade. CT-P13 drug product is supplied as a sterile, white, lyophilized powder for intravenous infusion (100 mg/vial).

The clinical development for CT-P13 relevant to US submission included three clinical studies. Pharmacokinetic (PK) similarity of CT-P13 to US-licensed Remicade was evaluated with the pivotal three-way PK similarity study to compare the PK, safety, tolerability, and immunogenicity of CT-P13, EU-approved Remicade and US-licensed Remicade in healthy subjects (Study CT-P13 1.4). PK and immunogenicity were also assessed for CT-P13 and EU-approved Remicade in patients with active ankylosing spondylitis (AS) (Study CT-P13 1.1) and in patients with active rheumatoid arthritis (RA) (Study CT-P13 3.1).

In Study CT-P13 1.4, the 90% CIs for the geometric mean ratios (GMR) of CT-P13 to EU-approved Remicade, CT-P13 to US-licensed Remicade, and EU-approved Remicade to US-licensed Remicade for the tested PK parameters (i.e., AUC_{0-inf}, AUC_{0-t}, and C_{max}) were all within the biosimilarity acceptance interval of 80-125%. These pairwise comparisons met the pre-specified criteria for PK similarity between CT-P13, US-licensed Remicade and EU-approved Remicade, thus a scientific PK bridge was established to support the relevance of the data generated using EU-approved Remicade in the comparative clinical efficacy trial (Study CT-P13 3.1). In Study CT-P13 1.1, the steady-state AUC τ and C_{max,ss} of CT-P13 were similar to those of EU-approved Remicade. In Study CT-P13 3.1, serum trough concentrations and peak concentrations assessed at Weeks 0, 2, 6, 14, 22, 30, 38, 46 and 54 were similar between CT-P13 and EU-approved Remicade treatment groups.

Comparison	Parameter	GMR%	90% CI (%)
CT-P13 vs US-licensed Remicade	C _{max}	105.7	(100.8, 110.8)
	AUC _{0-t}	101.4	(95.1, 108.1)
	AUC _{0-inf}	102.3	(95.1, 110.0)
CT-P13 vs EU-approved Remicade	C _{max}	106.9	(102.0, 112.1)
	AUC _{0-t}	98.2	(92.3, 104.5)
	AUC _{0-inf}	98.8	(92.1, 106.0)
EU-approved Remicade vs US-licensed Remicade	C _{max}	100.9	(96.8, 105.8)
	AUC _{0-t}	96.9	(91.7, 102.4)
	AUC _{0-inf}	96.6	(90.4, 103.3)

The incidence of anti-drug antibody (ADA) formation on Day 57 in healthy subjects was 26.7%, 25.3%, and 11.4% for CT-P13, EU-approved Remicade, and US-licensed Remicade,

respectively. Although the study had limited number of patients, the numerical ADA formation rate differences did not appear to impact the PK similarity between these three treatment groups. After multiple doses of i.v. infusions, the ADA formation rate was similar between CT-P13 and EU-approved Remicade in patients with RA (Study CT-P13 3.1) and patients with AS (Study CT-P13 1.1), respectively.

Overall, from the clinical pharmacology perspective, the submitted clinical pharmacology studies support a demonstration of PK similarity among CT-P13, EU-approved Remicade, and US-licensed Remicade.

2. Question Based Review

2.1 General Attributes

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of this drug?

Celltrion is developing CT-P13 as a proposed similar biological product to Remicade® (infliximab). Remicade® was approved in the United States (US) in 1998. During the clinical development of CT-P13, three key regulatory interactions with Celltrion occurred: the Type 3 BPD meeting discussing the development program (July 10, 2013), the Type 4 BPD meeting on the format and content of the proposed BLA submission (April 28, 2014), and a teleconference discussing iPSP (June 11, 2014).

Initially, as part of a global program, CT-P13 program was designed to demonstrate biosimilarity to EU-approved Remicade. Studies CT-P13 3.1 and CT-P13 1.1 were conducted for this purpose. Subsequently, the CT-P13 program was repurposed to collect additional 3-way CMC and clinical PK bridging data between CT-P13, EU-approved Remicade and US-licensed Remicade (Study CT-P13 1.4) to support a demonstration of biosimilarity to the reference product, US-licensed Remicade in order to demonstrate that CT-P13 is biosimilar to US-licensed Remicade in terms of its clinical pharmacology, efficacy and safety.

The review of BLA125544 is standard.

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

CT-P13 drug substance is a chimeric human-murine IgG1 monoclonal antibody that binds with high affinity to human TNF α . It is a glycoprotein with 1 N-linked glycosylation site in the CH2 domain of each heavy chain. Each heavy chain consists of 450 amino acids with 11 cysteine residues, and each light chain consists of 214 amino acids with 5 cysteine residues. All cysteines in the heavy and light chains are involved in either intra- or inter- disulfide bonding. CT-P13

drug substance is a colorless to light yellow and slightly opalescent to opalescent solution and free of foreign particles, with a pH of approximately 7.2.

The CT-P13 drug product is formulated as a white, lyophilized powder in a 20 mL type I borosilicate glass vial with a 20 mm (b)(4) butyl rubber stopper and a 20 mm flip-off seal. Each CT-P13 drug product vial contains 100 mg CT-P13 drug substance as the active ingredient, 2.2 mg sodium dihydrogen phosphate monohydrate, 6.1 mg di-sodium hydrogen phosphate dihydrate, 500 mg sucrose and 0.5 mg polysorbate 80 as excipients.

Infliximab (US-licensed Remicade) is a chimeric IgG1 κ monoclonal antibody specific for TNF α . It has a molecular weight of approximately 149.1 kilodaltons. Infliximab is produced by a recombinant cell line cultured by continuous perfusion and is purified by a series of steps that includes measures to inactivate and remove viruses.

US-licensed Remicade is supplied as a sterile, white, lyophilized powder for intravenous infusion. Following reconstitution with 10 mL of Sterile Water for Injection, USP, the resulting pH is approximately 7.2. Each single-use vial contains 100 mg infliximab, 500 mg sucrose, 0.5 mg polysorbate 80, 2.2 mg monobasic sodium phosphate, monohydrate, and 6.1 mg dibasic sodium phosphate, dihydrate. No preservatives are present.

2.1.3 What are the proposed mechanism of action and therapeutic indication(s)?

CT-P13 is a chimeric human IgG1 monoclonal antibody that binds with high affinity to the human TNF.

CT-P13 is proposed to be used for 8 indications identical to US-licensed Remicade, which are Rheumatoid Arthritis (RA), Crohn's Disease (CD), pediatric CD, Ulcerative Colitis (UC), pediatric UC, Plaque Psoriasis (Ps), Psoriatic Arthritis (PA), and Ankylosing Spondylitis (AS).

2.1.4 What are the proposed dosages and routes of administration?

The proposed dosages and routes of administration for CT-P13 are identical to those approved for US-licensed Remicade (Table 1).

Table 1. Dosage and routes of administration of US-licensed Remicade	
Indication	Dosage and Administration
RA	In conjunction with methotrexate, 3 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. Some patients may benefit from increasing the dose up to 10 mg/kg or treating as often as every 4 weeks.
CD (Adult)	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.
CD (Pediatric)	5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.

UC (Pediatric)	
UC (Adult)	
Ps	
AS	

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

Overall, the clinical development for CT-P13 included 7 completed clinical studies (Studies CT-P13 1.4, CT-P13 1.1, CT-P13 1.3, CT-P13 3.1, CT-P13 3.2, CT-P13 1.2 and B1P13101) plus 2 additional regional specific studies ongoing, one in Russia (Study CT-P13 3.3) and the extension study to B1P13101 in Japan (Study B2P13111).(Table 2)

Studies	Objective(s)	Study Design	Dosing Regimen	Study Population
CT-P13 1.4	Primary: To evaluate and compare the PK profiles of CT-P13, EU-approved Remicade and US-licensed Remicade in healthy subjects Secondary: Safety, tolerability, immunogenicity,	Randomized, double-blind, three-arm, parallel-group, single dose	CT-P13: 5 mg/kg IV US-licensed Remicade: 5 mg/kg IV EU-approved Remicade: 5 mg/kg IV	Healthy subjects (n=71/arm)
CT-P13 1.1	Primary: To demonstrate similar PK at steady-state in terms AUC _τ and C _{max,ss} between CT-P13 and EU-approved Remicade determined between Weeks 22 and 30 in patients with AS Secondary: long-term efficacy, PK and overall safety up to Week 54	Randomized, double-blind, two-arm, parallel-group, multiple dose	CT-P13: 5 mg/kg IV at weeks 0, 2, 6, and then q8w to week54 EU-approved Remicade: 5 mg/kg IV at weeks 0, 2, 6, and then q8w to week54	AS patients (n=125/arm)
CT-P13 1.3	Long term safety and efficacy of CT-P13 in patients with AS up to Week 102	Open-label, single-arm, extension study to demonstrate long-term efficacy and safety of CT-P13 in patients with AS who were treated with EU-approved Remicade or	CT-P13 (5 mg/kg) administered as 2h i.v. infusion at Week 62 and every 8 weeks up to Week 102	174 patients with AS who completed Study CT-P13 1.1 were enrolled CT-P13 maintenance group: 88 CT-P13 switch group: 86

		CT-P13 in Study CT-P13 1.1		
CT-P13 3.1	<p>Primary: To demonstrate that CT-P13 is equivalent to EU-approved Remicade, in terms of efficacy as determined by clinical response according to ACR20 at Week 30 in patients with RA</p> <p>Secondary: To evaluate other efficacy endpoints (e.g. ACR50, ACR70, DAS28, hybrid ACR), long-term efficacy, PK, PD, and overall safety up to Week 54</p>	Randomized, double-blind, two-arm, parallel-group, multiple dose	CT-P13 or EU-approved Remicade (3 mg/kg) administered as 2h i.v. infusion; at Weeks 0, 2 and 6, then every 8 weeks up to Week 54, co-administered with MTX (12.5-25 mg/week) and folic acid	Male or female patients with active RA who had an inadequate response to MTX (aged 18 to 75 years old) Randomized: 606 CT-P13: 302 EU-approved Remicade: 304
CT-P13 3.2	To confirm long term safety and efficacy of CT-P13 in patients with RA up to Week 102.	Open-label, single-arm, extension study to demonstrate long-term efficacy and safety of CT-P13 when coadministered with MTX in patients with RA who were treated with EU-approved Remicade or CT-P13 in Study CT-P13 3.1	CT-P13 (3 mg/kg) administered as 2h i.v. infusion, co-administered with MTX (12.5-25 mg/week) and folic acid at Week 62 and every 8 weeks up to Week 102	302 patients with RA who completed Study CT-P13 3.1 were enrolled. CT-P13 maintenance group: 158 CT-P13 switch group: 144
CT-P13 3.3	<p>Primary: To demonstrate that CT-P13 is equivalent to EU-approved Remicade in terms of efficacy as determined by clinical response according to ACR20 at Week 30 in patients with RA</p> <p>Secondary: other efficacy endpoints (e.g. ACR50, ACR70, DAS28, ACR hybrid), long term efficacy, PK, PD, and overall safety up to Week 54</p>	Prospective Phase 3, randomized, double-blind, multicenter, parallel-group study in patients with active RA	CT-P13 or EU-approved Remicade (3 mg/kg) administered as 2h i.v. infusion; at Weeks 0, 2, 6, then every 8 weeks up to Week 54, co-administered with MTX (12.5-25 mg/week) and folic acid	Male or female patients with active RA who had an inadequate response to MTX (aged 18 to 75 years old) Randomized:15 CT-P13: 6 EU-approved Remicade: 9
CT-P13 1.2	Primary: To determine C _{max} of CT-P13 and EU-approved Remicade at Weeks 0, 2, and 6 in patients with RA	Phase 1, randomized, double-blind, multicenter, multiple-dose	CT-P13 or EU-Remicade (3 mg/kg) administered as 2h i.v. infusion, co-	Male or female patients with active RA who had an inadequate response to MTX

	Secondary: PK profile, PD, efficacy, and safety of CT-P13 in comparison to EU-approved Remicade up to Week 54. Overall safety throughout the study (up to Week 102)	i.v. infusion, parallel-group study in patients with active RA who had an inadequate response to MTX	administered with oral MTX (12.5-25 mg/week) and folic acid; administered at Weeks 0, 2, 6 weeks, then every 8 weeks up to Week 54; Patients continuing beyond Week 54 received CT-P13 up to Week 102	(aged 18 to 75 years old) Randomized:19 CT-P13: 9 EU-approved Remicade: 10
B1P13101	Primary: To demonstrate the similarity of the PK parameters of CT-P13 and EU-approved Remicade following i.v. infusion to patients with active RA Secondary: Assessment of long-term efficacy, PD and safety up to Week 54	Phase 1/2, randomized, double-blind, multicenter, parallel-group, comparative study in patients with active RA who had an inadequate response to MTX	CT-P13 and EU-approved Remicade following i.v. infusion to patients with active RA Secondary: Assessment of long-term efficacy, PD and safety up to Week 54 CT-P13 or EU-approved Remicade (3 mg/kg) administered as 2 h i.v. infusion, co-administered with weekly oral MTX (6-16 mg/week) and folic acid; administered at Weeks 0, 2, 6 weeks, then every 8 weeks up to Week 54	Patients with active RA who had an inadequate response to MTX (aged 20 to 75 years old) Randomized: 108 Analysed: 104 (patients received at least 1 dose of treatment) CT-P13: 51 Remicade: 53
B2P13111	To confirm long term safety and efficacy of CT-P13 in patients with RA	Open-label, single-arm, multicenter, efficacy and safety extension study of the Phase 1/2 Study B1P13101	CT-P13 (3 mg/kg) administered as 2 h i.v. infusion co-administered with oral MTX (6-16 mg/week) and folic acid every 8 weeks up to at least 110 weeks The dose can be increased up to 10mg/kg for those who are not receiving an adequate response	72 patients with RA who completed Study B1P13101 were enrolled Administered: 71 CT-P13 maintenance group: 38 CT-P13 switch group: 33

The pivotal 3-way PK-bridging study comparing CT-P13, EU-approved Remicade and US-licensed Remicade was conducted in healthy subjects (Study CT-P13 1.4). In addition, PK bridging between CT-P13 and EU-approved Remicade was also assessed in adult patients with AS or RA (Study CT-P13 1.1 and Study CT-P13 3.1, respectively). The supporting pilot study CT-P13 1.2 and regional studies – Study CT-P13 3.3 (Russia) and Study B1P13101 (Japan) were conducted in RA patients. This clinical pharmacology review primarily focused on the pivotal PK similarity Study CT-P13 1.4. We also evaluated the PK and immunogenicity in Studies CT-P13 1.1 and CT-P13 3.1. The rest studies were either preliminary or conducted for other regional submissions. The PK findings from these studies were also briefly summarized in the appendix.

2.2.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

PK (AUC_{0-inf}, AUC_{0-t}, and C_{max}) was assessed as primary endpoint in the Study CT-P13 1.4 to evaluate and compare the PK profiles of CT-P13, EU-approved Remicade and US-licensed Remicade in healthy subjects. Safety, tolerability and immunogenicity were the secondary endpoints. For study CT-P1 1.1, the steady-state AUC and C_{max} were the primary PK endpoints to evaluating the steady-state PK similarity, whereas efficacy, safety and immunogenicity were the secondary endpoints, including SpondyloArthritis International Society (ASAS) 20% improvement scale (ASAS20), ASAS40, BASDAI, Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Metrology Index (BASMI), chest expansion, and quality-of-life questionnaire (SF-36). Study CT-13 3.1 was the comparative efficacy trial in RA patients. Therefore, the primary efficacy endpoint was the proportion of patients achieving clinical response (according to the ACR20 criteria) at Week 30, whereas PK, safety, immunogenicity and other efficacy endpoints (ACR20, ACR50, and ACR70, mean decrease in Disease Activity Score 28 (DAS28), and EULAR response criteria, CDAI, SDAI, joint damage progression, and general health status (SF-36)) were the secondary endpoints. The choice of these endpoints was consistent to the study objective and has been used in the development program of other drugs with the same indications.

2.2.3 What are the PK characteristics of the drug?

2.2.3.1 What are the known PK characteristics of the reference product US-licensed Remicade?

The PK and immunogenicity of infliximab (US-licensed Remicade) described in product labeling from BLA103772 are summarized in Table 3.

Table 3. PK and immunogenicity summary of US-licensed Remicade (BLA103772)

- PK is linear over the range of 3 to 20 mg/kg IV
- Distributed primarily within vascular compartment
- Thalf: 7.7-9.5 d
- No systemic accumulation upon repeated dosing with 3 mg/kg or 10 mg/kg at 4-

- or 8week intervals
- development increased infliximab clearance
- CL is not affected by age, weight, or gender PK similar across various populations including patients with RA, CD, and UC
- Concomitant MTX use may decrease the incidence of ADA production and increase infliximab concentrations.
- Upon initiation or discontinuation of REMICADE in patients being treated with CYP450 substrates, infliximab could antagonizes cytokine activity, normalize the formation of CYP450 enzymes, and therefore affecting the PK exposure of concomitant CYP450 substrates
- ADA rate is 15-51% across all the disease populations

In adults, single IV infusions of 3 mg/kg to 20 mg/kg showed a linear relationship between the dose administered and the maximum serum concentration. The volume of distribution at steady state was independent of dose and indicated that infliximab was distributed primarily within the vascular compartment. Pharmacokinetic results for single doses of 3 mg/kg to 10 mg/kg in rheumatoid arthritis, 5 mg/kg in Crohn's disease, and 3 mg/kg to 5 mg/kg in plaque psoriasis indicate that the median terminal half-life of infliximab is 7.7 to 9.5 days.

Following an initial dose of infliximab, repeated infusions at 2 and 6 weeks resulted in predictable concentration-time profiles following each treatment. No systemic accumulation of infliximab occurred upon continued repeated treatment with 3 mg/kg or 10 mg/kg at 4-or 8week intervals. Development of antibodies to infliximab increased infliximab clearance. At 8 weeks after a maintenance dose of 3 to 10 mg/kg of infliximab, median infliximab serum concentrations ranged from approximately 0.5 to 6 mcg/mL; however, infliximab concentrations were not detectable (<0.1 mcg/mL) in patients who became positive for antibodies to infliximab. No major differences in clearance or volume of distribution were observed in patient subgroups defined by age, weight, or gender. It is not known if there are differences in clearance or volume of distribution in patients with marked impairment of hepatic or renal function.

Infliximab pharmacokinetic characteristics (including peak and trough concentrations and terminal half-life) were similar in pediatric (aged 6 to 17 years) and adult patients with Crohn's disease or ulcerative colitis following the administration of 5 mg/kg infliximab.

Population pharmacokinetic analysis showed that in children with juvenile rheumatoid arthritis (JRA) with a body weight of up to 35 kg receiving 6 mg/kg infliximab and children with JRA with body weight greater than 35 kg up to adult body weight receiving 3 mg/kg infliximab, the steady state area under the concentration curve (AUC_τ) was similar to that observed in adults receiving 3 mg/kg of infliximab.

2.2.3.2 What are the single dose and multiple dose PK characteristics for CT-P13?

Single-Dose PK

The pivotal PK biosimilarity Study CT-P13 1.4 was a randomized, double-blind, three-arm, parallel-group, single-dose study in healthy subjects. In each arm of the study, a total of 71

subjects received a single dose 5 mg/kg of either CT-P13, EU-approved Remicade, or US-licensed Remicade by i.v. infusion for 120 min. The PK, safety, tolerability, and immunogenicity of CT-P13, EU-approved Remicade and US-licensed Remicade were assessed. Mean serum concentration-time profiles were similar between the CT-P13, EU-approved Remicade and US-licensed Remicade treatment groups (Figure 1). For the 3-way PK similarity comparisons (CT-P13 vs. US-licensed Remicade, CT-P13 vs. EU-approved Remicade and EU-approved Remicade vs. US-licensed Remicade), the 90% CIs for the geometric mean ratios of C_{max}, AUC_{0-t} and AUC_{0-inf} were all contained within the similarity range of 80%–125% (Table 4).

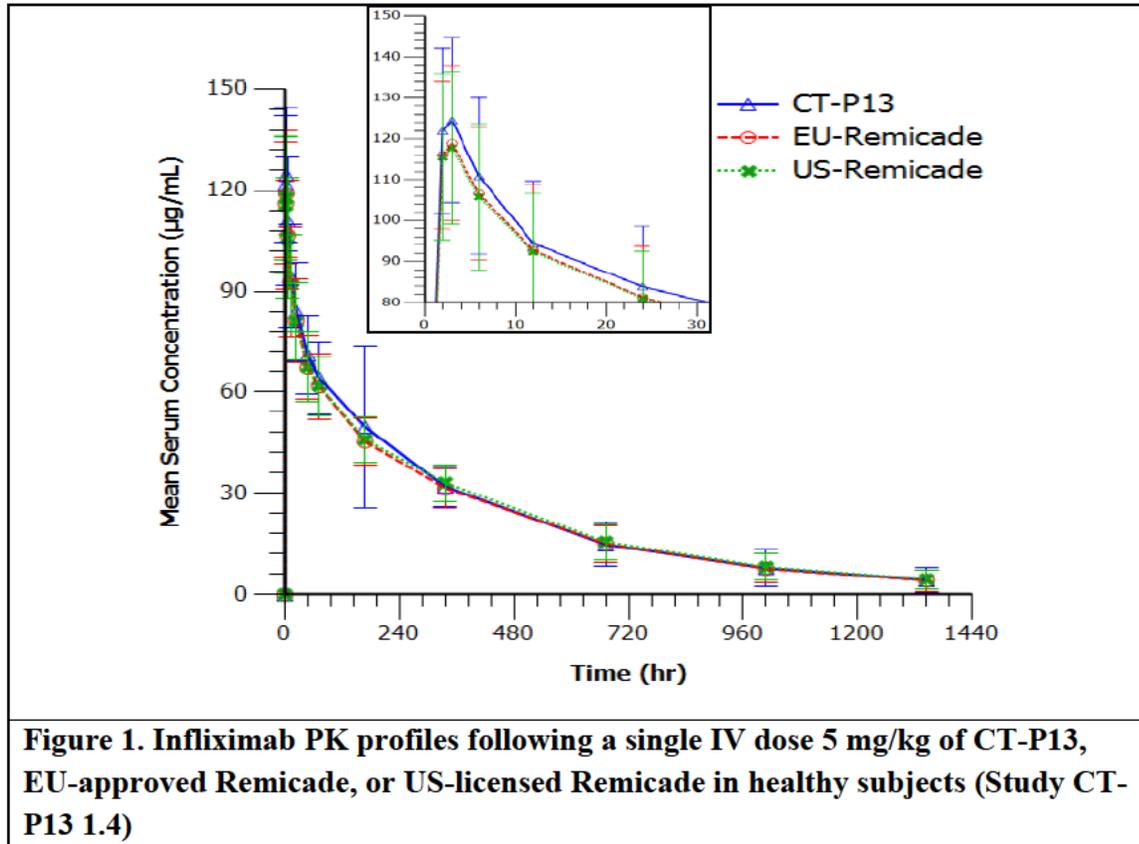


Figure 1. Infiximab PK profiles following a single IV dose 5 mg/kg of CT-P13, EU-approved Remicade, or US-licensed Remicade in healthy subjects (Study CT-P13 1.4)

Table 4. Statistical analysis of PK parameters (Study CT-P13 1.4)						
Average Bioequivalence Approach						
Study CT-P13 1.4 (Pivotal, 3-Way PK bridging/similarity study)						
CT-P13 (T) vs US-licensed Remicade (R)						
Parameter	LSM (T)	N	LSM (R)	N	GMR	90% CI
C _{max}	126.60	71	118.68	70	105.7	(100.8, 110.8)
AUC _{0-t}	30507.32	71	29434.79	70	101.4	(95.1, 108.1)
AUC _{0-inf}	33038.27	71	33434.17	70	102.3	(95.1, 110.0)
CT-P13 (T) vs EU-approved Remicade (R)						
C _{max}	126.60	71	119.77	71	106.9	(102.0, 112.1)
AUC _{0-t}	30507.32	71	30096.19	71	98.2	(92.3, 104.5)

AUC _{0-inf}	33038.27	71	32295.91	71	98.8	(92.1, 106.0)
EU-approved Remicade (T) vs US-licensed Remicade (R)						
C _{max}	119.77	71	118.68	70	100.9	(96.8, 105.8)
AUC _{0-t}	30096.19	71	29434.79	70	96.9	(91.7, 102.4)
AUC _{0-inf}	32295.91	71	33434.17	70	96.6	(90.4, 103.3)

The units of C_{max} and AUC are µg/mL and µg*h/mL, respectively.

