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

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

Memo to File

Addendum to Primary Clinical Review

BLA#: 125,544

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

Submission: August 8, 2014 (Original NDA)

Complete Response June 8, 2015

BLA Resubmission October 5, 2015

Reviewed: March 10, 2016

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

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

Sponsor: Celltrion

Recommendation on Regulatory Action

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

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

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

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

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

Background

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

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

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

Summary of Safety

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

Summary of Updated Safety Information

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

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

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

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

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

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

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

Study 4.2 (RA Registry)

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

Study 4.3 (IBD Registry)

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

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

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

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

Study 4.4 (AS Registry)

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

Korean Post-Marketing Surveillance (PMS) Study

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

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

Conclusions from CT-P13 Post-Marketing Data

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

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

Interim Immunogenicity Results from Study 3.4

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

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

Table 2. Interim Analysis of Immunogenicity Data in Study 3.4

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

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

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

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

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

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

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

Summary of Safety and Immunogenicity

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

Advisory Committee

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Labeling

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

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/s/

JUWARIA F WAHEED
03/11/2016

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03/11/2016