Multiple-Dose PK

The supporting PK biosimilarity Study CT-P13 1.1 is a randomized, double-blind, parallel-group, Phase 1 study to demonstrate the similarity with respect to the PK profile of CT-P13 and EU-approved Remicade in patients with ankylosing spondylitis. In this study, a total of 250 male and female patients aged 18 to 75 years old with active AS were enrolled and randomly assigned to receive either CT-P13 or EU-approved Remicade 5mg/kg administered by a 2-hour i.v. infusion in Weeks 0, 2, 6, 14, 22, 30, 38, 46, and 54. The primary objective of demonstrating PK similarity at steady state in terms of AUC_τ and C_{max,ss} was assessed between Weeks 22 and 30. Mean serum concentration-time profiles were similar between the CT-P1 and EU-approved Remicade treatment groups (Figure 2).

The 90% CIs for CT-P13 vs. EU-approved Remicade geometric mean ratios of C_{max} and AUC_τ were contained within the similarity range of 80% –125% (Table 5).

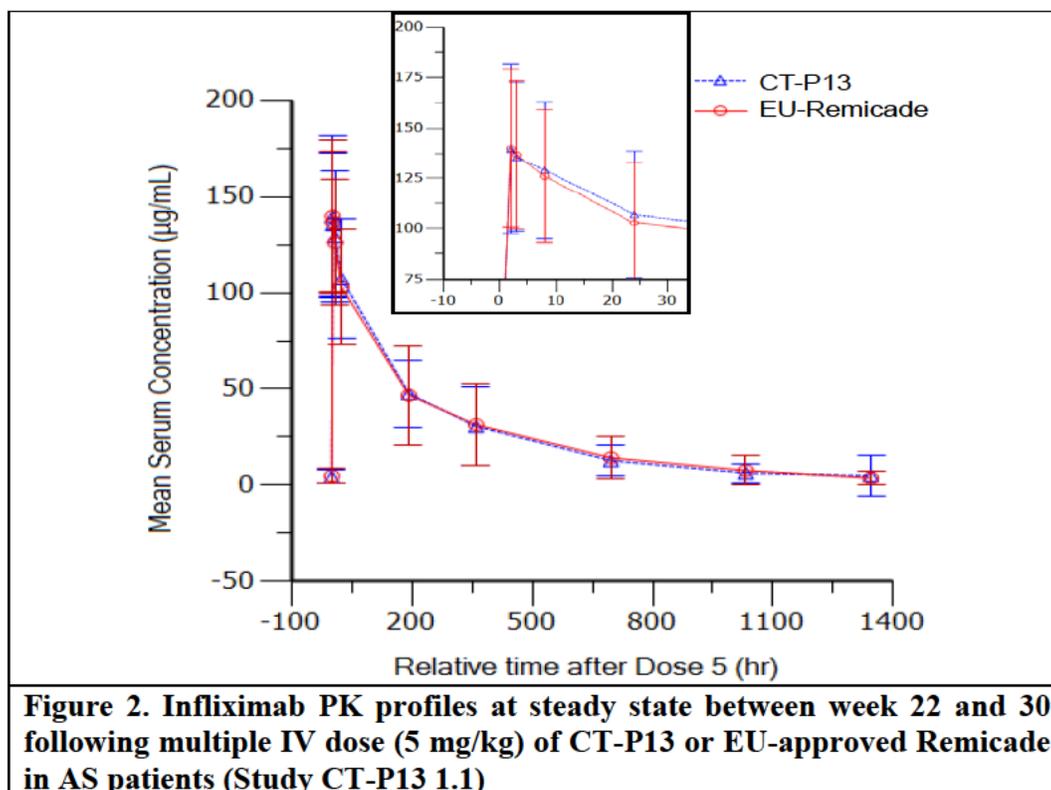
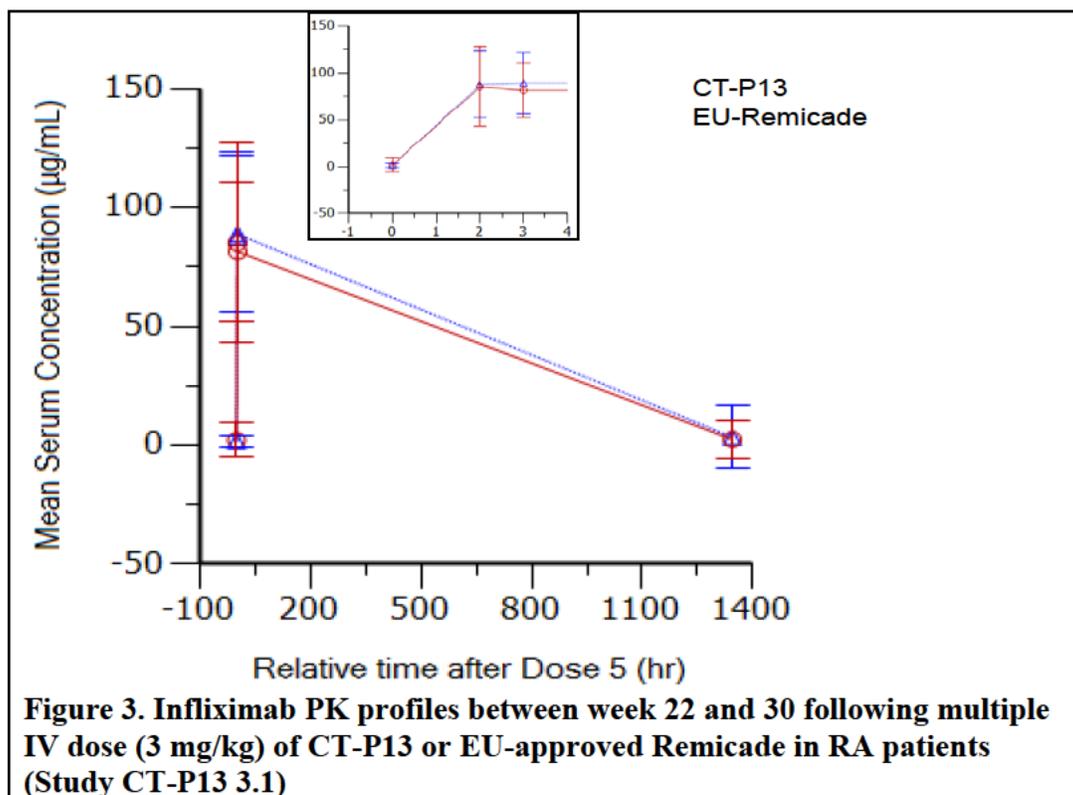


Figure 2. Infliximab PK profiles at steady state between week 22 and 30 following multiple IV dose (5 mg/kg) of CT-P13 or EU-approved Remicade in AS patients (Study CT-P13 1.1)

Table 5. Statistical analysis of PK parameters (Study CT-P13 1.1)						
Average Bioequivalence Approach						
Study CT-P13 1.1 (PK similarity study in AS patients)						
CT-P13 (T) vs EU-approved Remicade (R)						
Parameter	LSM (T)	N	LSM (R)	N	GMR (%)	90% CI (%)
C _{max}	149.90	119	144.79	116	103.5	(97.5, 109.9)
AUC _t	32155.86	119	30739.38	116	104.6	(94.8, 115.4)

The units of C_{max} and AUC are µg/mL and µg*h/mL, respectively.

In addition, the PK of CT-P13 was also compared to EU-approved Remicade in the comparative efficacy Study CT-P13 3.1. This prospective Phase 3 study was designed to assess the overall efficacy and safety of multiple doses of either CT-P13 or EU-approved Remicade when administered with MTX 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 receiving adequate response to MTX over at least 3 months. Six hundred and six male or female RA patients were enrolled in this study and were randomly assigned in a 1:1 ratio to receive either CT-P13 or EU-approved Remicade as a single dose of study treatment on the first day of each dosing period during the Dose-Loading Phase and the Maintenance Phase. The primary endpoint of the study is efficacy and PK is one of the secondary endpoints. The trough and peak concentrations of CT-P13 are comparable to those of EU-approved Remicade in RA patients (Figure 3, Table 6).



Parameter		CT-P13 3 mg/kg (N=290)		EU-approved Remicade [®] 3 mg/kg (N=288)
Dose 5 (Week 22)				
C _{max} (µg/mL)	n=256	98.27 (39.6)	n=254	92.69 (44.7)
C _{min} (µg/mL)	n=239	3.27 (413.1)	n=243	2.48 (335.5)
T _{max} (hr)	n=256	3.00 (2.00, 3.25)	n=254	2.21 (0.00, 4.50)
C _{av, ss} (µg/mL)	n=239	51.08 (41.0)	n=243	47.78 (44.9)
PTF	n=239	1.90 (13.2)	n=243	1.90 (10.9)

Source: CSR CT-P13 3.1 Post-text Table 14.2.7.3

2.2.3.3 How does the PK of CT-P13 in healthy adults compare to that in patients with the target disease?

The PK of CT-P13 is generally comparable across various populations including healthy subjects and patients with RA and AS. Similarly, the PK of EU-approved Remicade and/or US-licensed Remicade are also comparable across various populations including healthy subjects and patients with RA, AS, UC, Ps, CD, and JRA.

In this submission, the PK of CT-P13 was assessed in healthy subjects and patients with RA and AS and compared with EU-approved Remicade and/or US-licensed Remicade. The total exposure of CT-P13 is comparable in healthy subjects (AUC_{0-inf}: 33038 µg*h/mL) and AS patients (AUC_τ: 30739 µg*h/mL) after 5 mg/kg i.v. infusion (Tables 4 and 5). The dose-normalized peak concentrations of CT-P13 in AS patients at steady state (30.0 µg/mL mg/kg) are comparable to those in RA patients (32.7 µg/mL mg/kg) (Tables 5 and 6).

Similar findings also apply to Remicade. The total exposure of infliximab (EU-approved Remicade) is comparable in healthy subjects (AUC_{0-inf}: 32296 µg*h/mL) and AS patients (AUC_τ: 32155 µg*h/mL) after 5 mg/kg i.v. infusion (Tables 4 and 5). The dose-normalized peak concentrations of infliximab (EU-approved Remicade) in AS patients at steady state (29.0 µg/mL mg/kg) are comparable to those in RA patients (30.9 µg/mL mg/kg) (Tables 5 and 6). Per Remicade labeling, the half-life of infliximab (US-licensed Remicade) is comparable, in the range of 7.7 to 9.5 days, in RA patients after single doses of 3 mg/kg to 10 mg/kg, in patients with Crohn's disease after 5 mg/kg, and in patients with plaque psoriasis after 3 mg/kg to 5 mg/kg. Also, infliximab (US-licensed Remicade) pharmacokinetic characteristics (including peak and trough concentrations and terminal half-life) were similar in pediatric (aged 6 to 17 years) and adult patients with Crohn's disease or ulcerative colitis following the administration of 5 mg/kg infliximab. Further, steady state AUC in children with juvenile rheumatoid arthritis (JRA) was similar to that observed in adults receiving 3 mg/kg.

2.2.3.4 What is the variability of the PK parameters in volunteers and patients with the target disease?

The variability of C_{max} and AUC evaluated as coefficient of variation (%CV) was less than 30% after single dose administration of 5 mg/kg for all the three products. After multiple dose

administration, variability is increased up to 45% for C_{max} and 46% for AUC in patients with AS and RA.

Table 7. Variability of infliximab exposure				
Product	%CV			Dose
	C _{max} N=71	AUC _{0-inf} N=70	AUC _{0-last} N=70	
CT-P13 1.4				
US-licensed Remicade	16.3	23.3	18.6	5 mg/kg SD
EU-approved Remicade	16.3	23.7	19.6	5 mg/kg SD
CT-P13	19.6	25.4	23.3	5 mg/kg SD
CT-P13 1.1				
	C _{max} N=113	AUC _τ N=110		
EU-approved Remicade	26.9	45.7		5 mg/kg MD
CT-P13	27.4	34.2		5 mg/kg MD
CT-P13 3.1				
	C _{max}	C _{min}		
EU-approved Remicade	45 (n=256)	296 (n=242)		3 mg/kg MD
CT-P13	40 (n=238)	392 (n=254)		3 mg/kg MD

2.3 Intrinsic Factors

2.3.1 Immunogenicity

2.3.1.1 How was the immunogenicity assessed and what was the incidence of the formation of the anti-drug antibody (ADA)?

Immunogenicity was assessed using a validated ELISA method (Study CT-P13 1.4) and ECLA (Studies CT-P13 1.1 and 3.1). Using ELISA assay, the positive ADA rate for CT-P13, EU-approved Remicade and US-licensed Remicade in healthy subjects is 26.8%, 25.4%, and 11.4%, respectively. Using ECLA assay, the positive ADA rate for CT-P13, EU-approved Remicade and US-licensed Remicade in healthy subjects is 14.3%, 7%, and 2.9%, respectively. The positive ADA rate was up to 34.4% and 28.7% at week 62 for CT-P13, EU-approved Remicade, respectively, for AS patients was up to 52.3% and 50.3% at week 62 for CT-P13, EU-approved Remicade, respectively, for RA patients.

In study CT-P13 1.4, serum samples were collected at baseline and the end-of-study visit (Day 57) for assessment of the ADA and neutralizing antibodies (nAb) of CT-P13, EU-approved Remicade and US-licensed Remicade. Immunogenicity samples were initially analyzed using electrochemiluminescent assay (ECLA), but were switched to enzyme-linked immunosorbent assay (ELISA) later.

Comparing to ELISA, the ECLA assay exhibited a narrower range of drug tolerance and had a

lower threshold for free drug, indicating a higher degree of drug interference in the ECLA (Table 8). In addition, the range of drug tolerance of the ECLA overlapped with the range of actual mean PK concentrations detected in the study CT-P13 1.4 at Day 57, which varied between 0-19 µg/mL.

Table 8. Comparison of drug tolerance levels and total number of antibody positive subjects between ECLA and ELISA Assay, and mean PK concentration at Day 57 in Study CT-P13 1.4

	ECLA	ELISA
Drug Tolerance Levels (LPC to HPC)	2-5 µg/mL	5-50 µg/mL
Total Number of Antibody Positive Subjects (%)	17 (8.1 %)	43 (20.4 %)
Mean PK concentration at Day 57 (Min-Max) (µg/mL)	CT-P13: 4.243 (LLOQ*-19.021), EU-approved Remicade [®] : 4.092 (LLOQ*-12.458), US-licensed Remicade [®] : 4.484(LLOQ*-12.859)	

*<0.200µg/mL is Lower Limit of Quantification (LLOQ)
LPC: Low Positive Control. HPC: High Positive Control
(Source: Response to Information Request (04/15/2015), Table 1)

The ADA formation rate for CT-P13, EU-approved Remicade and US-licensed Remicade was 27%, 25%, and 11%, respectively, using ELISA assay (Table 9). Using ECLA assay, the ADA formation rate for CT-P13, EU-approved Remicade and US-licensed Remicade was 14%, 7%, and 2.9%, respectively. In this review, we use the more sensitive assay ELISA to summarize the immunogenicity results and the impact of immunogenicity on PK, safety and efficacy in Study CT-P13 1.4.

Table 9. Comparison of immunogenicity results of Study CT-P13 1.4 in healthy subjects using ECLA and ELISA.

	CT-P13 (n=71)*		EU-approved Remicade (n=71)		US-licensed Remicade (n=70)**		Total (n=212)	
	ADA Positive	ADA Negative	ADA Positive	ADA Negative	ADA Positive	ADA Negative	ADA Positive	ADA Negative
ECLA	10 (14.3%)	60 (85.7%)	5 (7%)	66 (93%)	2 (2.9%)	68 (97.1%)	17 (8.1%)	194 (91.9%)
ELISA	19 (26.8%)	52 (73.2%)	18 (25.4%)	53 (74.6%)	8 (11.4%)	62 (88.6%)	45 (21.2%)	167 (78.8%)

* According to the IR response from Celltrion, 70 subjects were included in CT-P13 group.

The sponsor mentioned that the pre-dose signal of subject 1004 (CT-P13 group) and 1049 (CT-P13 group) are higher than that of Day 57, so these 2 subjects may be false positive. However, these 2 subjects were included as ADA positive subjects in this review.

**For subject 1146 (US-licensed Remicade group), PK data was only available at predose, 3hr, and 6 hr, so T1/2 could not be calculated. In addition, the immunogenicity sample of subject 1146 was only available at predose (ADA negative). So, this subject was excluded in both PK and immunogenicity population in this review.

Immunogenicity of CT-P13 was also assessed in patients with AS (Study CT-P13 1.1) and with RA (Study CT-P13 3.1) and compared with that of EU-approved Remicade. In Study CT-P13

1.1, immunogenicity samples were taken at predose and Weeks 14, 30, 54, and 62. In Study CT-P13 3.1, immunogenicity samples were taken at predose and Weeks 14, 30, 54, and 62. The ADA formation rate increased from 23% at week 14 to 50% at week 62 for EU-approved Remicade, and from 23% at week 14 to 52% at week 62 for CT-P13 in patients with RA (Table 10, Study CT-P13 3.1). In Study CT-P13 1.1, the ADA formation rate increased from 11% at week 14 to 29% at week 62 for EU-approved Remicade, and from 9% at week 14 to 34% at week 62 for CT-P13 in patients with AS. Further examination of signal intensity and titer values from all ADA-positive subjects showed that these were comparable between all three treatment groups

Table 10. Comparison of immunogenicity results across three studies

Assay	The number (%) of ADA positive subjects at different visit	Study 1.4 in Healthy Subjects (5 mg/kg single dose)			Study 1.1 in AS (5 mg/kg at week 0, 2, 6, and then q8w to week 54)		Study 3.1 in RA (3 mg/kg at week 0, 2, 6, and then q8w to week 54)	
		CT-P13 (N=71)	EU (N=71)	US (N=70)	CT-P13 (N=125)	EU (N=125)	CT-P13 (N=302)	EU (N=304)
ECLA	Screening	--	--	--	2 (2%)	1 (<1%)	9 (3%)	6 (2%)
	Week 8	10 (14.3%)	5 (7%)	2 (2.9%)	--	--	--	--
	Week 14	--	--	--	11 (9%)	13 (11%)	69 (23%)	70 (23%)
	Week 30	--	--	--	32 (25%)	25 (20%)	122 (40%)	122 (40%)
	Week 54	--	--	--	25 (20%)	28 (23%)	124 (41%)	108 (36%)
	Week 62	--	--	--	44 (34.4%)	35 (28.7%)	158 (52.3%)	151 (50.3%)
ELISA	Week8	19 (26.8%)	18 (25.4%)	8 (11.4%)	-	-	-	-

2.3.1.2 Does the immunogenicity affect the PK similarity of the therapeutic protein?

The ADA formation did not affect the PK similarity between CT-P13, US-licensed Remicade, and EU-approved Remicade.

Per the product labeling for Remicade, patients who were antibody-positive were more likely to have higher rates of clearance of infliximab. In this submission, the systemic exposures of CT-P13 or Remicade in subjects who were antibody-positive were about 20-30% lower as compared to those in patients who were antibody-negative (Table 11). However, the establishment of PK similarity between CT-P13, EU-approved Remicade and US-licensed Remicade in Study CT-P13 1.4 indicated that the ADA formation did not significantly affect the PK similarity (see Section 2.2.3.2).

Table 11. Mean (%CV) serum PK parameters of infliximab (Study CT-P13 1.4)						
Parameter	CT-P13	N	US-licensed Remicade	N	EU-approved Remicade	N
ADA- Population						
C_{max}	127.88 (16.9)	52	121.76 (16.1)	62	119.75 (14.8)	53
AUC_{0-t}	33270.58 (21.8)	52	31699.49 (21.43)	62	31938.49 (16.4)	53
AUC_{0-inf}	37041.32 (26.6)	52	35108.09(21.7%)	62	35231.44 (20.9)	53
ADA+ Population						
C_{max}	131.03 (25.4)	19	107.93 (14.1)	8	125.81(19.7)	18
AUC_{0-t}	26420.63 (26.0)	19	26926.6 (22.6)	8	27130.84 (25.4)	18
AUC_{0-inf}	26921.74 (26.2)	19	28016.5 (26.2)	8	27472.8 (26.2)	18

The units of C_{max} and AUC are µg/mL and µg*hr/mL, respectively.

Additional analyses according to subject antibody (ADA) status were also conducted. The magnitude of the impact of ADAs on the PK parameters was comparable between three treatments as reflected in the tables below.

Table 12. Analysis of PK parameters of infliximab in Study CT-P13 1.4 (ADA negative population)						
CT-P13 (T) vs US-licensed Remicade (R)						
Parameter	LSM (T)	N	LSM (R)	N	GMR	90% CI
C _{max}	126.14	52	120.25	62	105.2	(100.0, 110.7)
AUC _{0-t}	32443.83	52	29857.48	62	102.2	(95.9, 108.9)
AUC _∞	35939.26	52	34333.05	62	104.7	(97.5, 112.3)
CT-P13 (T) vs EU-approved Remicade (R)						
Parameter	T	N	R	N	GMR	90% CI
C _{max}	126.14	52	118.47	53	106.5	(101.2, 112.0)
AUC _{0-t}	32443.83	52	31516.63	53	102.9	(96.4, 109.9)
AUC _∞	35939.26	52	34512.56	53	104.1	(96.8, 111.9)
EU-approved Remicade (T) vs US-licensed Remicade (R)						
Parameter	T	N	R	N	GMR	90% CI
C _{max}	118.47	53	120.25	62	98.9	(96.8, 105.8)
AUC _{0-t}	31516.63	53	29857.48	62	96.9	(94.2, 104.7)
AUC _∞	34512.56	53	34333.05	62	100.5	(94.2, 107.2)

The units of C_{max} and AUC are µg/mL and µg*h/mL, respectively.

Table 13. Analysis of PK parameters of infliximab in Study CT-P13 1.4 (ADA positive population)						
CT-P13 (T) vs US-licensed Remicade (R)						
Parameter	LSM (T)	N	LSM (R)	N	GMR	90% CI
C _{max}	127.88	19	107.08	8	119.4	(103.8, 137.4)
AUC _{0-t}	25778.23	19	26308.54	8	98.0	(83.6, 114.8)
AUC _∞	26241.01	19	27220.39	8	96.4	(81.6, 113.9)
CT-P13 (T) vs EU-approved Remicade (R)						
Parameter	T	N	R	N	GMR	90% CI
C _{max}	127.88	19	123.66	18	103.4	(92.4, 115.7)
AUC _{0-t}	25778.23	19	26274.80	18	98.1	(85.9, 121.1)

AUC _∞	26241.01	19	26561.97	18	98.8	(86.2, 113.3)
EU-approved Remicade (T) vs US-licensed Remicade (R)						
Parameter	T	N	R	N	GMR	90% CI
C _{max}	123.66	18	107.08	8	115.5	(101.7, 131.1)
AUC _{0-t}	26274.80	18	26308.54	8	99.9	(82.9, 120.3)
AUC _∞	26561.97	18	27220.39	8	97.6	(80.3, 118.5)

The units of C_{max} and AUC are µg/mL and µg*h/mL, respectively.

In patients with RA and AS, additional analyses according to subject antibody (ADA) status showed that systemic exposures of CT-P13 or Remicade in patients who were antibody-positive were also lower as compared to those in patients who were antibody-negative (Study CT-P13 1.1 and Study CT-P13 3.1). However, the magnitude of the impact of ADAs on the PK parameters was comparable between both treatments in patients (Tables 14, 15 and 16).

Table 14. Mean (%CV) serum PK parameters of infliximab after Dose 5 (Week 22) (Study CT-P13 1.1)				
Parameter	CT-P13	N	EU-approved Remicade	N
ADA- Population				
C _{max,ss}	160.0 (26.4)	74	158.44 (26.3)	74
AUC _{t,ss}	39704.98 (26.9)	74	40736.83 (36.5)	74
ADA+ Population				
C _{max,ss}	147.12 (24.4)	44	136.79 (26.2)	40
AUC _{t,ss}	26056.96 (33.7)	44	23986.76 (44.8)	40

The units of C_{max} and AUC are µg/mL and µg*h/mL, respectively.

Table 15. Mean (%CV) serum PK parameters of infliximab after Dose 5 (Week 22) (Study CT-P13 3.1)				
Parameter	CT-P13	N	EU-approved Remicade	N
ADA- Population				
C _{max,ss}	97.38 (42)	107	91.53 (37)	113
C _{min,ss}	1.93 (304)	97	1.95 (236)	108
ADA+ Population				
C _{max,ss}	110.4 (42)	95	96.6 (36)	97
C _{min,ss}	10.6 (231)	95	6.8 (291)	97

The unit of serum concentration is µg/mL.

Table 16. Analysis of PK parameters of infliximab in Study CT-P13 1.1					
ADA- Population					
Parameter	Treatment	N	LSM	GMR	90% CI
C _{max,ss}	CT-P13	74	154.56	100.8	(93.8, 108.4)
	EU-approved Remicade	74	153.21		
AUC _{t,ss}	CT-P13	74	38363.16	99.3	(91.7, 107.5)
	EU-approved Remicade	74	38637.71		

ADA+ Population					
Parameter	Treatment	N	LSM	GMR	90% CI
C _{max,ss}	CT-P13	44	142.99	109.3	(98.2, 121.6)
	EU-approved Remicade	40	130.85		
AUC _{t,ss}	CT-P13	44	24494.18	115.7	(97.6, 137.2)
	EU-approved Remicade	40	21169.67		

The units of C_{max} and AUC are µg/mL and µg*h/mL, respectively.

2.3.1.3 Do the anti-drug antibodies have neutralizing activities?

Almost all subjects who develop ADA also developed neutralizing activities.

In Studies CT-P13 1.3 and 3.1, nearly all subjects who developed ADAs also developed neutralizing antibodies (Table 17). All ADA positive subjects developed neutralizing activities in Study CT-P13 1.4. This result is expected considering the mouse (Fab)-human chimeric nature of infliximab.

Table 17. The incidence of nAb at different visits in Study CT-P13 1.1 and Study CT-P13 3.1

Visit	Study CT-P13 1.1		Study CT-P13 3.1	
	CT-P13 nAb+/ADA+ (Percentage)	EU-Remicade nAb+/ADA+ (Percentage)	CT-P13 nAb+/ADA+ (Percentage)	EU-Remicade nAb+/ADA+ (Percentage)
Screening	1/2 (50%)	1/1 (50%)	3/9 (33.3%)	2/6 (33.3%)
Week 14	10/11 (90.9%)	13/13 (100%)	69/69 (100%)	67/70 (100%)
Week 30	31/32 (96.9%)	24/25 (96.0%)	121/122 (99.2%)	122/122 (100%)
Week 54	25/25 (100%)	28/28 (100%)	123/124 (99.2%)	104/108 (96.3%)
End of Study	43/44 (97.7%)	35/35 (100%)	155/158 (98.1%)	148/158 (98.0%)

Note that the percentages for the neutralizing antibody (nAb) result are based on the number of positive ADA results at that visit.

2.3.1.4 Does the immunogenicity affect the efficacy comparison of the therapeutic protein?

No, the immunogenicity does not appear to affect the efficacy similarity between CT-P13 and EU-approved Remicade.

Per the product labeling for Remicade, patients who were antibody-positive were more likely to have reduced efficacy. In this submission, the ACR20 response rate of CT-P13 or EU-approved Remicade in subjects who were antibody-positive were about 20% lower as compared to those in

patients who were antibody-negative (Table 18). However, the establishment of efficacy similarity between CT-P13 and EU-approved Remicade Study CT-P13 3.1 indicated that the ADA formation did not significantly affect the efficacy similarity.

The efficacy of CT-P13 was also comparable to that of EU-approved Remicade in ADA negative, or positive patients with RA and AS (Study CT-P13 1.1 and 3.1), respectively. Please refer to medical review for details.

Table 18. Summary of proportion of patients achieving clinical response according to the ACR20 and ACR50 criteria (Study CT-P13 3.1)

ADA result	Endpoint	Treatment	ACR Response n/N ¹ (%)		
			Week 14	Week 30	Week 54
All-Randomized population					
ADA Positive	ACR 20	CT-P13	38/69 (55.1)	74/121 (61.2)	77/123 (62.6)
		EU-approved Remicade®	38/70 (54.3)	75/123 (61.0)	65/109 (59.6)
ADA Negative	ACR 20	CT-P13	148/202 (73.3)	106/129 (82.2)	95/112 (84.8)
		EU-approved Remicade®	135/202 (66.8)	100/132 (75.8)	90/111 (81.1)
Per-Protocol population					
ADA Positive	ACR 20	CT-P13	36/57 (63.2)	73/116 (62.9)	75/118 (63.6)
		EU-approved Remicade®	36/60 (60.0)	74/117 (63.2)	63/105 (60.0)
	ACR 50	CT-P13	11/57 (19.3)	34/116 (29.3)	36/118 (30.5)
		EU-approved Remicade®	16/60 (26.7)	39/117 (33.3)	33/105 (31.4)
ADA Negative	ACR 20	CT-P13	139/185 (75.1)	105/127 (82.7)	93/108 (86.1)
		EU-approved Remicade®	124/185 (67.0)	98/129 (76.0)	89/109 (81.7)
	ACR 50	CT-P13	85/185 (45.9)	70/127 (55.1)	62/108 (57.4)
		EU-approved Remicade®	69/185 (37.3)	61/129 (47.3)	59/109 (54.1)

Source: Section 5.3.5.3.2 Tables 5.03A and 5.04A

Note: ADA Visit Subgroups are defined based on result of the Remicade® tagged assay at each visit.

The immunogenicity results were obtained from samples taken at the same time points as efficacy was assessed (i.e. ADA at Week 14, 30 and 54).

N¹: number of subjects with an assessment, n: number of subjects with the event, (%): n/N¹*100.

2.3.1.5 Does the immunogenicity affect the safety comparison of the therapeutic protein?

No, the immunogenicity does not appear to affect the safety comparison between CT-P13 and EU-approved Remicade.

Overall, the incidence of infusion reaction is low and appears similar between ADA+ and AD- patients (Table 19). Anaphylactic reaction incidence is also low and comparable between CT-P13 (1.6%) and EU-approved Remicade (1.6%). Please also refer to medical review for details.

Table 19. Percent infusion reaction incidence of CT-P13 and EU-approved Remicade					
TEAE	ADA Status	Rheumatoid Arthritis		Ankylosing Spondylitis	
		Study 3.1		Study 1.1	
		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)
Infusion Related Reaction	ADA +	23/169 (14)	35/164 (21)	6/44 (14)	11/39 (28)
	ADA -	7/133 (5)	8/135 (6)	5/84 (6)	4/83 (5)
Anaphylaxis	ADA +	4/169 (2)	2/164 (1)	1/44 (2)	3/39 (8)
	ADA -	2/133 (2)	2/135 (2)	0/84	0/83

2.4 General Biopharmaceutics

2.4.1 What is the *in vivo* relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?

The clinical formulation was the same as the proposed to-be-marketed formulation; therefore, no bridging study is needed.

2.5 Analytical Section

2.5.1 What are the analytical methods used to measure CT-P13 or Remicade in serum?

The serum concentrations of CT-P13, EU-approved Remicade and US-licensed Remicade were quantified by a validated Gyrolab Immunofluorescence Assay. Based on the bioanalytical establishment inspection report, the bioanalytical portions of Study CT-P13 1.4 are acceptable (<http://darrrts.fda.gov:9602/darrrts/ViewDocument?documentId=090140af8037a669>).

Human serum concentrations of CT-P13, US-licensed Remicade and EU-approved Remicade were measured with an automated Gyros flow-through immunoassay. This assay utilized the miniature columns containing Streptavidin coated beads on Compact Discs. First, the Biotinylated anti-TNF antibody capture antibody was immobilized on the beads. A second capture solution containing recombinant TNF alpha was added to the Compact Discs and captured by the initial capture already immobilized on the beads. The standards, QC samples, and test samples were then bound to the respective columns. Finally, an Alexa647-labeled detection antibody was added to the columns. To determine the amount of fluorescence (i.e., amount of captured protein) per structure, each Compact Disc was automatically transferred to a laser-induced fluorescence detector, which was incorporated into Gyrolab. Detection at the 1% PMT setting was used to generate sample analysis data. The response (fluorescence) versus concentration was determined from a standard curve by plotting response (fluorescence) versus concentration using a five-parameter logistic curve-fitting program with weighting by response. The assay validation was described as below and the validation results were shown in Table 20.

Intra-run and inter-run precision and accuracy

In each of six analysis runs (performed over two days by three analysts), two replicates (4 wells) of QC samples at five concentrations (200, 550, 12,500, 40,000, and 50,000 ng/mL in 100% human serum) were analyzed. Precision of the method, defined by the percent coefficient of variation (%CV = [(standard deviation / mean) x 100]), was determined from the interpolated (observed) results. Accuracy of the method was defined by the percent relative error (%Accuracy = [100 x (mean observed concentration / nominal concentration)]). The QC samples met the acceptance criteria: the intra-run or inter-run accuracy should not deviate by more than ± 20.0% of the nominal value (± 25.0% at the lower limit of quantitation (LLOQ)) and the intra-run or inter-run precision should not deviate by more than 20.0% (25.0% at LLOQ).

Limits of quantification

The lower limit of quantitation is defined as the lowest analyte concentration that can be quantitated with acceptable accuracy and precision (± 25.0%). The concentration that met this criterion was determined to be 200 ng/mL.

An upper limit of quantitation is defined as the highest analyte concentration that can be quantitated with acceptable accuracy and precision (± 20.0%). The concentration that met this criterion was determined to be 50,000 ng/mL.

Matrix effect/selectivity

To assess possible matrix effects, ten individual lots of blank normal human serum were spiked with CT-P13 or EU-approved or US-licensed Remicade (prepared in 100% serum and diluted to the minimum dilution) at a concentration equivalent to the 550 ng/mL and 40,000 ng/mL QC samples (in 100% serum). Matrix effects samples were analyzed in replicates of three (6 wells) against an Infliximab (US) calibration curve. All ten individual lots met the acceptance criteria: the observed concentrations of at least two-thirds of the QC samples must be within ± 20.0% of their nominal values and precision ≤ 20.0%. The blank lots met the acceptance criteria: the observed concentrations of the blank matrix must be < LLOQ in at least 80% of the lots tested. The possible effects of hemolysis and lipemia were also assessed. There were no observed

effects of hemolysis and lipemia since at least two-thirds of the QC samples were within $\pm 20.0\%$ of their nominal values and precision $\leq 20.0\%$.

Dilution Integrity

A QC sample was prepared containing CT-P13, EU-approved Remicade or US-licensed Remicade at a concentration of 500,000 ng/mL in 100% human serum. The 500,000 ng/mL sample was first diluted 100-fold with buffer (minimum dilution) followed by subsequent dilutions with 1% human serum to yield the following overall dilutions: 1:100, 1:500, 1:2,000, 1:20,000, 1:100,000, and 1:10,000,000 (overall dilutions include the minimum dilution). The final concentrations were 500,000, 100,000, 25,000, 2500, 500, and 5.00 ng/mL, respectively, as expressed in 100% human serum. Dilution integrity was analyzed against an Infliximab (US) calibration curve. The reported dilution integrity is 1:100,000 (overall dilution) since the QC samples met the acceptance criteria: the observed concentrations of at least two-thirds of the within-range QC samples should not deviate by more than $\pm 20.0\%$ of the nominal value with precision $\leq 20.0\%$.

Specificity

Selectivity and matrix effect experiments provide appropriate evaluation of specificity of the method relative to endogenous antibodies.

Stability

Solution stability: not assessed.

Whole blood stability: not assessed.

Benchtop stability: QC samples at two concentrations (550 ng/mL and 40,000 ng/mL in 100% human serum) were stored at ambient temperature for 28 hours prior to processing. After storage, the samples were diluted, processed, and analyzed in replicates of three (6 wells) against an Infliximab (US) calibration curve. Results indicate that CT-P13, EU-approved Remicade, and US-licensed Remicade are stable in human serum for at least 28 hours at ambient temperature since at least two-thirds of the QC samples did not deviate by more than $\pm 20.0\%$ from their nominal concentration and the precision was $\leq 20.0\%$

Freeze-thaw stability: QC samples at two concentrations (550 ng/mL and 40,000 ng/mL in 100% human serum) were subjected to five freeze (-70°C) and thaw (ambient temperature) cycles. At the end of the fifth freeze/thaw cycle, the samples were diluted, processed, and analyzed in replicates of three (6 wells) against an Infliximab (US) calibration curve. The results indicate that CT-P13, EU-approved Remicade, and US-licensed Remicade are stable in human serum for at least five freeze/thaw cycles before analysis since at least two-thirds of the QC samples did not deviate by more than $\pm 20.0\%$ from their nominal concentration and the precision was $\leq 20.0\%$.

Long term storage stability: QC samples at two concentrations (550 ng/mL and 40,000 ng/mL in 100% human serum) were stored at -20°C and -70°C for 26 days. After storage, the samples were diluted, processed, and analyzed in replicates of three (6 wells) against an Infliximab (US) calibration curve. Results indicated CT-P13, EU-approved Remicade, and US-licensed Remicade are stable in human serum for at least 26 days at -20°C and -70°C since at least two-thirds of the

QC samples did not deviate by more than $\pm 20.0\%$ from their nominal concentration and the precision was $\leq 20.0\%$. Long term freezer storage stability is ongoing and will be established at a later date. Note that the EU-approved Remicade QC samples stored at -70°C for 26 days did not meet the acceptance criteria and were repeated at 27 days. More long term stability data should be updated when it is available (Reviewer's comments).

Processed sample stability: QC samples at two concentrations (550 ng/mL and 40,000 ng/mL in 100% human serum) were diluted and placed onto the loading plate. The loading plate was then sealed and stored at $2-8^{\circ}\text{C}$ for 73 hours. After storage, freshly prepared plate acceptance calibration standards and QC samples (Infliximab (US)) were added and the plate was analyzed in replicates of three (6 wells). The results indicate that CT-P13, EU-approved Remicade, and US-licensed Remicade are stable in diluted human serum for at least 73 hours at $2-8^{\circ}\text{C}$ since at least two-thirds of the QC samples did not deviate by more than $\pm 20.0\%$ from their nominal concentration and the precision was ≤ 20.0 .

Table 20. Infliximab PK assay validation				
Information Requested	CT-P13	US-licensed Remicade	EU-approved Remicade	Acceptance Criteria
Bioanalytical method validation report title	Validation Report for the Determination of CT-P13, Infliximab (EU), or Infliximab (US) in Human Serum by a Quantitative Gyrolab Immunoassay			
Assay method title	The Determination of CT-P13 or Infliximab (US) or Infliximab (EU) in Human Serum by Gyrolab Immunofluorescence Assay			
Method description	Immunofluorescence assay using the Gyros system			
Analyte	CT-P13	US-licensed Remicade	EU-approved Remicade	
Limit of quantitation	200 ng/mL	200 ng/mL	200 ng/mL	
LLOQ Intrarun precision (%)	3.71 (n=6)	4.60 (n=6)	4.73 (n=6)	25%
LLOQ Intrarun accuracy (%)	110.1 (n=6)	88.8 (n=6)	91.25 (n=6)	75-125%
LLOQ Interrun precision (%)	4.46 (n=11)	9.46 (n=12)	5.64 (n=12)	25%
LLOQ Interrun accuracy (%)	110 (n=11)	89.0 (n=12)	91.5 (n=12)	75-125%
Standard curve concentrations (ng/mL)	200, 500, 1000, 5000, 10000, 25000, 50000			
QC concentrations (ng/mL)	550 (LQC), 12500(MQC), 40000(HQC)			
QC Intrarun precision (%)	LQC= 2.85 MQC= 2.81 HQC= 10.5	LQC= 2.52 MQC= 5.21 HQC=8.60	LQC= 3.32 MQC= 1.86 HQC=2.30	20%
QC Intrarun accuracy (%)	LQC= 96.2 MQC= 99.9 HQC=100.3	LQC= 103.1 MQC= 100.7 HQC=102.1	LQC= 105.1 MQC= 100.4 HQC=91.5	80-120%
QC Interrun precision (%)	LQC= 5.40 MQC= 2.88 HQC=9.37	LQC= 5.26 MQC= 6.49 HQC=9.43	LQC= 5.23 MQC=3.32 HQC=6.01	20%
QC Interrun accuracy (%)	LQC= 96.3 MQC=99.9 HQC=100.3	LQC= 103.1 MQC= 100.7 HQC=102.1	LQC= 94.9 MQC= 100.4 HQC=91.5	80-120%
Bench-top stability (28 hrs)	LQC: %precision: 3.87, 0.43, 4.63 %accuracy: 92.7, 96.0, 88.4 HQC: %precision:1.25, 6.21, 2.59	LQC: %precision: 4.22, 1.16, 4.54 %accuracy: 95.4, 99.3, 96.7 HQC: %precision: 3.16, 4.21, 0.24	LQC: %precision: 1.17, 1.78, 8.07 %accuracy: 102.5, 101.3, HQC: %precision: 0.76, 2.68, 5.26	At least 2/3 QC meet: precision<20 %, accuracy within 80-120%

	%accuracy: 104.9, 93.7, 92.3	%accuracy: 103.2, 94.7, 93.2	%accuracy: 96.7, 97.9, 90.3
Stock stability (days)	Not assessed	Not assessed	Not assessed
Processed stability (73 hrs)	LQC: %precision: 0.75, 2.14, 7.53 %accuracy: 94.6, 106, 94.7 HQC: %precision: 1.41, 7.35, 0.24 %accuracy: 88.7, 90.7, 99.3	LQC: %precision: 3.48, 4.89, 4.51 %accuracy: 96.0, 97.3, 98.0 HQC: %precision: 8.32, 0.19, 5.46 %accuracy: 101.5, 87.4, 87.1	LQC: %precision: 1.25, 7.02, 9.29 %accuracy: 95.5, 108.5, 104.5 HQC: %precision: 5.26, 2.73, 3.59 %accuracy: 89.2, 93.5, 98.8
Freeze-thaw stability (5 cycles)	LQC: %precision: 2.19, 2.79, 1.11 %accuracy: 91.6, 91.5, 92.2 HQC: %precision: 1.08, 1.26, 0.46 %accuracy: 87.8, 94.3, 95.7	LQC: %precision: 4.47, 3.76, 2.75 %accuracy: 94.5, 99.3, 96.0 HQC: %precision: 2.26, 2.95, 1.26 %accuracy: 89.2, 96.7, 103.4	LQC: %precision: 2.13, 1.12, 3.10 %accuracy: 104.2, 105.6, 101.4 HQC: %precision: 0.68, 2.47, 4.29 %accuracy: 92.9, 94.7, 99.5
Long-term storage stability (26 Days, -20°C and -70°C)*	LQC (-20°C): %precision: 9.05, 2.28, 0.94 %accuracy: 107.4, 116.2, 120.5 LQC (-70°C): %precision: 5.09, 0.85, 2.69 %accuracy: 95.5, 94.5, 97.3 HQC (-20°C): %precision: 6.44, 5.74, 0.82 %accuracy: 87.3, 97.1, 96.2 HQC (-70°C): %precision: 2.37, 4.09, 0.58 %accuracy: 96.4, 89.0, 103.3	LQC (-20°C): %precision: 3.84, 6.15, 13.3 %accuracy: 101.6, 98.0, 98.0 LQC (-70°C): %precision: 2.24, 2.05, 0.07 %accuracy: 95.8, 95.5, 99.8 HQC (-20°C): %precision: 9.25, 3.86, 0.98 %accuracy: 90.9, 96.7, 103.1 HQC (-70°C): %precision: 4.34, 6.38, 2.06 %accuracy: 103.2, 93.2, 87.9	LQC (-20°C): %precision: 0.89, 5.42, 0.70 %accuracy: 104.4, 107.3, 105.6 LQC (27 days, -70°C): %precision: 1.57, 1.11, 0.99 %accuracy: 91.4, 89.8, 84.4 HQC (-20°C): %precision: 2.44, 2.27, 1.42 %accuracy: 105.3, 121.0, 101.0 HQC (27 days, -70°C): %precision: 1.53, 6.87, 1.72 %accuracy: 86.2, 92.0, 85.6
Dilution integrity (dilution factor,	1:100,000(overall dilution) (500,000 ng/mL diluted to 500 ng/mL)		
	500 ng/ml QC	500 ng/ml QC	500 ng/ml QC

concentration, precision, accuracy)	%Precision: 0.311, 8.81, 0.35 %Accuracy:104.8, 103.6, 103.0	%Precision: 20.2, 0.51, 16.6 %Accuracy: 110.6, 97.8, 98.2	%Precision: 1.40, 0.75, 7.44 %Accuracy:146, 110.6, 105.8	
Matrix effect /Selectivity	10/10 HQC and 10/10 LQC meet acceptance criteria	10/10 HQC and 10/10 LQC meet acceptance criteria	10/10 HQC and 10/10 LQC meet acceptance criteria	

* Note that the EU-approved Remicade QC samples stored at -70°C for 26 days did not meet the acceptance criteria and were repeated at 27 days.

2.5.2 Which metabolites have been selected for analysis and why?

No metabolites were measured in PK samples.

2.5.3 For all moieties measured, is free, bound, or total measured?

Free drug concentrations were measured in PK samples.

2.5.4 What bioanalytical methods are used to assess concentrations of the measured moieties?

Details of the bioanalytical method for determination of serum concentrations of CT-P13, EU-approved Remicade and US- Remicade are discussed in section 2.5.1.

2.5.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?

The standard curve for CT-P13, EU-approved Remicade and US-licensed Remicade serum concentration analysis ranged from 200 to 50000 ng/mL. The infliximab or (fluorescence) versus concentration were determined from a standard curve by plotting response (fluorescence) versus concentration using a five-parameter logistic curve-fitting program with weighting by response.

2.5.6 What is the sample stability under conditions used in the study?

Details of stability conditions are described in section 2.5.1.

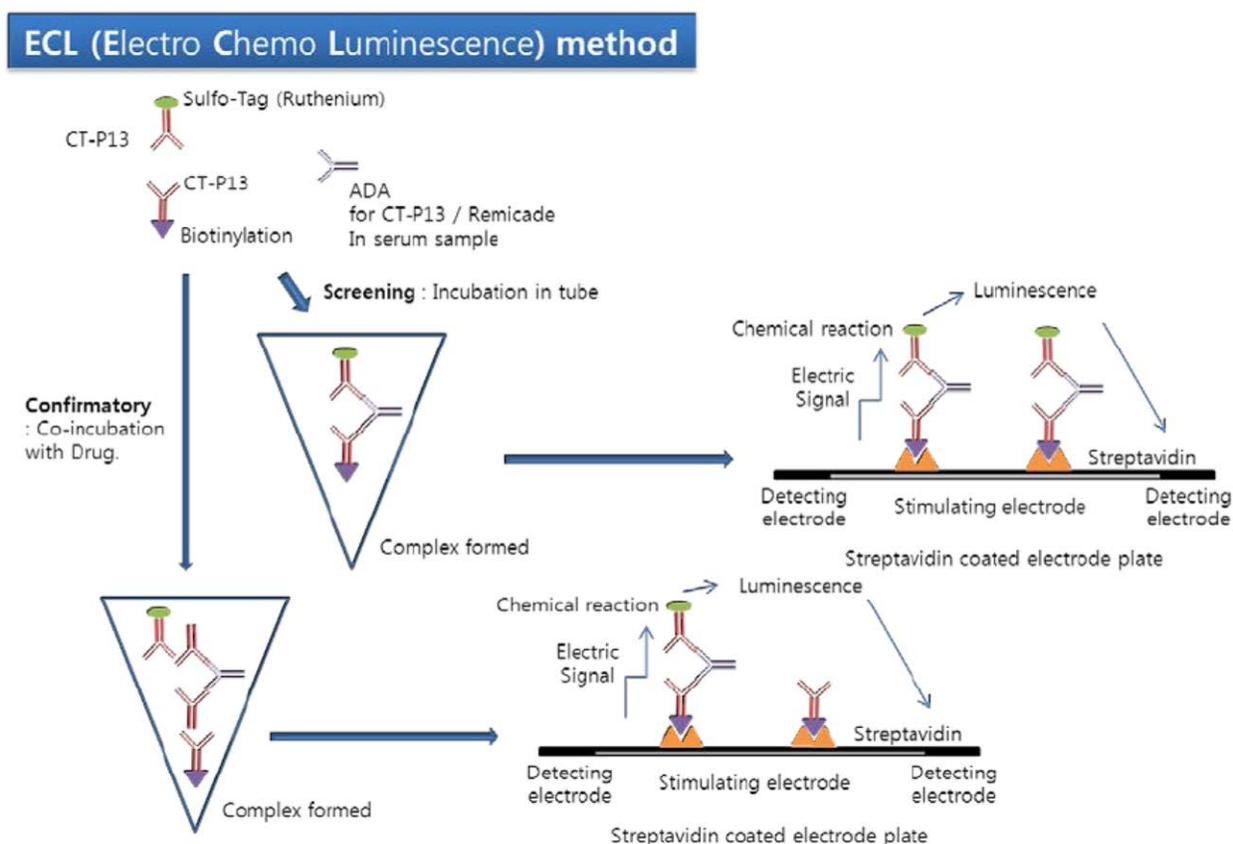
2.5.7 What bioanalytical methods are used to assess the immunogenicity?

ECLA were used for all CT-P13 clinical studies. In Study CT-P13 1.4, immunogenicity samples were initially analyzed using ECLA, but were switched to ELISA. Neutralizing anti-drug antibodies against CT-P13 and Remicade were measured using Gyros assay, a competitive ligand binding assay.

ECLA Assay for ADA Detection

In brief, diluted samples were acidified by the addition of an equal volume of 0.8% Acetic Acid in Diluent Buffer. After approximately 15 min-incubation, samples were neutralized by the addition of a combination of Ruthenylated (Sulfo-tagged) Remicade (US) and Biotinylated Remicade (US) labels and followed by about one hour incubation. During this incubation, anti-

CT-P13, anti-Remicade (EU), and anti-Remicade (US) antibodies will bind to both the Sulfo-tagged and Biotinylated Remicade (US) molecules to form an antibody complex bridge. Samples are then dispensed from the transfer plate onto a streptavidin coated MSD assay plate that has been blocked for at least one hour. Samples are incubated on the streptavidin coated assay plate for approximately one hour. The Biotinylated Remicade (US) in the complex will bind to the streptavidin in the wells, allowing unbound material to be washed away. Only the samples that contain antibody bound to both the Biotinylated Remicade (US) and the Sulfo-tagged Remicade (US) will generate an ECL signal. The plate is then washed and a tripropylamine (TPA)-containing Read Buffer is added to the plate. In the presence of TPA, ruthenium produces a chemiluminescent signal that is triggered when voltage is applied. The signal produced is proportional to the amount of anti-CT-P13, anti-Remicade (EU), or anti-Remicade (US) antibodies present. (Figure 4)



In the upper panel the screening method is illustrated while ADA is bridged between capture biotinylated drug and detection sulfo-tagged drug, which results in a signal, which is directly proportional to the amount of ADA bound. During the confirmatory step, the additional test illustrated in the lower panel is carried out in parallel with repeated screening assay shown in upper panel. Excess unlabeled drug incubation results in signal reduction compared to screening method because unlabeled drug compete with biotinylated and sulfo-tagged drug to the ADA binding.

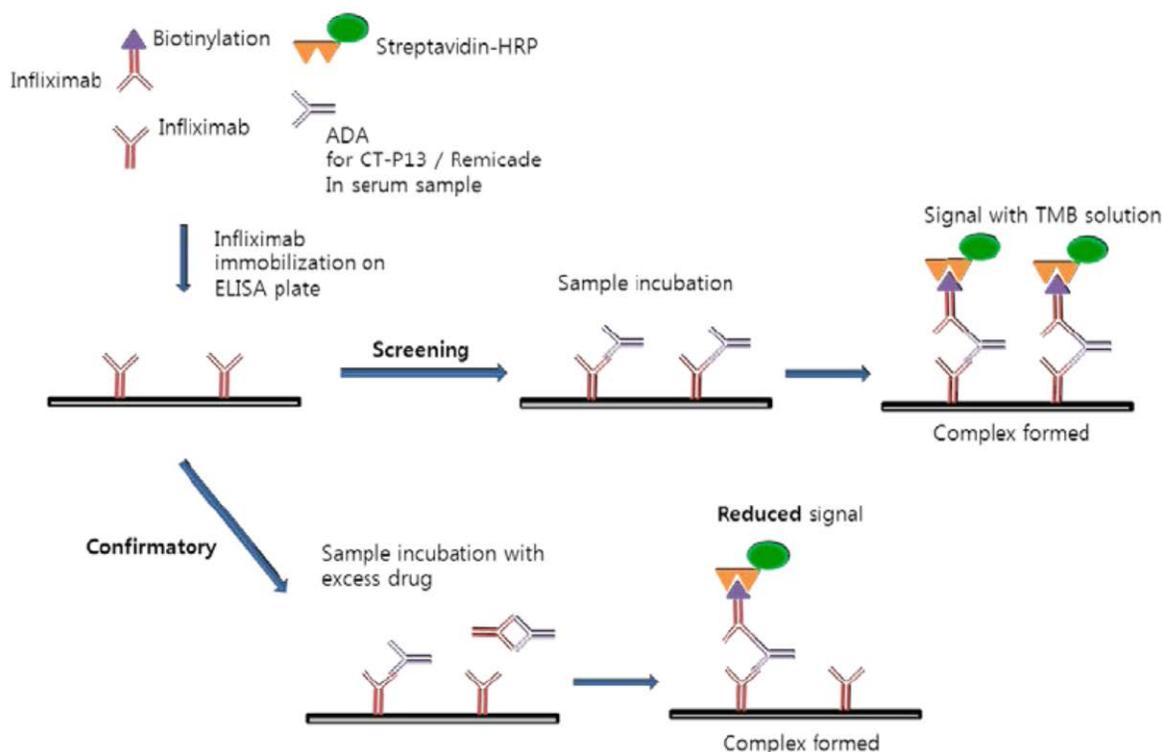
Figure 4. Schematic Diagram of ECL based ADA Screening and Confirmatory Method

(Source: Summary of Biopharmaceutical Studies and Associated Analytical Methods, Figure 2.7.1-1)

ELISA Assay for ADA Detection

In brief, samples were diluted 1:10 in 300 mM acetic acid and allowed to incubate for approximately 1 hour at room temperature. The plate is washed and Remicade (US)-Biotin (prepared in a diluent buffer) and 1M Neutralization Buffer were added to the assay plate. The acidified samples and controls are then added to the assay plate containing the Remicade-Biotin and 1M Neutralization Buffer and allowed to incubate for approximately 2 hours at room temperature. The plates are then washed and a Streptavidin HRP solution is added to the plate and incubated for approximately 1 hour at room temperature. A tetramethylbenzidine (TMB) peroxidase substrate solution is added and incubated for approximately 20 minutes. The reaction is stopped with a Phosphoric Acid Stop Solution. Color develops in proportion to the amount of the anti-Remicade antibodies present. Plates are read on a plate reader using two filters (450 nm for detection and 620 nm for background). (Figure 5)

ELISA method



In the upper panel the screening method is illustrated while ADA is bridged between solid phase capture drug and biotinylated detection drug, which results in a signal, which is directly proportional to the amount of ADA bound. During the confirmatory step, the additional test illustrated in the lower panel is carried out in parallel with repeated screening assay shown in upper panel. Excess unlabeled drug incubation results in signal reduction compared to screening method because unlabeled drug compete with biotinylated drug to the ADA binding.

Figure 5. Schematic Diagram of ELISA based ADA Screening and Confirmatory Method for 1.4 Study

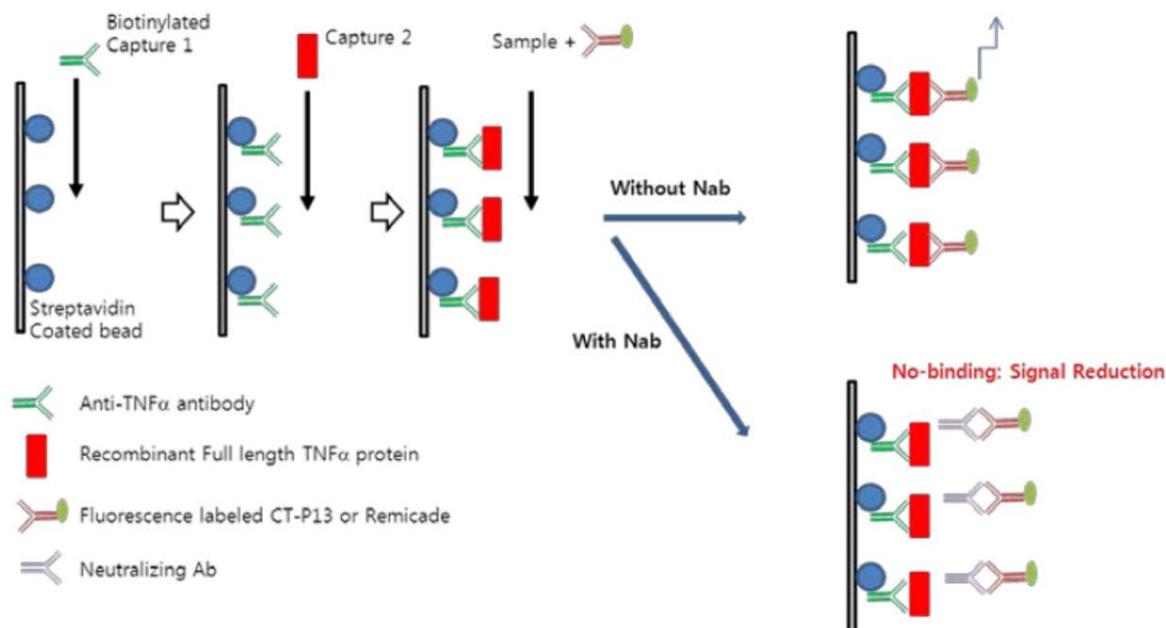
(Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods, Figure 2.7.1-2)

Gyros Assay for Neutralizing Antibody Detection

A Gyros assay (a flow through immunoassay platform) was used to detect the neutralizing activity of anti-drug antibodies against CT-P13/Remicade in human serum. The assay is based on

conventional sandwich immunoassay. In brief, samples were loaded into wells on polypropylene plates and run through an acidification phase and incubated for an hour with Alexa labeled Remicade. Detection of anti-CT-P13/Remicade neutralizing antibodies is based on the binding of the neutralizing antibodies to the TNF α binding site and to the CT-P13/Remicade Alexa labeled drug. (Figure 6)

Gyros method



From left to right: biotinylated anti-TNF α antibodies are fixed to the streptavidin coated solid phase which present the target TNF α , if Nabs are bound to the fluorescence-labeled CT-P13 or Remicade[®], these detection antibodies cannot bind to TNF α , thus resulting in a signal reduction (lower panel), while in the absence of Nabs, the maximum signal is generated (upper panel).

Figure 6. Schematic Diagram of Nab Assay Format with Gyros

(Source: Summary of Biopharmaceutical Studies and Associated Analytical Methods, Figure 2.7.1-3)

Assay Performance Comparison between ECLA and ELISA

In order to reduce the impact of drug interference, the ADA analysis was changed from ECLA to ELISA in Study CT-P13 1.4. Comparing to ELISA, the ECLA assay exhibited a narrower range of drug tolerance and had a lower threshold for free drug, indicating a higher degree of drug interference in the ECLA. The range of drug tolerance of the ECLA overlapped with the range of actual mean PK concentrations detected in the study CT-P13 1.4 at Day 57, which varied between 0-19 $\mu\text{g/mL}$.

The distribution of ADA-positive and negative subjects in accordance with the drug tolerance of low, medium and high positive controls shown in Tables 21 and 22 illustrate that the ELISA assay had reduced drug interference. The difference of the drug tolerance levels at LPC for US-licensed Remicade in ECLA assay results from a slight difference between the plate cut points (Table 23).

Table 21. ADA positive and negative results by free drug level (ECLA assay)

	CT-P13 (N=70)		EU-approved Remicade [®] (N=71)		US-licensed Remicade [®] (N=70)	
	ADA Positive	ADA Negative	ADA Positive	ADA Negative	ADA Positive	ADA Negative
x<LPC	10	10	5	18	2	43
LPC≤x<MPC	-	27	-	25	n/a	n/a
MPC≤x<HPC	n/a	n/a	n/a	n/a	n/a	n/a
HPC≤x	-	23	-	23	-	25

x: PK concentration at Day 57, N/A: Not Applicable, LPC: Drug Tolerance level at Low Positive Control (CT-P13, EU-Remicade[®]: 2 µg/mL, US-Remicade[®]: 5 µg/mL), MPC: Drug Tolerance level at Medium Positive Control (CT-P13, US-Remicade[®], EU-Remicade[®]: 5 µg/mL), HPC: Drug Tolerance level at High Positive Control (CT-P13, US-Remicade[®], EU-Remicade[®]: 5 µg/mL)

(Source: Response to Information Request, 04/15/2015, Table 2)

Table 22. ADA positive and negative results by free drug level (ELISA assay)

	CT-P13 (N=70)		EU-approved Remicade [®] (N=71)		US-licensed Remicade [®] (N=70)	
	ADA Positive	ADA Negative	ADA Positive	ADA Negative	ADA Positive	ADA Negative
x<LPC	19*	47	18	30	8	59
LPC<x<MPC	-	4	-	23	-	3
MPC<x<HPC	-	-	-	-	-	-

* In 2 positive samples (Subject number 1004 and 1049), pre-dose signal are higher than that of Day 57 so the patient were excluded from ADA positive calculation.

x: PK concentration at Day 57, LPC: Drug Tolerance level at Low Positive Control (CT-P13, US-Remicade[®]: 10 µg/mL, EU-Remicade[®]: 5 µg/mL), MPC: Drug Tolerance level at Medium Positive Control (CT-P13, US-Remicade[®], EU-Remicade[®]: 20 µg/mL), HPC: Drug Tolerance level at High Positive Control (CT-P13, US-Remicade[®], EU-Remicade[®]: 50 µg/mL)

(Source: Response to Information Request, 04/15/2015, Table 3)

Table 23. Comparison of cut point and signal of positive control by free drug level (ECLA assay)

Interference drug	Cut point for plate		Signal of Positive Control at Free Drug Level		
			10.0 µg/mL	5.0 µg/mL	2.0 µg/mL
CT-P13	1721	HPC	1640	3080	5973
		MPC	1456	2142	4366
		LPC	1689	1500	2136
EU-approved Remicade®	1462	HPC	1301	2269	5100
		MPC	1172	1831	3525
		LPC	1370	1345	2082
US-licensed Remicade®	1935	HPC	1617	2673	6469
		MPC	1761	2411	4232
		LPC	1694	1939	2634

*Signals at each drug tolerance level are bolded.

(Source: Response to Information Request (04/15/2015), Table 4)

Please refer to OBP review for more detailed information regarding assay validation.

3. Detailed Labeling Recommendations

Compared with the labeling of US-licensed Remicade, (b) (4)

(b) (4) were added in Section 6.1 Clinical Trial Experience and Section 12.3 Pharmacokinetics of the proposed labeling of CT-P13, respectively. Clinical pharmacology recommends removing all the changes to be consistent with the labeling of US-licensed Remicade.

The clinical pharmacology relevant revisions are summarized as below. The ~~strikethrough in red~~ text indicates recommended deletion by the reviewer.

6.1 Clinical Trial Experience

(b) (4)

(b) (4)

12.1 Pharmacokinetics

(b) (4)

In adults, single intravenous infusions of 3 mg/kg to 20 mg/kg of (b) (4) infliximab

(b) (4) showed a linear relationship between the dose administered and the maximum serum concentration. The volume of distribution at steady state was independent of dose and indicated that infliximab was distributed primarily within the vascular compartment. Pharmacokinetic results for single doses of 3 mg/kg to 10 mg/kg in rheumatoid arthritis, 5 mg/kg in Crohn's disease, and 3 mg/kg to 5 mg/kg in plaque psoriasis indicate that the median terminal half-life of infliximab is 7.7 to 9.5 days.

Following an initial dose of (b) (4) infliximab (b) (4), repeated infusions at 2 and 6 weeks resulted in predictable concentration-time profiles following each treatment. No systemic accumulation of infliximab occurred upon continued repeated treatment with 3 mg/kg or 10 mg/kg at 4- or 8-week intervals. Development of antibodies to infliximab increased infliximab clearance. At 8 weeks after a maintenance dose of 3 to 10 mg/kg of (b) (4) infliximab (b) (4), median infliximab serum concentrations ranged from approximately 0.5 to 6 mcg/mL; however, infliximab concentrations were not detectable (<0.1 mcg/mL) in patients who became positive for antibodies to infliximab. No major differences in clearance or volume of distribution were observed in patient subgroups defined by age, weight, or gender. It is not known if there are differences in clearance or volume of distribution in patients with marked impairment of hepatic or renal function.

Infliximab pharmacokinetic characteristics (including peak and trough concentrations and terminal half-life) were similar in pediatric (aged 6 to 17 years) and adult patients with Crohn's disease or ulcerative colitis following the administration of 5 mg/kg of (b) (4) infliximab (b) (4).

Population pharmacokinetic analysis showed that in children with JRA with a body weight of up to 35 kg receiving 6 mg/kg of the reference infliximab product and children with JRA with body weight greater than 35 kg up to adult body weight receiving 3mg/kg (b) (4) infliximab product, the steady state area under the concentration curve (AUC_{τ}) was similar to that observed in adults receiving 3 mg/kg of (b) (4) infliximab (b) (4).

4. Appendix

4.1 Appendix – Individual Study Review

INDIVIDUAL STUDY REVIEW

BLA	125544
Submission Date:	08/08/2014
Proposed Brand Name:	Inflectra
Nonproprietary Name:	TBD
Clinical Pharmacology Reviewer:	Lei He, Ph.D.
Clinical Pharmacology Team Leader (Acting):	Ping Ji, Ph.D.
OCP Division:	Division of Clinical Pharmacology II
OND Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Sponsor:	Celltrion
Submission Type; Code:	351(k); standard review
Formulation; Strength(s)	Lyophilized powder for intravenous infusion; 100 mg/vial
Proposed Indications:	Rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PA), plaque psoriasis (Ps), ulcerative colitis (UC), pediatric UC ¹ , Crohn's disease (CD), pediatric CD ¹
Proposed Dosage Regimens:	RA: 3-10 mg/kg at 0, 2, 6 weeks, and then every 4-8 weeks. AS: 5 mg/kg at 0, 2, 6 weeks, and then every 6 weeks. Ps, PA, CD, UC, Pediatric UC, Pediatric CD: 5 mg/kg at 0, 2, 6 weeks, and then every 8 weeks.

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>.

CT-P13 1.4	39
CT-P13 1.1	46
CT-P13 3.1	50
CT-P13 1.2	53

CT-P13 B1P1310	56
CT-P13 3.3	59
CPT_PCIP_2014_003	63

Study CT-P13 1.4 (3-way PK Bridge/Similarity Study in Healthy Subjects)

Report # CT-P13 1.4

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

Objectives

Primary: To evaluate and compare the pharmacokinetic (PK) profiles of CT-P13, EU-approved Remicade and US-licensed Remicade in healthy subjects (CT-P13 to EU-approved Remicade, CT-P13 to US-licensed Remicade and EU-approved Remicade to US-licensed Remicade).

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

Study Population

Healthy male and female subjects, aged 18-55 years

Table 1. Test Products

IMP Name	Formulation	Strength	Mode of Administration	Batch Number
CT-P13	Lyophilized powder	100 mg	IV	12B1C004
EU-approved Remicade	Lyophilized powder	100 mg	IV	3RMKA82501 and 3RMA65101
US-licensed Remicade	Lyophilized powder	100 mg	IV	DCD26014P1 and DED38015P1

(Source: Study CT-P13 1.4 report, Table 9-2)

Study Design

This was a double-blind, three-arm, parallel group, single-dose clinical study at a single study center. A total of 213 healthy subjects were 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 minutes on Day 1 followed by 8 weeks during which the PK, 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. The scheme of study design is shown in Figure 1.

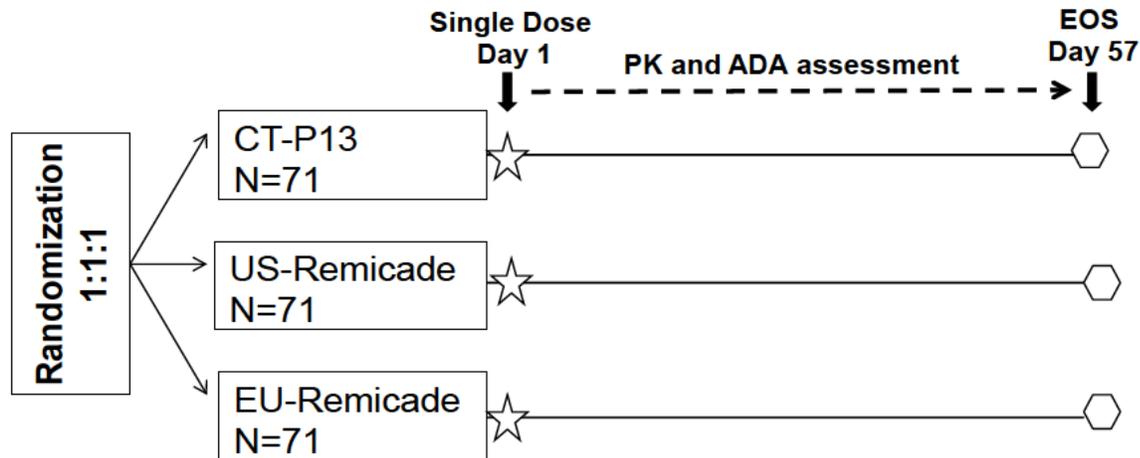


Figure 1. The study design of Study CT-P13 1.4

PK Assessment

PK sample: Blood samples for PK analysis were collected on Day 1 at 0 hour (predose); at the end of infusion (EOI); 1 hour after EOI; then at 6, 12, 24, 48 and 72 hours after start of infusion; and on Days 8, 15, 29, 43 and 57 (after start of infusion).

Primary endpoints: C_{max}, AUC_{0-t}, AUC_{0-inf}

Secondary endpoints: time to C_{max} (T_{max}), volume of distribution during terminal phase (V_z), terminal elimination rate constant (λ_z), terminal half-life (T_{1/2}), total body clearance (CL), area under the concentration-time curve extrapolated from time zero to infinity as a percentage of total AUC (%AUC_{extrap}), mean residence time (MRT)

Immunogenicity Assessment

Immunogenicity sample: Blood samples for immunogenicity assessment were collected on Day 1 (predose) and Day 57.

Safety and Tolerability Assessment

- Vital signs (blood pressure [BP], heart rate [HR], body temperature [BT], and respiratory rate [RR])
- Physical examination
- Signs and symptoms of tuberculosis infection
- Clinical laboratory tests including hematology, chemistry, and urinalysis
- Twelve-lead electrocardiogram (ECG)
- AEs and concomitant medication

Results

Demographics

A total of 213 subjects were enrolled and randomized. The demographics of all randomized subjects are shown in Table 2 and the demographics of three treatment arms are comparable. The

subject's inclusion/exclusion in data analysis was shown in Table 3. According to the PK and immunogenicity results, subjects were also included in PK population, ADA negative, and ADA positive population in data analysis (Table 4).

Table 2. Demographics profile of all randomized subjects in Study CT-P13 1.4

(Study CT-P13 1.4)				
Category		Treatment Groups		
		CT-P13 (N = 71)	EU-approved Remicade (N = 71)	US-licensed Remicade (N = 71)
Age (years)	Mean ±SD Range	40.5 ± 10.11 (22.00 -55.00)	42.6 ± 8.87 (24.00 -55.00)	39.1 ± 10.71 (18.00 -55.00)
Sex	Male	61 (85.92 %)	61 (85.92 %)	61 (85.92 %)
	Female	10 (14.08 %)	10 (14.08 %)	10 (14.08 %)
Ethnicity	Hispanic or Latino	1 (1.41%)	1 (1.41%)	0 (0)
	Other	70 (98.59)	70 (98.59)	71 (100%)
Race	Black	0 (0)	1 (1.41 %)	0 (0)
	Caucasian	71 (100%)	69 (97.18%)	70 (98.59%)
	Other	0 (0)	1 (1.41 %)	1 (1.41%)
Height (cm)	Mean ± SD Range	178.5 ± 8.36 (158 – 193)	177.5 ± 7.77 (159 – 200)	177.6 ± 8.82 (154 – 196)
Weight (kg)	Mean ± SD Range	79.98 ± 9.86 (60.4 – 99.2)	78.89 ± 10.58 (55.6 – 99.3)	77.65 ± 10.92 (55.4 – 99.9)
BMI (kg/m ²)	Mean ± SD Range	25.07 ± 2.40 (18.8 – 29.7)	25.02 ± 2.72 (18.6 – 29.6)	24.59 ± 2.68 (18.8 – 29.7)

(Source: adapted from Table 11-2, Study CT-P13 report)

Table 3. Inclusion or exclusion information in Study CT-P13 1.4 data analysis

Subject ID.	Treatment	Inclusion/exclusion in data analysis (Sponsor)	Inclusion/exclusion in data analysis (Reviewer)
1146	US-licensed Remicade	Excluded in all data analysis. Withdraw due to private reason.	Excluded in all data analysis. Limited PK data.
1154	CT-P13	Excluded in all data analysis due to protocol violation. Subject withdrawn from the study approximately 7 days after dosing as this subject was randomized with an indeterminate IGRA test result (Tuberculosis test).	Included in all data analysis.

1004	CT-P13	Excluded in immunogenicity analysis. The pre-dose signal was higher than that of Day 57, so subject may be false ADA positive.	Included as ADA positive subject.
1049	CT-P13	Excluded in immunogenicity analysis. The pre-dose signal was higher than that of Day 57, so subject may be false ADA positive.	Included as ADA positive subject.

Table 4. Summary of study population

	CT-P13	EU-approved Remicade	US-licensed Remicade	Total
All Randomized Subject	71 (100%)	71 (100%)	71 (100%)	213 (100%)
PK Population	71/71 (100%)	71/71 (100%)	70/71 (98.6%)	212/213 (99.5%)
ADA-positive Population	19/71 (26.8%)	18/71 (25.3%)	8/70 (11.4%)	45/212 (21.2%)
ADA-negative Population	52/71 (73.2%)	53/71 (74.6%)	62/70 (88.6%)	167/212 (78.8%)

Note: The sponsor mentioned that the pre-dose signal of subject 1004 (CT-P13 group) and 1049 (CT-P13 group) are higher than that of Day 57, so these 2 subjects may be false positive.

However, these 2 subjects were included as ADA positive subjects in this review.

For subject 1146 (US-licensed Remicade group), PK data was only available at predose, 3hr, and 6 hr, so T1/2 could not be calculated. In addition, the immunogenicity sample of subject 1146 was only available at predose (ADA negative). So, this subject was excluded in both PK and immunogenicity population in this review.

PK Results

The infliximab serum concentration vs time profiles and PK similarity analysis are shown in Figure 2 and Table 5. Results indicated the infliximab PK profiles following a single IV infusion (5 mg/kg) of CT-P13, EU-approved Remicade, or US-licensed Remicade in healthy subjects are similar. In the pairwise comparisons, the 90% CI of the geometric mean ratio of AUC0-inf, AUC0-last, and Cmax are all within the PK similarity criteria limits of 80-125%.

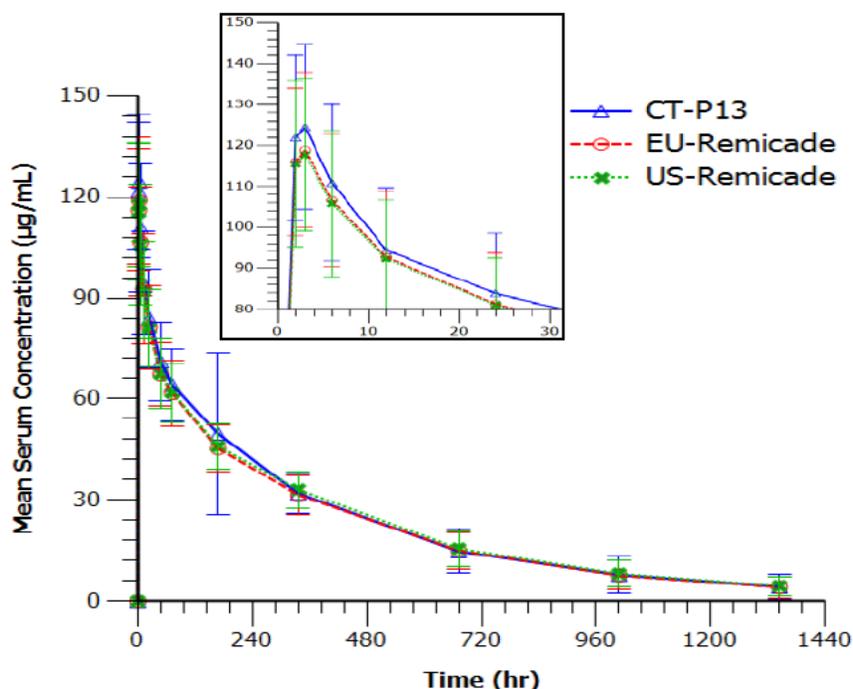


Figure 2. Infiximab PK profiles following a single IV dose (5 mg/kg) of CT-P13, EU-approved Remicade, or US-licensed Remicade in healthy subjects (Study CT-P13 1.4)

Table 5. Statistical analysis of PK parameters (Study CT-P13 1.4) (PK population)

Average Bioequivalence Approach						
Study CT-P13 1.4 (Pivotal, 3-Way PK bridging/similarity study)						
CT-P13 (T) vs US-licensed Remicade (R)						
Parameter	LSM (T)	N	LSM (R)	N	GMR (%)	90% CI (%)
C _{max}	126.60	71	118.68	70	105.7	(100.8, 110.8)
AUC _{0-t}	30507.32	71	29434.79	70	101.4	(95.1, 108.1)
AUC _∞	33038.27	71	33434.17	70	102.3	(95.1, 110.0)
CT-P13 (T) vs EU-approved Remicade (R)						
C _{max}	126.60	71	119.77	71	106.9	(102.0, 112.1)
AUC _{0-t}	30507.32	71	30096.19	71	98.2	(92.3, 104.5)
AUC _∞	33038.27	71	32295.91	71	98.8	(92.1, 106.0)
EU-approved Remicade (T) vs US-licensed Remicade (R)						
C _{max}	119.77	71	118.68	70	100.9	(96.8, 105.8)
AUC _{0-t}	30096.19	71	29434.79	70	96.9	(91.7, 102.4)
AUC _∞	32295.91	71	33434.17	70	96.6	(90.4, 103.3)

The units of C_{max} and AUC are µg/mL and µg*h/mL, respectively.

Immunogenicity Results

As mentioned, ECLA assay has been used for immunogenicity assessment for all CT-P13 clinical studies, including Study CT-P13 1.4. However, the ECLA assay exhibited a narrower range of

drug tolerance and had a lower threshold for free drug compared to ELISA, indicating a higher degree of drug interference in the ECLA. In addition, the range of drug tolerance of the ECLA overlapped with the range of actual mean PK concentrations detected in the study CT-P13 1.4 at Day 57, which varied between 0-19 µg/mL. Therefore, CELLTRION changed the method of ADA analysis from ECLA to ELISA. The immunogenicity results using ECLA and ELISA were shown in Table 6. Almost all antibodies were found to be neutralizing, which is expected considering the mouse (Fab)-human chimeric nature of infliximab.

Table 6. Comparison of immunogenicity results of Study CT-P13 1.4 in healthy subjects using ECLA and ELISA.

	CT-P13 (n=71)*		EU-approved Remicade (n=71)		US-licensed Remicade (n=70)**		Total (n=212)	
	ADA Positive	ADA Negative	ADA Positive	ADA Negative	ADA Positive	ADA Negative	ADA Positive	ADA Negative
ECLA	10 (14.3%)	60 (85.7%)	5 (7%)	66 (93%)	2 (2.9%)	68 (97.1%)	17 (8.1%)	194 (91.9%)
ELISA	19 (26.8%)	52 (73.2%)	18 (25.4%)	53 (74.6%)	8 (11.4%)	62 (88.6%)	45 (21.2%)	167 (78.8%)

The PK similarity was also assessed in both ADA negative and ADA positive population (Table 7 and Table 8). Results indicated the PK remains similar among CT-P13, EU-approved Remicade and US-licensed Remicade in ADA negative population. For ADA positive population, in comparisons between CT-P13 and EU-approved Remicade, and between EU-and US-licensed Remicade, the 90% CIs of C_{max} fell out of the acceptance limits of 80-125%. However, due to the small subject size, the similarity analysis in ADA positive population was inconclusive.

Table 7. Statistical analysis of PK parameters (Study CT-P13 1.4) (ADA negative population)

Average Bioequivalence Approach						
Study CT-P13 1.4 (Pivotal, 3-Way PK bridging/similarity study)						
CT-P13 (T) vs US-licensed Remicade (R)						
Parameter	LSM (T)	N	LSM (R)	N	GMR (%)	90% CI (%)
C _{max}	126.14	52	120.25	62	105.2	(100.0, 110.7)
AUC _{0-t}	32443.83	52	29857.48	62	102.2	(95.9, 108.9)
AUC _∞	35939.26	52	34333.05	62	104.7	(97.5, 112.3)
CT-P13 (T) vs EU-approved Remicade (R)						
C _{max}	126.14	52	118.47	53	106.5	(101.2, 112.0)
AUC _{0-t}	32443.83	52	31516.63	53	102.9	(96.4, 109.9)
AUC _∞	35939.26	52	34512.56	53	104.1	(96.8, 111.9)
EU-approved Remicade (T) vs US-licensed Remicade (R)						
C _{max}	118.47	53	120.25	62	98.9	(96.8, 105.8)

AUC _{0-t}	31516.63	53	29857.48	62	96.9	(94.2, 104.7)
AUC _∞	34512.56	53	34333.05	62	100.5	(94.2, 107.2)

The units of C_{max} and AUC are µg/mL and µg*h/mL, respectively.

Table 8. Statistical analysis of PK parameters (Study CT-P13 1.4) (ADA positive population)

Average Bioequivalence Approach						
Study CT-P13 1.4 (Pivotal, 3-Way PK bridging/similarity study)						
CT-P13 (T) vs US-licensed Remicade (R)						
Parameter	LSM (T)	N	LSM (R)	N	GMR Ratio (%)	90% CI (%)
C _{max}	127.88	19	107.08	8	119.4	(103.8, 137.4)
AUC _{0-t}	25778.23	19	26308.54	8	98.0	(83.6, 114.8)
AUC _∞	26241.01	19	27220.39	8	96.4	(81.6, 113.9)
CT-P13 (T) vs EU-approved Remicade (R)						
C _{max}	127.88	19	123.66	18	103.4	(92.4, 115.7)
AUC _{0-t}	25778.23	19	26274.80	18	98.1	(85.9, 121.1)
AUC _∞	26241.01	19	26561.97	18	98.8	(86.2, 113.3)
EU-approved Remicade (T) vs US-licensed Remicade (R)						
C _{max}	123.66	18	107.08	8	115.5	(101.7, 131.1)
AUC _{0-t}	26274.80	18	26308.54	8	99.9	(82.9, 120.3)
AUC _∞	26561.97	18	27220.39	8	97.6	(80.3, 118.5)

The units of C_{max} and AUC are µg/mL and µg*h/mL, respectively.

Conclusions

- The infliximab PK profiles following a single IV infusion (5 mg/kg) of CT-P13, EU-approved Remicade, or US-licensed Remicade in healthy subjects are similar. In the pairwise comparisons, the 90% CI of the geometric mean ratio of AUC_{0-inf}, AUC_{0-last}, and C_{max} are all within the PK similarity criteria limits of 80-125%.
- The number of subjects who had positive ADA results on Day 57 was 19 (26.8%), 18 (25.4%) and 8 (11.4%) subjects in CTP13, EU-approved Remicade and US-licensed Remicade arms, respectively. Almost all antibodies were found to be neutralizing, which is expected considering the mouse (Fab)-human chimeric nature of infliximab. The presence of antibodies reduced infliximab serum concentrations, however, the magnitude of the impact of ADAs on the PK parameters was comparable between treatments.
- Overall, CT-P13 was well tolerated and the safety profile of CT-P13 was similar to those of both EU-approved Remicade and US-licensed Remicade.

Study CT-P13 1.1 (PK Similarity Study in AS)

Report # CT-P13 1.1

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

Objectives

Primary: to demonstrate comparable pharmacokinetics at steady state in terms of the area under the concentration-time curve over a dosing interval (AUC_{τ}) and observed maximum serum concentration at steady state ($C_{max,ss}$) between CT-P13 and EU-approved Remicade reference product in patients with active ankylosing spondylitis (AS) up to Week 30. The primary objective was assessed between Weeks 22 and 30.

Secondary: assess the long-term efficacy, pharmacokinetics, and overall safety of CT-P13 in comparison with EU-approved Remicade reference product up to Week 54.

Study Population

Male or female patients aged 18 to 75 years old, inclusive, who had been diagnosed with AS

Study Design

This was a randomized, double-blind, multicenter, parallel-group, prospective Phase 1 study designed to assess the PK equivalence and safety of multiple doses of either CT-P13 or EU-approved Remicade reference product (5 mg/kg) administered up to Week 30, by a 2-hour intravenous (IV) infusion per dose in patients with active AS. Patients were randomized (1:1) to receive either CT-P13 or EU-approved Remicade.

The Dose-Loading Phase of the study consisted of 3 doses of study treatment. On the first day of each dosing period (Day 0, Week 0; Day 14, Week 2; and Day 42, Week 6), patients received a single 2-hour IV infusion dose of either CT-P13 or EU-approved Remicade reference product.

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) while patients continued their assigned treatment, with the last dose to be administered no later than Week 54. Each dosing period consisted of a single-dose administration of study treatment followed by an off-dose period of 8 weeks. At Week 30, the study was unblinded for reporting purposes and efficacy, PK, and safety endpoints were evaluated. The study remained blinded to the investigators and patients. At Week 54, the secondary efficacy, PK, and safety endpoints were evaluated.

	Dose-Loading Phase				Maintenance Phase ¹		
	Dose 1 Week 0 (Day 0)	Dose 2 Week 2 (Day 14)	Dose 3 Week 6 (Day 42)	Dose 4 Week 14 (Day 98)	Dose 5 Week 22 (Day 153)	Dose 6 Week 30 (Day 210)	Doses 7, 8, & 9 Weeks 38, 46, & 54 (Days 266, 322, & 378)
CT-P13 ²	X	X	X	X	X	X	X
Remicade ²	X	X	X	X	X	X	X
Primary Pharmacokinetic Evaluation					←————→		
30-Week Pharmacokinetic Evaluation	←————→						
30-Week Efficacy Evaluation	←————→						
30-Week Safety Evaluation	←————→						
Pharmacokinetic Evaluation	←————→						
Efficacy Evaluation	←————→						
Safety Evaluation	←————→						

1. Following Dose 3, further doses could be administered every 8 weeks up to Week 54 continuing with assigned treatment.
2. A dose visit window of ±3 days was allowed up to and including Dose 6; a dose visit window of ±5 days was allowed thereafter, including the End-of-Study Visit.

(Source: Study 1.1 report, page 3)

PK Assessment

PK sampling: serum samples were obtained predose, EOI, and 1 hour after EOI following all doses. Several additional serum blood samples were collected between Weeks 22 and 30 for steady-state PK assessment.

Primary PK endpoints: AUC_τ at steady state and C_{max,ss} between Weeks 22 and 30.

Secondary PK endpoints assessed up to Week 30: average concentration at steady state (C_{av,ss}), minimum concentration at steady state (C_{min,ss}), swing ((C_{max} - C_{min})/C_{min}), degree of fluctuation((C_{max} - C_{min})/C_{av}), MRT, T_{1/2}(calculated from the PK profile between the fifth and the sixth doses), total body clearance at steady state (CL_{ss}), volume of distribution at steady state (V_{ss}).

Secondary PK endpoints assessed up to Week 54: C_{max}, C_{min}, T_{max}

Immunogenicity Assessment

Immunogenicity sampling: samples for immunogenicity assess were collected at various time points from screening visit to the end of study.

Results

250 patients were enrolled in the study (all-randomized population). Of these, 223 patients were included in the PK population, 157 patients were included in the PK (antibody negative subset) population, and 250 patients were included in the safety population.

PK Results

Following multiple IV doses (5 mg/kg), the infliximab PK profiles of CT-P13 and EU-approved Remicade in AS patients are comparable at steady state between Week 22 and 30 (Figure 3). The 90% CI of the geometric mean ratio of $AUC_{\tau,ss}$ and $C_{max,ss}$ are well within the PK similarity criteria limits of 80-125% in both PK and ADA negative population. (Table 9 and Table 10)

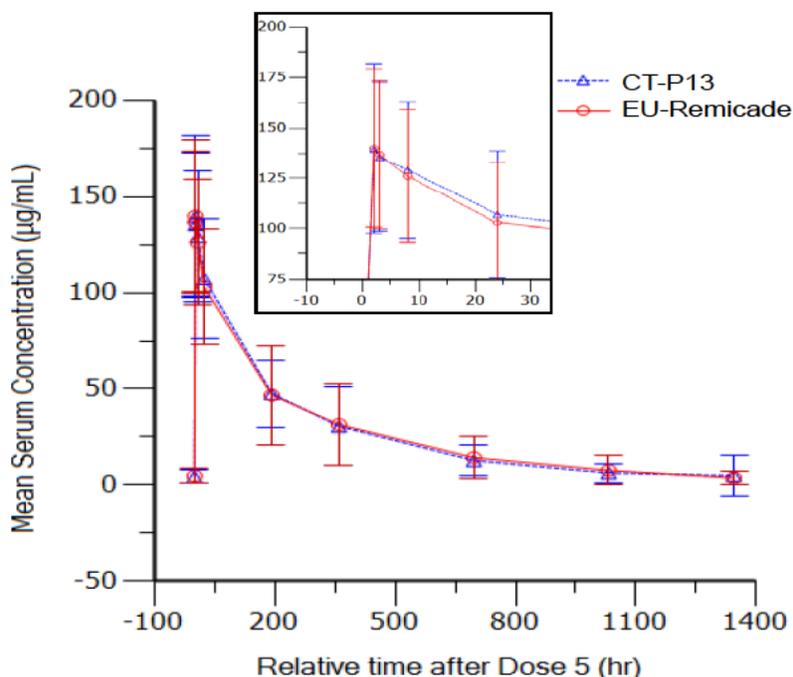


Figure 3. Infliximab PK profiles at steady state between week 22 and 30 following multiple IV dose (5 mg/kg) of CT-P13 or EU-approved Remicade in AS patients (Study CT-P13 1.1)

Table 9. Statistical analysis of PK parameters (Study CT-P13 1.1)

Average Bioequivalence Approach						
Study CT-P13 1.1 (PK similarity study in AS patients)						
CT-P13 (T) vs EU-approved Remicade (R)						
Parameter	LSM (T)	N	LSM (R)	N	GMR (%)	90% CI (%)
C_{max}	149.90	119	144.79	116	103.5	(97.5, 109.9)
AUC_{τ}	32155.86	119	30739.38	116	104.6	(94.8, 115.4)

Table 10. Analysis of Serum Pharmacokinetic Parameters of Infliximab (ADA Negative Population)

Parameter	Treatment	n	Geometric Mean	Ratio (%) of Geometric Means	90% CI of Ratio (%)
AUC _t (µg•h/mL)	CT-P13	80	37750.06	101.46	(92.57 – 111.19)
	Remicade	76	37208.21		
C _{max,ss} (µg/mL)	CT-P13	81	152.74	103.32	(95.39 – 111.91)
	Remicade	76	147.84		

(Source: Study CT-P13 1.1 report, Table 11-6)

Immunogenicity Results

The ADA incidence increased over time in both arms and was comparable between CT-P13 and EU-approved Remicade. The number of subjects who had positive ADA results on Week 30 was 32 (25%) and 25 (20.5%) subjects in CTP13, EU-approved Remicade arms, respectively (Table 11). Almost all antibodies were found to be neutralizing.

Table 11. The ADA Incidence by Treatment in Study CT-P13 1.1

	CT-P13	EU-Remicade
Screening	2 (1.6%)	1 (0.8%)
Week 14	14 (8.6%)	13 (10.7%)
Week 30	32 (25%)	25 (20.5%)
Week 54	25 (19.5%)	28 (23%)
EOS visit	44 (34.4%)	35 (28.7%)

Conclusions:

- At steady state, the PK (AUC_t and C_{max}) of CT-P13 was similar to EU-approved Remicade in both PK and ADA negative population.
- The ADA incidence increased over time in both arms and was comparable between CT-P13 and EU-approved Remicade.
- The efficacy was similar between CT-P13 and EU-approved Remicade.
- Overall, CT-P13 was well tolerated, and the safety profile of CT-P13 was similar to that of EU-approved Remicade.

Study CT-P13 3.1 (Efficacy Study in RA)

Report # CT-P13 3.1

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

Objectives

Primary: to demonstrate that CT-P13 was similar to EU-approved 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 EU-approved Remicade reference product up to Week 54.

Study Design

This was a randomized, double-blind, multicenter, parallel-group, prospective Phase 3 study designed to assess efficacy equivalence, and to evaluate long-term efficacy, pharmacokinetics, pharmacodynamics, and overall safety of multiple doses of CT-P13 compared with EU-approved Remicade reference product.

Both products 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 over at least 3 months. The study was unblinded at Week 30 for reporting; however, the study remained blinded to the investigators and patients until the end of the study.

Patients were randomly assigned in a 1:1 ratio to receive either CT-P13 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.

The Dose-Loading Phase of the study consisted of 3 doses of study treatment. On the first day of each dosing period (Day 0, Week 0; Day 14, Week 2; and Day 42, Week 6), patients received a single 2-hour IV infusion dose of either CT-P13 or EU-approved Remicade coadministered with methotrexate and folic acid.

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).

Figure 4. Mean (\pm SD) Serum Concentration of Infliximab Vs Time by Treatment (Linear Scale): Pharmacokinetic Population

(Source: Study CT-P13 3.1 report, Figure 11-2)

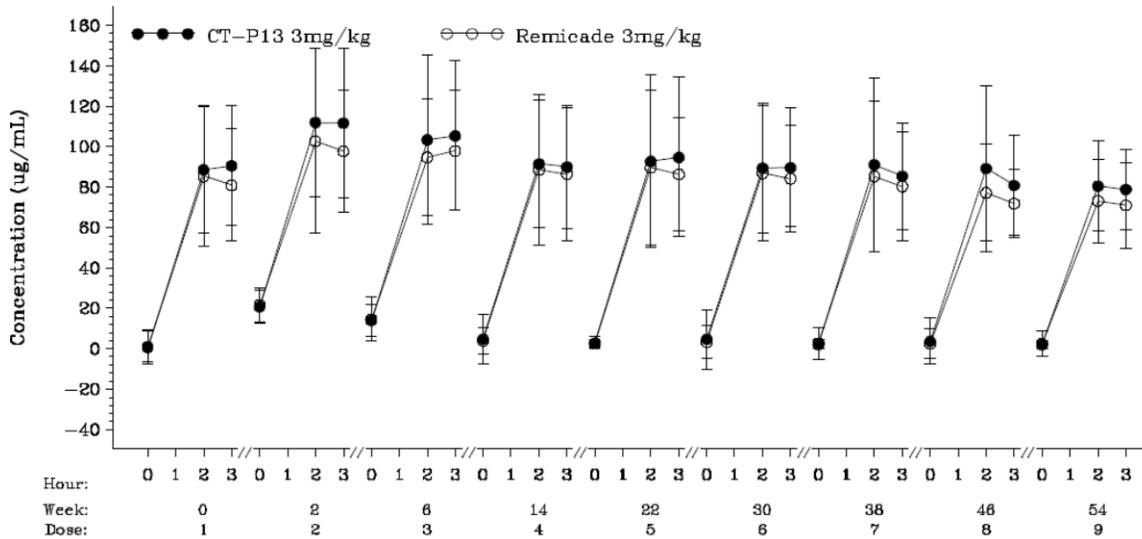


Figure 5. Mean (\pm SD) Serum Concentration of Infliximab Vs Time by Treatment (Linear Scale): Pharmacokinetic (ADA Negative Subset) Population

(Source: Study CT-P13 3.1 report, Figure 11-3)

Immunogenicity Results

The ADA incidence increased over time in both arms and was comparable between CT-P13 and EU-approved Remicade (Table 12). Almost all antibodies were found to be neutralizing.

Table 12. The ADA incidence by treatment in Study CT-P13 3.1

	CT-P13	EU-Remicade
Screening	9 (3.0%)	6 (2.0%)
Week 14	69 (22.8%)	70 (23.3%)
Week 30	122 (40.4%)	122 (40.7%)
Week 54	124 (41.1%)	108 (36.0%)
EOS visit	158 (52.3%)	151 (50.3%)

Conclusions

- The PK was similar between CT-P13 and EU-approved Remicade in RA patients.
- Overall, CT-P13 was well tolerated and the safety profile of CT-P13 was comparable to that of EU-approved Remicade.

Study CT-P13 1.2 (Pilot Study)

Report # CT-P13 1.2

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

Objectives

Primary: to demonstrate comparable observed C_{max} between CT-P13 and EU-approved Remicade reference product in patients with active RA at Weeks 0, 2 and 6.

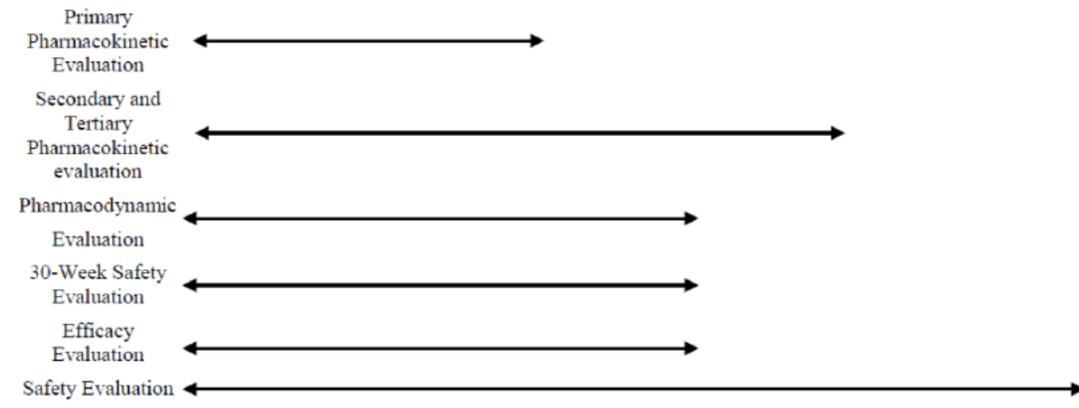
Secondary: to assess the PK and PD profiles, efficacy, and overall safety of CT-P13 in comparison with EU-approved Remicade reference product.

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.

The study consisted of 3 phases, a Dose Loading Phase, Treatment Phase I and Treatment Phase II. During the Dose Loading Phase, patients were randomized to double-blind study drug and received Doses 1, 2 and 3 (Weeks 0, 2, and 6). Patients received a further 6 doses of randomized study drug every 8 weeks (Weeks 14, 22, 30, 38, 46 and 54) during Treatment Phase I. Treatment Phase II was open-label and all patients received a further 6 doses of CT-P13 every 8 weeks (Weeks 62, 70, 78, 86, 94, and 102); additional consent to switching from Remicade to CT-P13 or maintain treatment with CT-P13 was required for this phase.

	Dose Loading Phase			Treatment Phase I ¹		Treatment Phase II ²
	Dose 1 Week 0 (Day 0)	Dose 2 Week 2 (Day 14)	Dose 3 Week 6 (Day 42)	Doses 4,5 & 6 Weeks 14, 22 & 30 (Days 98, 154 & 210)	Doses 7, 8 & 9 Weeks 38, 46 & 54 (Days 266, 322 & 378)	Doses 10 to 15 Weeks 62 to 102 (Days 434 to 714)
CT-P13 ³	X	X	X	X	X	X
Remicade ³	X	X	X	X	X	



PK Assessment

PK sampling: Blood samples were obtained before dosing, at the end of infusion, and 1 hour after infusion.

Primary endpoint: C_{max} (Weeks 0, 2, 6)

Secondary endpoint: C_{trough} (Weeks 0, 2, 6)

Tertiary endpoint: C_{av}, degree of fluctuation, T_{max}, and C-terminal lysine level at Weeks 0, 2, 6; C_{max}, C_{trough,ss}, C_{av,ss}, fluctuation at steady state, T_{max}, C-terminal lysine level at Weeks 14, 22, 30, 38, 46.

PD Assessment

PD sampling: Blood samples were obtained pre-dose.

Secondary endpoints: Concentration of CRP, rheumatoid factor (RF) and anticyclic citrullinated peptide (anti-CCP) at Weeks 0, 14 and 30.

Immunogenicity Assessment

Immunogenicity throughout the study

Results

A total of 19 patients were randomized and received treatment. Nine out of 19 patients were randomized and received CT-P13 and four completed the study. Ten out of 19 patients were randomized and received EU-approved Remicade and six completed the study.

PK Results

C_{max} at Doses 1, 2 and 3 (Weeks 0, 2 and 6) are shown in Table 13. Mean C_{max} in the CT-P13 group ranged from 75.1 to 84.8 µg/mL and mean C_{max} in the EU-approved Remicade group ranged from 64.6 to 78.3 µg/mL.

Table 13. Maximum concentration at weeks 0, 2, and 6 (PK population)

Week	CT-P13			Remicade			Patient 1016		
	0	2	6	0	2	6	0	2	6
Dose Number	1	2	3	1	2	3	1	2	3
Concentration (µg/mL)									
n*	9	9	9	9	9	9	1	1	1
Mean	76.3	84.8	75.1 ¹	68.1	78.3	64.6	68.8	69.2	59.4
Standard Deviation	22.2	10.3	16.9 ¹	18.0	13.9	12.2	-	-	-
Minimum	41.2	70.6	44.8 ¹	41.4	57.6	40.2	-	-	-
Maximum	114.8	101.4	96.4	91.0	100.2	79.8	-	-	-
Median	71.8	83.2	78.6	67.2	79.2	65.8	-	-	-
Geometric Mean	73.3	84.3	73.3 ¹	66.0	77.2	63.4	-	-	-
CV (%)	29.1	12.1	22.5 ¹	26.4	17.7	18.9	-	-	-

Note that Patient 1016 was randomized to Remicade but received both CT-P13 and Remicade.
(Source: Study CT-P13 1.2 report, Table 11)

Ctrough are presented in Table 14. In line with the increasing dosing interval, mean Ctrough values decreased steadily before Doses 2, 3 and 4: from 13.7 to 8.9 µg/mL to 1.2 µg/mL, respectively, in the CT-P13 group; and from 9.5 to 4.8 µg/mL to 1.2 µg/mL, respectively, in the EU-approved Remicade group.

Table 14. Trough concentration at doses 1, 2, and 3 (PK population)

Week	CT-P13			Remicade			Patient 1016		
	0	2	6	0	2	6	0	2	6
Dose Number	1	2	3	1	2	3	1	2	3
Concentration (µg/mL)									
n*	9	9	7	9	6	2			
Mean	13.7	8.9 ¹	1.2	9.5 ²	4.8	1.2	10.0	3.9	0.7
Standard Deviation	3.1	4.9	0.9	3.9 ²	2.1	0.2	-	-	-
Minimum	10.0	1.0	0.5	2.1	1.2	1.0	-	-	-
Maximum	19.1	17.6	3.1	16.3	7.5	1.3	-	-	-
Median	12.4	9.2	1.0	9.7	5.1	1.2	-	-	-
Geometric Mean	13.4	7.0	1.0	8.5 ²	4.2	1.2	-	-	-
CV (%)	22.5	54.8 ¹	72.3 ¹	41.4 ²	44.3 ¹	16.2	-	-	-

Note that Patient 1016 was randomized to Remicade but received both CT-P13 and Remicade. (Source: Study CT-P13 1.2 report, Table 12)

Immunogenicity Results

All of patients were negative at Screening and up to Dose 3. In the CT-P13 group, 2 and 6 patients showed positive results at least one time during Treatment Phase I and II, respectively. In the Remicade group, all of patients showed positive results at least one time during Treatment Phase I and the positive results were maintained in most of doses for the patients during Treatment Phase II. Although some of positive results converted to negative by visit or vice versa, there is no difference in the trend of immunogenicity during Treatment Phase II compared to that during Treatment Phase I, in patients switched from Remicade to CT-P13. (Table 15)

Table 15. Immunogenicity Test Result by Dose Visit: Safety Population

Week	Dose Loading Phase			Treatment Phase I						Treatment Phase II					
	0	2	6	14	22	30	38	46	54	62	70	78	86	94	102
Dose number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
CT-P13 Test Result															
N	9	9	9	8	7	7	7	7	7	7	7	7	6	6	3
Positive, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	2 (28.6)	2 (28.6)	2 (28.6)	1 (14.3)	1 (14.3)	1 (14.3)	3 (42.9)	4 (57.1)	3 (50.0)	3 (50.0)	2 (66.7)
Negative, n (%)	9 (100.0)	9 (100.0)	9 (100.0)	7 (87.5)	5 (71.4)	5 (71.4)	5 (71.4)	6 (85.7)	6 (85.7)	6 (85.7)	4 (57.1)	3 (42.9)	3 (50.0)	3 (50.0)	1 (33.3)
Remicade* Test Result															
N	9	9	9	9	9	8	8	8	8	8	8	8	5	4	-
Positive, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	6 (66.7)	7 (77.8)	6 (75.0)	7 (87.5)	6 (75.0)	6 (75.0)	7 (87.5)	7 (87.5)	5 (62.5)	2 (40.0)	2 (50.0)	-
Negative, n (%)	9 (100.0)	9 (100.0)	9 (100.0)	3 (33.3)	2 (22.2)	2 (25.0)	1 (12.5)	2 (25.0)	2 (25.0)	1 (12.5)	1 (12.5)	3 (37.5)	3 (60.0)	2 (50.0)	-
Patient 1016 Test Result															
N	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Positive, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	0 (0.0)	1 (100.0)	0 (0.0)	1 (100.0)	1 (100.0)	-
Negative, n (%)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	-

Conclusions

- C_{max} values were comparable in two groups after Doses 1, 2 and 3 with a spike in C_{max} in both treatment groups at Dose 2 (Week 2).
- PTF and T_{max} were comparable between CT-P13 and EU-approved Remicade.
- Safety profiles were consistent with what were expected based on the existing literature about infliximab (Remicade) in the CT-P13 group and Remicade group over 2 years. In addition, there were no significant safety issues for patient who switched to CT-P13.

Study CT-P13 B1P13101 (Local Registration Study, Japan)

Report # CT-P13 B1P13101

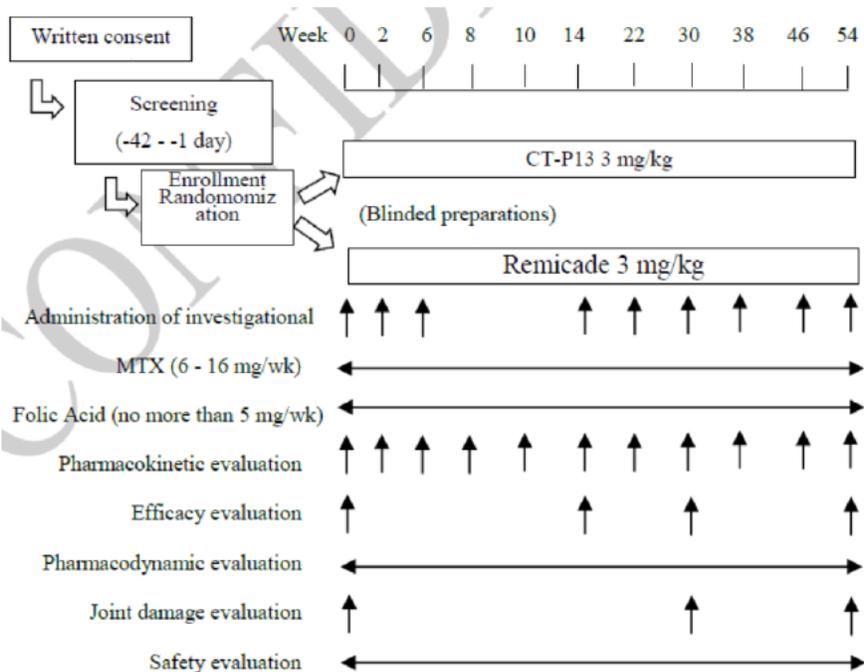
Title: A Double-Blind, Parallel-Group, Comparative Study of CT-P13 and Remicade in Treatment of Patients with Rheumatoid Arthritis

Objectives

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. Secondly, to make a comparative study of efficacy and safety.

Study Design

This study was a multi-center, randomized, double-blind, parallel-group, comparative study. 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. With a screening period of 6 weeks and 8 weeks ±1 week until final tests, the study period was 68 weeks ±1 week.



(Source: Study CT-P13 B1P1 3101 study report, page 3)

Primary endpoint:

Statistical verification of the equivalence of AUC_τ (weeks 6–14) and C_{max} (week 6) between the two groups

Secondary endpoints

- Efficacy assessment: proportion of patients achieving ACR20, ACR50 and ACR70 at weeks 14, 30 and 54; ACR endpoints at weeks 14, 30 and 54; Time to onset of 20% ; improvement in ACR; and others
- PK assessment: C_{max}, C_{av}, C_{min}, fluctuation, T_{max}, MRT, T_{1/2}, CL, V_{d,ss}
- PD assessment: CRP, RF, anti-CCP antibody, ESR
- Safety assessment: immunogenicity, newly positive IFN-γ release assay results, ECG findings, adverse events

Results

A total of 108 subjects were enrolled in the study and randomly assigned. Investigational drug was administered to 104 of these subjects, 51 in the CT-P13 group and 53 in the Remicade group. In both groups, the majority of subjects completed the study up to week 54, 42 (82.4%) in the CT-P13 group and 40 (75.5%) in the Remicade group.

PK Results

In the PK analysis, the geometric mean ratio (90% confidence interval) of CT-P13 to Remicade (90% CI) was 111.62% (100.24-124.29%) for AUC_τ and 104.09% (92.12~117.61%) for C_{max}. The 90% CI of the geometric mean ratios of AUC_τ and C_{max} were within the range of 80– 125%, verifying that CT-P13 and Remicade are pharmacokinetically equivalent. (Table 16)

Table 16. Statistical analysis of PK parameters

	Administration group	Number of subjects	Geometric mean	CV assuming log normal distribution	Geometric mean ratio (%)	90% confidence interval of ratio (%)
AUC _τ (μg · hr/mL)	CT-P13	39	27600	27.5	111.62	100.24 – 124.29
	Remicade®	39	24700	30.7		
C _{max} (μg/mL)	CT-P13	39	115	30.2	104.09	92.12 – 117.61
	Remicade®	39	111	36.2		

(Source: Study CT-P13 B1P1 3101 study report, Table 11-6)

Immunogenicity Results

The number of subjects positive at each evaluation point (positive ratio %) was shown in Table 17. All subjects were negative for anti-drug antibody during screening. The positive ratio for anti-drug antibody increased over time at week 14, 30, and 54 in both groups.

Among anti-drug antibody-positive subjects, the positive ratio for neutralizing antibody was 100% in both groups at every timepoint. The number of subjects positive for neutralizing antibody increased over time at weeks 14, 30, and 54 in both groups.

Table 17. Anti-drug antibody positive ratio: safety analysis set

Time	Result	CT-P13 (N=51)		Remicade [®] (N=53)		Total (N=104)	
		Number of subjects	(%)	Number of subjects	(%)	Number of subjects	(%)
On enrollment		51	(100.0)	53	(100.0)	104	(100.0)
Antibody-positive		0	(0.0)	0	(0.0)	0	(0.0)
Neutralizing antibody- positive		0	(-)	0	(-)	0	(-)
Antibody-negative		51	(100.0)	53	(100.0)	104	(100.0)
Week 14		50	(98.0)	49	(92.5)	99	(95.2)
Antibody-positive		10	(19.6)	8	(15.1)	18	(17.3)
Neutralizing antibody- positive		10	(100.0)	8	(100.0)	18	(100.0)
Antibody-negative		40	(78.4)	41	(77.4)	81	(77.9)
Week 30		45	(88.2)	44	(83.0)	89	(85.6)
Antibody-positive		13	(25.5)	14	(26.4)	27	(26.0)
Neutralizing antibody- positive		13	(100.0)	14	(100.0)	27	(100.0)
Antibody-negative		32	(62.7)	30	(56.6)	62	(59.6)
Week 54		42	(82.4)	40	(75.5)	82	(78.8)
Antibody-positive		13	(25.5)	17	(32.1)	30	(28.8)
Neutralizing antibody- positive		13	(100.0)	17	(100.0)	30	(100.0)
Antibody-negative		29	(56.9)	23	(43.4)	52	(50.0)
On completion or discontinuation		50	(98.0)	53	(100.0)	103	(99.0)
Antibody-positive		18	(35.3)	24	(45.3)	42	(40.4)
Neutralizing antibody- positive		18	(100.0)	24	(100.0)	42	(100.0)
Antibody-negative		32	(62.7)	29	(54.7)	61	(58.7)

Antibody-positive ratio (%) = (number of positive subjects at that timepoint / total number of subjects*) x 100. Antibody-negative ratio (%) = (number of negative subjects at that timepoint / total number of subjects*) x 100. Neutralizing antibody-positive ratio (%) = (number of neutralizing antibody-positive subjects at that timepoint / number of antibody-positive subjects at that timepoint) x 100. *: Collated by drug for the safety analysis set.

(Source: Study CT-P13 B1P1 3101 study report, Table 12-11)

Conclusions

- For AUC_t (weeks 6-14) and C_{max} (week 6), the 90% confidence intervals for the geometric mean ratio of the CTP13 group and the Remicade group were within the permissible range for similarity of 80-125%, confirming that CT-P13 and Remicade are similar in terms of pharmacokinetics.

- Other secondary PK parameters are similar in the two groups.
- The anti-drug antibody positive ratio tended to increase over the course of the study, but no major differences were observed between the groups.
- Overall, CT-P13 had good tolerability and its safety profile was considered to be similar to that for Remicade.

Study CT-P13 3.3 (Local Registration Study, Russia)

Report # CT-P13 3.3

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

Objectives

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. 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 will be evaluated.

Parameter	CT-P13		Remicade	
		3 mg/kg (N=298)		3 mg/kg (N=295)
Dose 1 (Week 0)				
C _{max} (µg/mL)	n=296	91.22 (35)	n=292	88.34 (37)
C _{min} (µg/mL)	n=290	15.82 (57)	n=285	16.82 (44)
T _{max} (h)	n=296	3.00 (1.83, 4.08)	n=292	2.11 (1.50, 5.17)
Dose 2 (Week 2)				
C _{max} (µg/mL)	n=294	111.86 (32)	n=292	104.58 (36)
C _{min} (µg/mL)	n=285	6.25 (74)	n=286	7.71 (84)
T _{max} (h)	n=294	2.25 (0.25, 4.03)	n=293	3.00 (0.50, 3.75)
Dose 3 (Week 6)				
C _{max} (µg/mL)	n=284	98.16 (40)	n=284	95.19 (33)
C _{min} (µg/mL)	n=274	1.51 (299)	n=269	1.44 (185)
T _{max} (h)	n=284	2.25 (0.08, 7.33)	n=284	2.98 (1.00, 3.33)
Dose 4 (Week 14)				
C _{max} (µg/mL)	n=275	90.46 (35)	n=271	84.26 (40)
C _{min} (µg/mL)	n=267	1.06 (135)	n=257	1.08 (138)
T _{max} (h)	n=275	2.97 (1.17, 3.20)	n=270	2.25 (0.22, 4.00)
Dose 5 (Week 22)				
C _{max} (µg/mL)	n=264	90.91 (39)	n=261	83.71 (44)
C _{min} (µg/mL)	n=246	0.99 (391)	n=249	1.03 (294)
T _{max} (h)	n=264	3.00 (2.00, 3.25)	n=261	2.25 (2.00, 4.50)
C _{av,ss} (µg/mL)	n=246	47.12 (40)	n=249	43.09 (45)
PTF	n=246	1.86 (11)	n=249	1.88 (10)
Dose 6 (Week 30)				
C _{max} (µg/mL)	n=249	84.03 (38)	n=251	84.04 (35)
T _{max} (h)	n=249	2.08 (2.00, 3.58)	n=251	2.25 (0.10, 3.33)

(Source: Study CT-P13 3.3 report, Table 11-14)

Table 19. Geometric mean (%CV) serum pharmacokinetic parameters of infliximab: pharmacokinetic (antibody negative subset) population

Parameter	CT-P13		Remicade	
		3 mg/kg (N=122)		3 mg/kg (N=128)
Dose 1 (Week 0)				
C _{max} (µg/mL)	n=121	93.27 (31)	n=127	86.93 (39)
C _{min} (µg/mL)	n=119	18.27 (40)	n=126	19.93 (38)
T _{max} (h)	n=121	3.00 (1.83, 3.17)	n=127	2.08 (1.92, 3.33)
Dose 2 (Week 2)				
C _{max} (µg/mL)	n=122	117.97 (30)	n=128	104.82 (41)
C _{min} (µg/mL)	n=120	10.58 (57)	n=128	11.81 (75)
T _{max} (h)	n=122	2.13 (1.58, 3.50)	n=128	2.63 (0.50, 3.13)
Dose 3 (Week 6)				
C _{max} (µg/mL)	n=122	111.54 (35)	n=128	101.59 (28)
C _{min} (µg/mL)	n=121	2.59 (252)	n=125	2.62 (158)
T _{max} (h)	n=122	2.73 (2.00, 7.33)	n=128	3.00 (1.00, 3.33)
Dose 4 (Week 14)				
C _{max} (µg/mL)	n=121	96.55 (30)	n=127	87.64 (38)
C _{min} (µg/mL)	n=115	1.95 (103)	n=118	1.86 (79)
T _{max} (h)	n=121	2.13 (2.00, 3.20)	n=127	2.22 (1.95, 3.15)
Dose 5 (Week 22)				
C _{max} (µg/mL)	n=114	96.79 (41)	n=120	91.41 (37)
C _{min} (µg/mL)	n=105	1.86 (308)	n=115	1.89 (237)
T _{max} (h)	n=114	3.00 (2.00, 3.25)	n=120	2.22 (2.00, 3.55)
C _{av,ss} (µg/mL)	n=105	51.66 (42)	n=115	47.11 (37)
PTF	n=105	1.77 (14)	n=115	1.84 (10)
Dose 6 (Week 30)				
C _{max} (µg/mL)	n=108	97.33 (31)	n=116	90.64 (35)
T _{max} (h)	n=108	2.11 (2.00, 3.58)	n=116	2.96 (2.00, 3.20)

(Source: Study CT-P13 3.3 report, Table 11-15)

Immunogenicity Results

The number of patients with positive immunogenicity results generally increased throughout the study, and the number of patients with positive immunogenicity results was similar in each treatment group at each time point. Three (1.0%), 71 (23.1%), 123 (40.1%) patients in the CT-P13 treatment group and 3 (1.0%), 69 (22.3%), 121 (39.0%) patients in the Remicade treatment group had positive immunogenicity results at Screening, Week 14 and Week 30, respectively.

For the Russian patient subgroup, the number of patients with positive immunogenicity results was similar in each treatment group at each time point. One (16.7%) and 1 (16.7%) patient in the CT-P13 treatment group and 0 and 1 (11.1%) patient in the Remicade treatment group had positive immunogenicity results at Screening and Week 30, respectively. No patient in either treatment group had positive immunogenicity results at Week 14.

Conclusions

- Overall, the efficacy results of CT-P13 up to Week 30 were comparable to those of Remicade.
- The PK were similar in the CT-P13 and Remicade treatment groups for both the PK and PK (antibody negative subset) populations. For the Russian patient subgroup, the PK endpoint results were also similar for each treatment group in the PK and PK (antibody negative subset) populations.
- There was no evidence of a difference between the CT P13 and Remicade treatment groups in change from Baseline in CRP, ESR, IgA RF, or IgM RF at each time point.
- Overall, CT-P13 was well tolerated and the safety profile of CT P13 was comparable to that of Remicade.

Study CT-P13 Population PK Analysis

Report # CPT_PCIP_2014_003

Title: Dose Proportionality of CT–P13 Extrapolated from Population Pharmacokinetic Analysis

Objective: to evaluate the dose proportionality of CT–P13 based upon the population pharmacokinetic model of CT–P13 and EU-approved Remicade in patients with rheumatoid arthritis and Crohn’s disease and previously published pharmacokinetic data on Remicade.

Software: Non-linear mixed effects population pharmacokinetic analysis was performed using NONMEM (version 7.3) with the G77 FORTRAN compiler. For dataset construction, data presentation, construction of plots, and graphical exploration, Excel 2010 and R (version 3.0.1) was used.

Data Source:

Study CT-P13 1.1 Data

Data from the subjects who received at least the first 5 doses through the trial were included in the population pharmacokinetic analysis. The final NONMEM dataset for population PK analysis of Study CT–P13 1.1 included a total of 6,583 (3,335 for CT–P13, 3,248 for Remicade) quantifiable concentration–time records from 223 active AS patients. In addition to the concentration–time data, covariate information (age, sex, height, weight, BMI, ethnicity, and treatment group) for each subject was incorporated into the dataset.

Study CT-P13 3.1 Data

Data from subjects who received the study treatments over the 30 weeks blinded study period were included in the external validation. The demographic variables at baseline were collected as the same method used in CT–P13 1.1 data.

Data Handling Conventions: The analysis and reporting of results were performed in accordance with the FDA guidance on population pharmacokinetics. Serum concentration values determined before the first dosing and those below lower limit of quantification were considered as missing.

Population PK Model Development Scheme: The schematic for population PK model development is Base model development → Covariate model development → Final PK model evaluation → External validation using Study CT-P13 3.1 data.

Base Model Development: The first-order conditional estimation method with interaction was used throughout the model building process. One-, two-, and three-compartment distribution models with first-order elimination were tested for the serum concentration-time profiles of CT-P13 and Remicade. The inter-individual variability (IIV) of each parameter was applied exponentially. Additive, proportional, or combined error models were evaluated for residual variability. The population pharmacokinetics of CT-P13 and Remicade was best described by a three-compartment model with combined additive and proportional error term for residual variability. The goodness-of-fit plots were used to evaluate the ability of the PK models to describe the available data.

Covariate Model Development: The covariate model building was performed in a stepwise fashion with forward inclusion and backward deletion. Potential covariates identified based on generalized additive modeling implemented in Xpose4 and inspection of ETA-covariate and covariate-covariate plots were incorporated into the model. Contribution of the remaining covariates was evaluated by eliminating each covariate from the model, one at a time. A covariate was excluded if the OFV did not increase by more than 6.63 (χ^2 , $p < 0.01$, $df = 1$). Continuous variables were transformed using a power model centered on the median value for the corresponding variable. Categorical variables were coded as linear models. The likelihood ratio test and boxplots of the individual PK parameters were used to evaluate the effect of treatment on each PK parameter.

The demographic variables investigated as potential covariates included age, sex, ethnicity, height, weight, BMI. In addition, the effect of treatment (Remicade versus CT-P13) was evaluated. The model for CT-P13 and Remicade allowed for IIV terms on CL, V1, V2, and V3 with covariance between CL and V1. Body weight was a significant covariate for CL [$CL = \Theta_1 \times (WT/73)^{0.447}$] and V1 [$V1 = \Theta_2 \times (WT/78)^{0.57}$] of CT-P13 and Remicade. Sex was incorporated into the model as a covariate for CL, V1, and V3. The mean half-lives for alpha, beta, and gamma phases of female/male patients were calculated as 0.83/0.84, 42.8/53.5, and 293.0/357.7 hours, respectively.

Final PK Model Evaluation: The basic goodness-of-fit plots for CT-P13 and Remicade as below (Figure 6) indicated the final PK model successfully describes the observed data. The final model has been re-run by the reviewer.

Model validation was conducted using a bootstrap-resampling method and visual predictive checks (VPC).

The final population PK model was evaluated using 1,000 bootstrap replicates. The bootstrap estimates were used to obtain confidence intervals for all model parameters, including those for the covariate estimates. Parameter estimates and corresponding relative standard error (RSE)

from the final PK model and bootstrap results (bootstrap medians and 95% CIs) for CT-P13 and Remicade are summarized in Table 20.

In the VPC step, the final parameter estimates were used to simulate 1,000 data points (concentrations) for each observation based on the covariates, actual PK sampling times and the dosing histories recorded in the original dataset. Observed data points overlaid with 5th, 50th, and 95th percentile curves of 1,000 simulated datasets were visually inspected. The VPC plot of the final population pharmacokinetic model for CT-P13 and Remicade is shown in Figure 7. The model-predicted confidence intervals as well as medians corresponded adequately to the observed data. The VPC plots of the final population pharmacokinetic model for CT-P13 and Remicade stratified by sex and treatment group are shown in Figure 8. The model-predicted confidence intervals as well as medians corresponded adequately to the observed data. No marked differences were observed in VPC plots between groups for sex and treatment.

Comparison of PK Parameters between CT-P13 and EU-approved Remicade: Likelihood ratio tests and visual inspection of boxplots were used to confirm the effect of treatment (CT-P13 and Remicade) on the individual pharmacokinetic parameters. In the likelihood ratio test, there are no statistically significant parameters for the inclusion of the treatment effect. In addition, the distribution profile of individual pharmacokinetic parameters of CT-P13 and Remicade were highly similar in boxplots. This implied that the concentration-time curves of Remicade and CT-P13 are explained by the same PK parameter values. Boxplots of each pharmacokinetic parameter are presented in Figure 9.

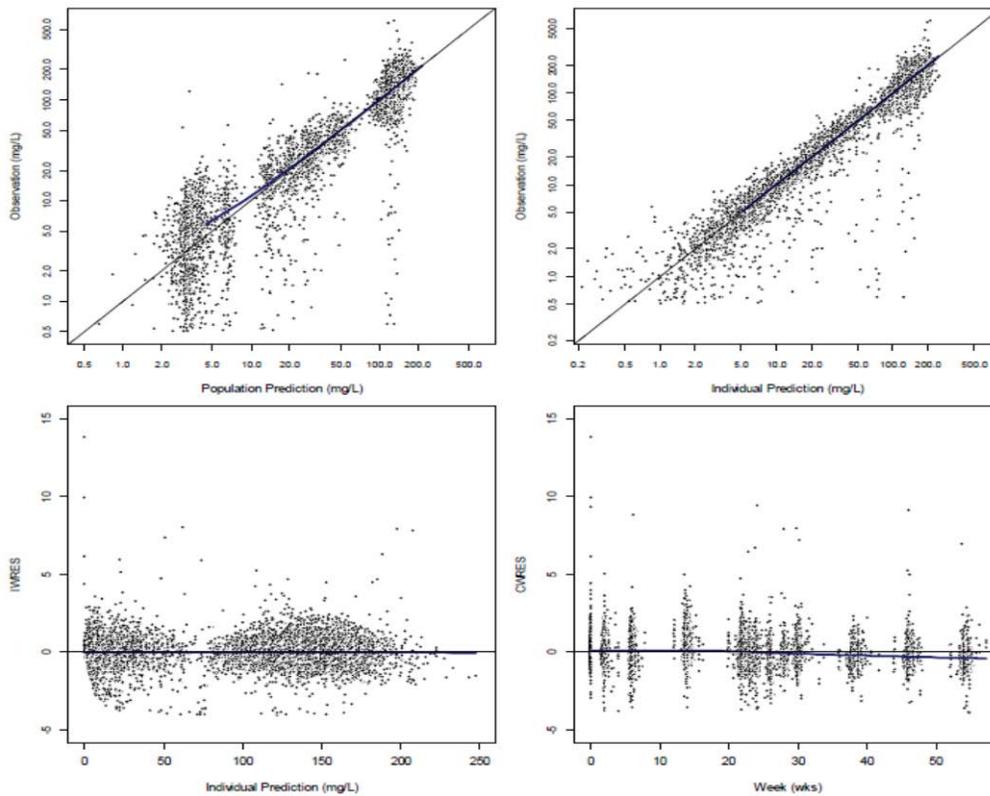


Figure 6. Basic goodness-of-fit plots of the final PK model for CT-P13 and EU-approved Remicade

(Source: CPT_PCIP_2014_003 report, Figure 1)

Table 20. Final parameter estimates and bootstrap results for CT-P13 and EU-approved Remicade

Parameter	Description (units)	Estimate (% RSE)	Bootstrap Median (95% CI)
Fixed effect			
$CL = (\theta_1 + SEX \times \theta_7) \times (WT/73)^{\theta_8}$			
θ_1	Clearance for female subjects (L/h)	0.0104 (5.96)	0.0105 (0.00924 – 0.0119)
θ_7	Difference of clearance according to SEX (L/h)	0.00163 (45.5)	0.00165 (0.0000543 – 0.00314)
θ_8	Exponent to weight	0.447 (27.5)	0.449 (0.199 – 0.685)
$V1 = (\theta_2 + SEX \times \theta_9) \times (WT/73)^{\theta_{10}}$			
θ_2	Volume of central compartment for female subjects (L)	2.38 (4.37)	2.55 (2.18 – 2.74)
θ_9	Difference of V1 according to SEX (L)	0.231 (34.9)	0.242 (0.0627 – 0.392)
θ_{10}	Exponent to weight	0.57 (12.4)	0.544 (0.420 – 0.716)
V2	Volume of 1 st peripheral compartment (L)	0.465 (21.9)	0.571 (0.241 – 1.57)
Q2	Intercompartmental clearance between V1 and V2 (L/h)	0.324 (52.8)	0.212 (0.0218 – 0.664)
$V3 = \theta_5 + SEX \times \theta_{11}$			
θ_5	Volume of V3 for female subjects (L)	1.2 (10.5)	1.06 (0.0770 – 1.41)
θ_{11}	Difference of V3 according to SEX (L)	0.493 (23.1)	0.483 (0.234 – 0.751)
Q3	Intercompartmental clearance between V1 and V3 (L/h)	0.0126 (19.9)	0.0105 (0.00161 – 0.0185)
Inter-individual variability			
ω_{CL}	Inter-individual variability for CL (%)	31.4 (6.98)	30.9 (26.7 – 36.2)
ω_{V1}	Inter-individual variability for V1 (%)	17.0 (12.2)	15.8 (13.7 – 23.0)
ω_{V2}	Inter-individual variability for V2 (%)	80.2 (22.0)	77.5 (35.4 – 151)
ω_{V3}	Inter-individual variability for V3 (%)	42.9 (18.1)	47.1 (28.2 – 100)
ρ_{CL-V1}	Correlation between CL and V1	0.219	0.222 (0.052 – 0.404)
Residual error			
σ_{add}	Additive error (mg/L)	1.68 (19.0)	1.64 (0.780 – 2.22)
σ_{prop}	Proportional error (%)	24.6 (4.15)	24.7 (22.6 – 27.1)

RSE, relative standard error; SEX, (female=0, male=1); WT, body weight (kg)

(Source: CPT_PCIP_2014_003 report, Table 4)

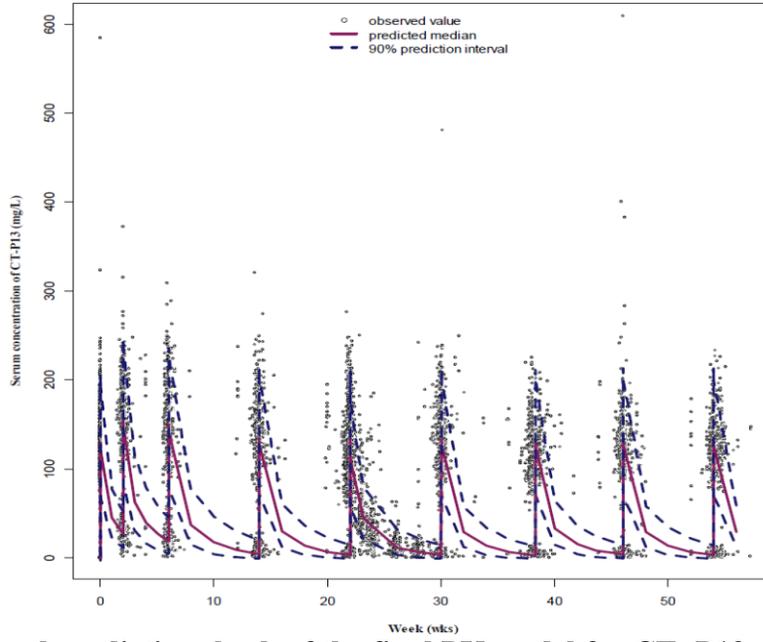


Figure 7. Visual predictive check of the final PK model for CT-P13 and Remicade
(Source: CPT_PCIP_2014_003 report, Figure 2)

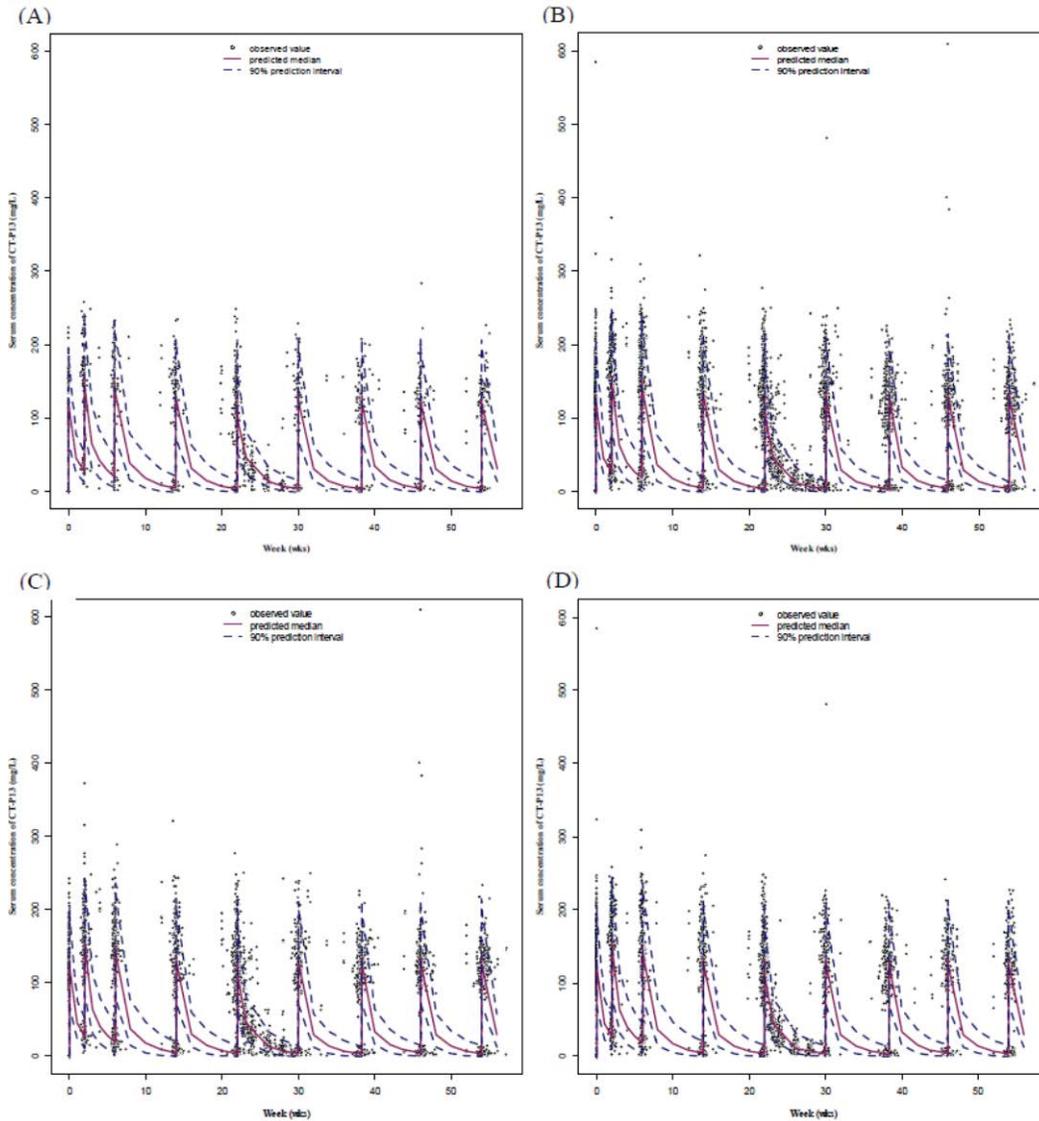


Figure 8. Visual predictive check plots of the final PK model for CT-P13 and Remicade stratified by sex and treatment group: (A) female patients (B) male patients (C) Remicade (D) CT-P13

(Source: CPT_PCIP_2014_003 report, Figure 3)

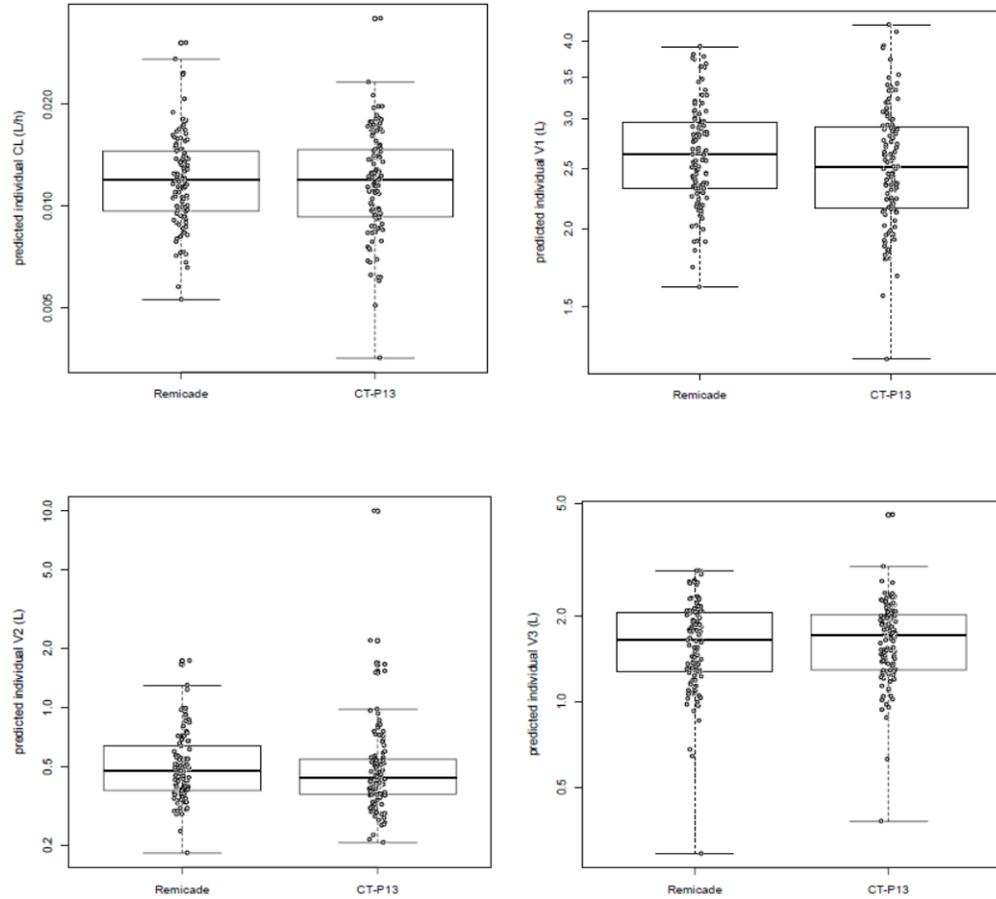


Figure 9. Boxplots of individual pharmacokinetic parameters stratified by treatment Group

(Source: CPT_PCIP_2014_003 report, Figure 4)

External Validation Using CT-P13 3.1 Data: This external validation was conducted to evaluate the dose proportionality in the dose range of 3–5 mg/kg. Major differences between the two studies are summarized in following Table 21. The population PK parameters developed from CT-P13 1.1 data were successfully evaluated using the PK data from CT-P13 3.1 as an external validation dataset and showed that there are no marked differences in Remicade and CT-P13 pharmacokinetics (Figure 10, and Figure 11). The predicted plot of CT-13 serum concentrations after administration of CT-P13 10 mg/kg using the final pharmacokinetic model are shown in Figure 12.

Table 21. Comparison of CT-P13 1.1 and CT-P13 3.1 studies

Characteristic	CT-P13 1.1 study	CT-P13 3.1 study
Patient group	ankylosing spondylitis (AS)	rheumatoid arthritis (RA)
Methotrexate co-therapy	no	yes
Dose	5 mg/kg	3 mg/kg

(Source: CPT_PCIP_2014_003 report, Table 3)

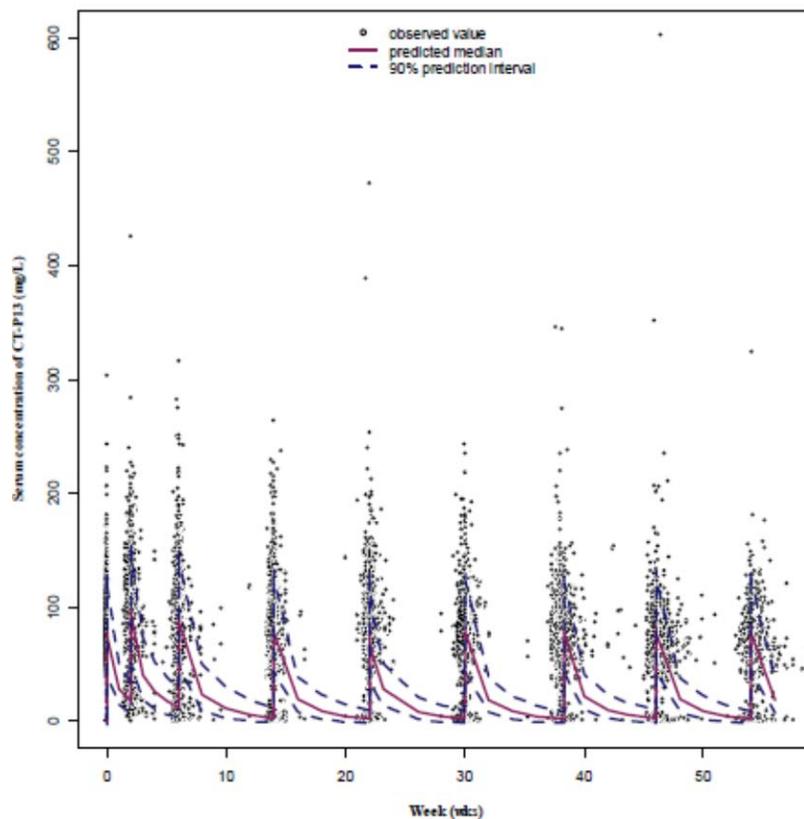


Figure 10. External predictive check of the final pharmacokinetic model using CT-P13 3.1 data

(Source: CPT_PCIP_2014_003 report, Figure 5)

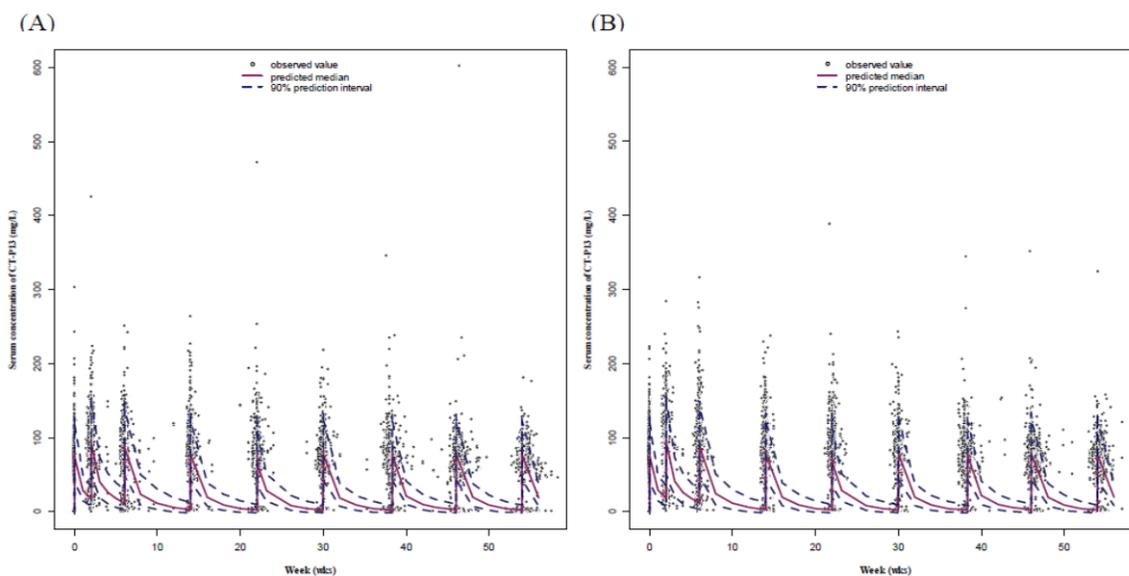


Figure 11. External predictive check stratified by treatment group: (A) Remicade (B) CT-P13

(Source: CPT_PCIP_2014_003 report, Figure 6)

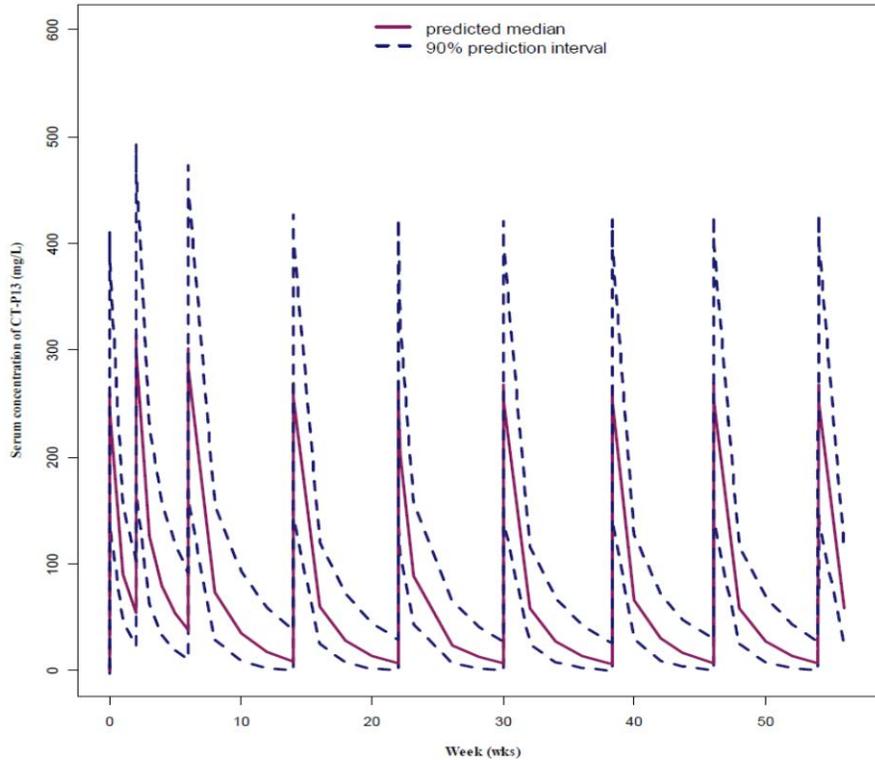


Figure 12. Predicted plot of CT-P13 serum concentrations after administration of CT-P13 10 mg/kg

(Source: CPT_PCIP_2014_003 report, Figure 7)

Conclusions

- A three-compartment model adequately described the pharmacokinetic properties of CT-P13 and EU-approved Remicade. Body weight was positively correlated with CL, V1. Male patients had slightly higher CL, V1, and V3 than those in female patients.
- There are no differences in PK parameters between EU-approved Remicade and CT-P13. Both EU-approved Remicade and CT-P13 appear to be dose proportional in the dose range of 3–5 mg/kg based on the external validation. The PK parameters of EU-approved Remicade are previously known to be proportional to the doses of 5 and 10 mg/kg in patients with CD, and 5, 10, and 20 mg/kg in patients with RA.
- In conclusion, no PK differences were observed between EU-approved Remicade and CT-P13 and pharmacokinetics of CT-P13 was expected to be linear in the dose range of 3–10 mg/kg in approved indications such as RA and CD.

4.2 Appendix – Office of Clinical Pharmacology Filing Memo

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	125544	Brand Name	(b) (4)
OCP Division (I, II, III, IV, V)	II	Generic Name	Infliximab
Medical Division	570	Drug Class	Anti-TNFalpha
OCP Reviewer	Lei He, Ph.D.	Indication(s)	Rheumatoid Arthritis, Ankylosing Spondylitis, Crohn's Disease, Pediatric Crohn's Disease, Ulcerative (b) (4) Colitis, Plaque Psoriasis, Psoriatic Arthritis
OCP Team Leader	Satjit Brar, Pharm.D, Ph.D.	Dosage Form	Lyophilized powder for IV infusion
Pharmacometrics Reviewer		Dosing Regimen	RA: 3mg/kg at week 0, 2, 6, and q8w; AS: 5mg/kg at week 0, 2, 6, and q6w; CD, Pediatric CD, UC, (b) (4) Ps, and PA: 5mg/kg at week 0, 2, 6, and q8w
Date of Submission	August 8, 2014	Route of Administration	IV infusion
Estimated Due Date of OCP Review	March 1, 2015	Sponsor	Celltrion
Medical Division Due Date	March 1, 2015	Priority Classification	Standard
PDUFA Due Date	June 8, 2015		

Clin. Pharm. and Biopharm. Information

	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	x	1		CT-P13 3.1
Population Analyses -				
Data rich:				
Data sparse:	x	1		
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	x	4		CT-P13 1.4 CT-P13 BIP13 101 CT-P13 1.1 CT-P13 1.2
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	x	1		
Literature References				
Total Number of Studies		7	6	CT-P13 1.2 is a pilot study

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x			

	Content Parameter	Yes	No	N/A	Comment
2	Has the applicant provided metabolism and drug-drug interaction information?			x	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			x	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

 Yes

Celltrion has submitted the BLA125544 under section 351(k) of the Public Health Service Act seeking the marketing approval for CT-P13, a biosimilar product using Remicade® (infliximab) as the reference product.

Infliximab is a chimeric IgG1 κ mAb and is used as a TNF α inhibitor. CT-P13 is proposed to be used for 8 indications identical to Remicade, which are Rheumatoid Arthritis (RA), Crohn's Disease (CD), pediatric CD, Ulcerative Colitis (UC), pediatric UC, Plaque Psoriasis (Ps), Psoriatic Arthritis (PA), and Ankylosing Spondylitis (AS).

Overall, the clinical development program included 7 completed studies (Studies CT-P13 1.4, CT-P13 1.1, CT-P13 3.1, CT-P13 1.2, CT-P13 1.3, CT-P13 3.2, and B1P13101), 2 ongoing local registration studies (Studies CT-P13 3.3 and B2P13111), 6 ongoing post-marketing studies (Studies CT-P13 3.4, PMS in South Korea, CT-P13 4.1, CT-P13 4.2, CT-P13 4.3, CT-P13 4.4), and (b) (4) (Table 1).

Table 1. Studies of CT-P13 Clinical Development Program

Study Identifier	Type of Study	Objectives	Study Status
CT-P13 1.4	Pivotal study	3-way PK bridging study in HV	Completed
CT-P13 1.1	Pivotal study	PK similarity in AS	Completed
CT-P13 3.1	Pivotal study	Therapeutic equivalence in RA	Completed
CT-P13 1.2	Pilot study	PK	Completed
CT-P13 1.3,	Extension study of Study CT-P13 1.1	Long-term efficacy and safety	Completed
CT-P13 3.2	Extension study of Study CT-P13 3.1	Long-term efficacy and safety	Completed
B1P13101	Local registration study in Japan	PK similarity	Completed
CT-P13 3.3	Local registration study in Russia	Efficacy and safety	Ongoing
B2P13111	Extension study of Study B1P13101	Efficacy and safety	Ongoing
CT-P13 3.4, PMS in South Korea, CT-P13 4.1, CT-P13 4.2, CT-P13 4.3, CT-P13 4.4	Post-marketing studies	Efficacy and/or safety	Ongoing

Study CT-P13 1.4 was a Phase 1, randomized, double blind, three-arm, single dose, parallel-group, 3-way PK bridging study in healthy subjects comparing CT-P13, EU-approved Remicade, and US-licensed Remicade. Subjects were randomized to receive a single dose (5 mg/kg) of either CT-P13, or EU-approved Remicade, or US-licensed Remicade through 2-hour IV infusion. The concentrations of infliximab in human serum were determined by a quantitative Gyrolab immunoassay, the antibodies against CT-P13, Remicade (EU), and Remicade (US) in human

serum were measured using an enzyme-linked immunosorbent assay (ELISA) method, and the neutralizing anti-CT-P13, anti-Remicade (EU), or anti-Remicade (US) antibodies in human serum were measured by a gyrolab immunoassay. A total of 213 subjects were enrolled and 211 (89%) of them completed the study. C_{max}, AUC_{last}, and AUC_{inf} were used as primary endpoints. According to data analysis, sponsor concluded that the PK similarity has been demonstrated between any two of CT-P13, EU-approved Remicade, and US-licensed Remicade in healthy subjects.

The PK similarity between CT-P13 and EU-approved Remicade has also been demonstrated in AS and RA patients in Study CT-P13 1.1 and 3.1, respectively. Study CT-P13 1.1 is a Phase 1, randomized, double blind, parallel-group study in AS patients. CT-P13 or EU-approved Remicade was administered at the dose of 5 mg/kg at weeks 0, 2, 6, and followed by Q8W. AUC_{τ,ss} and C_{max,ss} between week 22 and 30 were used as the primary endpoints. Study CT-P13 3.1 is a Phase 3, randomized, double blind, parallel-group study in RA patients. CT-P13 or EU-approved Remicade was administered at the dose of 3 mg/kg at weeks 0, 2, 6, and followed by Q8W. Clinical response was used as primary endpoint and PK parameters, such as C_{max}, C_{min}, C_{av,ss}, and T_{max}, were used as secondary endpoints.

In addition, the PK similarity between CT-P13 and EU-approved Remicade has been investigated in RA patients in a completed pilot PK study (CT-P13 1.2), a completed local registration study in Japan (B1P13101), and an ongoing local registration study in Russia (CT-P13 3.3). According to sponsor's data analysis, all current data meets the PK similarity criteria.

Since Study CT-P13 1.4 was conducted outside the United States, the OSI inspections for both study center and bioanalytical lab will be requested.

Identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None

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/s/

LEI HE
05/04/2015

PING JI
05/04/2015

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	125544	Brand Name	(b) (4)
OCP Division (I, II, III, IV, V)	II	Generic Name	Infliximab
Medical Division	570	Drug Class	Anti-TNFalpha
OCP Reviewer	Lei He, Ph.D.	Indication(s)	Rheumatoid Arthritis, Ankylosing Spondylitis, Crohn's Disease, Pediatric Crohn's Disease, Ulcerative Colitis, (b) (4) (b) (4) Plaque Psoriasis, Psoriatic Arthritis
OCP Team Leader	Satjit Brar, Pharm.D, Ph.D.	Dosage Form	Lyophilized powder for IV infusion
Pharmacometrics Reviewer		Dosing Regimen	RA: 3mg/kg at week 0, 2, 6, and q8w; AS: 5mg/kg at week 0, 2, 6, and q6w; CD, Pediatric CD, UC, (b) (4) Ps, and PA: 5mg/kg at week 0, 2, 6, and q8w
Date of Submission	August 8, 2014	Route of Administration	IV infusion
Estimated Due Date of OCP Review	March 1, 2015	Sponsor	Celltrion
Medical Division Due Date	March 1, 2015	Priority Classification	Standard
PDUFA Due Date	June 8, 2015		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	x	1		CT-P13 3.1
Population Analyses -				
Data rich:				
Data sparse:	x	1		
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	x	4		CT-P13 1.4 CT-P13 BIP13 101 CT-P13 1.1 CT-P13 1.2
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	x	1		
Literature References				
Total Number of Studies		7	6	CT-P13 1.2 is a pilot study

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x			
2	Has the applicant provided metabolism and drug-drug interaction			x	

	Content Parameter	Yes	No	N/A	Comment
	information?				
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			x	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

__Yes__

Celltrion has submitted the BLA125544 under section 351(k) of the Public Health Service Act seeking the marketing approval for CT-P13, a biosimilar product using Remicade® (infliximab) as the reference product.

Infliximab is a chimeric IgG1 κ mAb and is used as a TNFα inhibitor. CT-P13 is proposed to be used for 8 indications identical to Remicade, which are Rheumatoid Arthritis (RA), Crohn’s Disease (CD), pediatric CD, Ulcerative Colitis (UC), pediatric UC, Plaque Psoriasis (Ps), Psoriatic Arthritis (PA), and Ankylosing Spondylitis (AS).

Overall, the clinical development program included 7 completed studies (Studies CT-P13 1.4, CT-P13 1.1, CT-P13 3.1, CT-P13 1.2, CT-P13 1.3, CT-P13 3.2, and B1P13101), 2 ongoing local registration studies (Studies CT-P13 3.3 and B2P13111), 6 ongoing post-marketing studies (Studies CT-P13 3.4, PMS in South Korea, CT-P13 4.1, CT-P13 4.2, CT-P13 4.3, CT-P13 4.4), (b) (4) (b) (4) (Table 1).

Table 1. Studies of CT-P13 Clinical Development Program

Study Identifier	Type of Study	Objectives	Study Status
CT-P13 1.4	Pivotal study	3-way PK bridging study in HV	Completed
CT-P13 1.1	Pivotal study	PK similarity in AS	Completed
CT-P13 3.1	Pivotal study	Therapeutic equivalence in RA	Completed
CT-P13 1.2	Pilot study	PK	Completed
CT-P13 1.3,	Extension study of Study CT-P13 1.1	Long-term efficacy and safety	Completed
CT-P13 3.2	Extension study of Study CT-P13 3.1	Long-term efficacy and safety	Completed
B1P13101	Local registration study in Japan	PK similarity	Completed
CT-P13 3.3	Local registration study in Russia	Efficacy and safety	Ongoing
B2P13111	Extension study of Study B1P13101	Efficacy and safety	Ongoing
CT-P13 3.4, PMS in South Korea, CT-P13 4.1, CT-P13 4.2, CT-P13 4.3, CT-P13 4.4	Post-marketing studies	Efficacy and/or safety	Ongoing

Study CT-P13 1.4 was a Phase 1, randomized, double blind, three-arm, single dose, parallel-group, 3-way PK bridging study in healthy subjects comparing CT-P13, EU-approved Remicade, and US-licensed Remicade. Subjects were randomized to receive a single dose (5 mg/kg) of either CT-P13, or EU-approved Remicade, or US-licensed Remicade through 2-hour IV infusion. The concentrations of infliximab in human serum were determined by a quantitative Gyrolab immunoassay, the antibodies against CT-P13, Remicade (EU), and Remicade (US) in human serum were measured using an enzyme-linked immunosorbent assay (ELISA) method, and the

neutralizing anti-CT-P13, anti-Remicade (EU), or anti-Remicade (US) antibodies in human serum were measured by a gyrolab immunoassay. A total of 213 subjects were enrolled and 211 (89%) of them completed the study. C_{max}, AUC_{last}, and AUC_{inf} were used as primary endpoints. According to data analysis, sponsor concluded that the PK similarity has been demonstrated between any two of CT-P13, EU-approved Remicade, and US-licensed Remicade in healthy subjects.

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In addition, the PK similarity between CT-P13 and EU-approved Remicade has been investigated in RA patients in a completed pilot PK study (CT-P13 1.2), a completed local registration study in Japan (B1P13101), and an ongoing local registration study in Russia (CT-P13 3.3). According to sponsor's data analysis, all current data meets the PK similarity criteria.

Since Study CT-P13 1.4 was conducted outside the United States, the OSI inspections for both study center and bioanalytical lab will be requested.

Identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None

Attachment: Presentation slides in filing meeting

BLA 125544 CT-P13
-- a Biosimilar Product to Remicade (Infliximab)

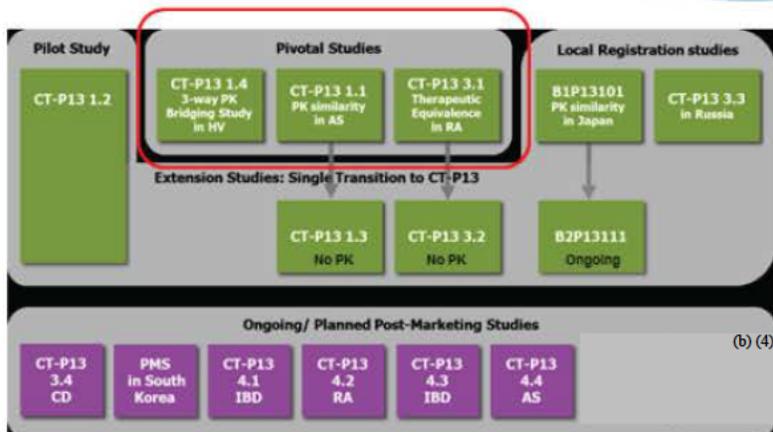
Filing Meeting
September 29, 2014

Lei He, Ping Ji, Satjit Brar
Clinical Pharmacology

Clinical Pharmacology Summary

- Application is fileable from a clinical pharmacology perspective.
- Topline results
 - CT-P13 1.4:
 - ❖ PK was similar in healthy subjects between
CT-P13 and US-Remicade
CT-P13 and EU-Remicade
EU-Remicade and US-Remicade
 - ❖ OSI inspection?
 - CT-P13 was similar to EU-Remicade in RA and AS patients.
- Potential labeling issue

Clinical Development Program



Major Studies for Clin Pharm to Review

Study	Objective	Population	Dose	Product Comparison
CT-P13 1.4	3-way bridging PK study	Healthy subjects	5 mg/kg SD	CT-P13 vs EU-Remicade CT-P13 vs US-Remicade EU-Remicade vs US-Remicade
CT-P13 1.1	PK similarity study	AS patients	5 mg/kg MD	CT-P13 vs EU-Remicade
CT-P13 3.1	Comparative clinical study	RA patients	3 mg/kg MD	CT-P13 vs EU-Remicade

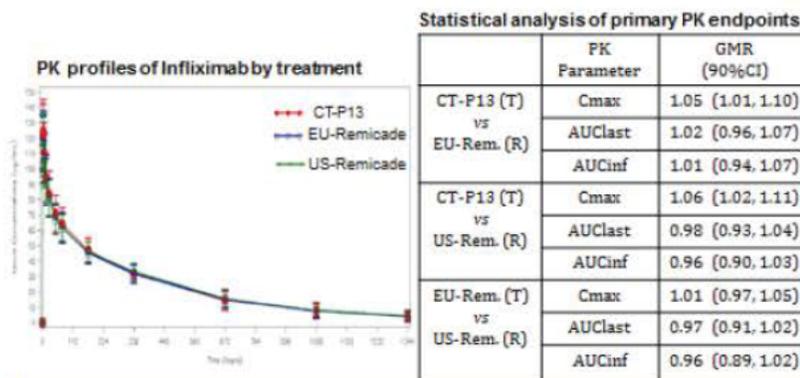
Study CT-P13 1.4

Pivotal 3-way PK Bridging/Similarity Study in HS

- Primary objective: evaluate and compare the PK of CT-P13, EU-Remicade and US-Remicade
- Study design: R, DB, three arm, parallel group, single-dose, Phase 1 study in HS
- Dose: a single dose (5 mg/kg) of either CT-P13, EU-Remicade, or US-Remicade, 2hr IV infusion
- Endpoints:
 - Primary: C_{max} , AUC_{last} , AUC_{inf}
 - Secondary: PK, safety and tolerability, immunogenicity
- 213 subjects were enrolled and 211 subjects completed (99%) the study.

Study CT-P13 1.4: Results

- ❖ PK (C_{max} , AUC_{last} , and AUC_{inf}) were found to be similar between any two of CT-P13, EU-Remicade, and US-Remicade in healthy subjects.



Study CT-P13 1.4: Immunogenicity

- ❖ The number of subjects developing ADA among three treatment arms.

	CT-P13	EU-Remicade	US-Remicade
ADA-positive subjects on Day 57	17 (24.29%)	18 (25.35%)	8 (11.43%)

- ❖ All (100%) subjects who were positive for ADA were detected positive for nAb in each treatment group.

Study CT-P13 1.1

PK Similarity Study (CT-P13 vs EU-Remicade) in AS

- Primary objective: PK similarity at SS between week 22 and 30
- Study design: R, DB, MC, parallel-group, Phase 1 study in AS patients
- Dosing: CT-P13 (T) and EU-Remicade (R), 5 mg/kg, 2 hr IV infusion

	Dose-Loading Phase				Maintenance Phase ^a		
	Dose 1 Week 0 (Day 0)	Dose 2 Week 2 (Day 14)	Dose 3 Week 6 (Day 42)	Dose 4 Week 14 (Day 98)	Dose 5 Week 22 (Day 153)	Dose 6 Week 30 (Day 210)	Doses 7, 8, & 9 Weeks 38, 46, & 54 (Days 266, 322, & 378)
CT-P13 ^b	X	X	X	X	X	X	X
Remicade ^c	X	X	X	X	X	X	X

- Endpoints:
 - Primary: AUC_{0-t} at SS and C_{max,ss} (week 22-30)
 - Secondary: long-term efficacy, PK, safety
- 250 patients were enrolled, 223 patients (89%) were included in the PK population.

Study CT-P13 1.1: Results

- ❖ PK of CT-P13 was similar to EU-Remicade at steady state in AS patients.

Statistical analysis of PK endpoints

PK Parameter	GMR (90%CI)
AUC _{0-t}	1.04 (0.94, 1.16)
C _{max,ss}	1.01 (0.95, 1.09)

- ❖ The number of patients with positive ADA was similar in each treatment group at each time point.

Immunogenicity results of Study 1.1

	CT-P13	EU-Remicade
Screening	2 (1.6%)	1 (0.8%)
Week 14	14 (8.6%)	13 (10.7%)
Week 30	32 (25%)	25 (20.5%)
Week 54	25 (19.5%)	28 (23%)
EOS visit	44 (34.4%)	35 (28.7%)

Study CT-P13 3.1

Comparative Clinical Study in RA (CT-P13 vs EU-Remicade)

- Primary objective: to demonstrate that CT-P13 is therapeutically (efficacy) equivalent to EU-Remicade up to week 30
- Study design: R, DB, MC, parallel-group, Phase 3 study in RA patients
- Dosing: 3 mg/kg of CT-P13 or EU-Remicade, 2 hr IV infusion

	Dose-Loading Phase ¹			Maintenance Phase ²	
	Dose 1 Week 0 (Day 0)	Dose 2 Week 2 (Day 14)	Dose 3 Week 6 (Day 42)	Dose 4, 5, & 6 Weeks 14, 22, & 30 (Days 98, 154, & 210)	Dose 7, 8, & 9 Weeks 38, 46, & 54 (Days 266, 322, & 378)
CT-P13 ³	X	X	X	X	X
Remicade ³	X	X	X	X	X

- Endpoint:
 - Primary: ACR20 response rate at week 30
 - Secondary: efficacy, PK (C_{max}, C_{min}, C_{av,ss}, T_{max}), PD, and safety
- 606 patients were enrolled in the study, 578 patients (95%) were included in the PK population.

Study CT-P13 3.1: PK and Immunogenicity Results

- ❖ The PK results (C_{max} and C_{min}) were similar between CT-P13 and EU-Remicade in RA patients.
- ❖ The number of patients with positive ADA was similar in each treatment group at each time point.

	CT-P13	EU-Remicade
Screening	9 (3.0%)	6 (2.0%)
Week 14	69 (22.8%)	70 (23.3%)
Week 30	122 (40.4%)	122 (40.7%)
Week 54	124 (41.1%)	108 (36.0%)
EOS visit	158 (52.3%)	151 (50.3%)

Draft Labeling

- Clinical Pharmacology (12.3)
 - (b) (4)
 - PK summary of reference product (same as Remicade labeling)
 - Linear range, drug distribution, T_{1/2}, drug accumulation
 - ADA development and impact on PK
 - PK in pediatric patients (study results and pop PK analysis)

Clinical pharmacology information in labeling will be reviewed.

Midcycle Deliverables

- PK Results
 - Confirmation of all results

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/s/

LEI HE
10/07/2014

SATJIT S BRAR
10/07/2014