

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125544Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	April 05, 2016
From	Nikolay P. Nikolov, M.D.
Subject	Cross-Discipline Team Leader Review
BLA #	351(k) BLA 125,544
Applicant	Celltrion
Date of Submission	August 08, 2014
Date of Re-submission	October 05, 2015
PDUFA Goal Date	April 05, 2016
Proprietary Name (Proposed) / Nonproprietary names	Inflectra/ CT-P13 ¹ , infliximab-dyyb
Dosage Forms / Strength	Sterile lyophilized powder in a 20 mL capacity vial/ 100 mg per vial
Route of Administration	Intravenous
Proposed Indication(s)	<ul style="list-style-type: none">• Crohn's Disease (Adult and Pediatric)• Ulcerative colitis (Adult and Pediatric²)• Rheumatoid arthritis• Ankylosing spondylitis• Psoriatic arthritis• Plaque psoriasis
Recommended:	<i>Approval as a biosimilar to US-licensed Remicade for the same indications except for pediatric ulcerative colitis, as Remicade's indication for pediatric ulcerative colitis is protected by orphan drug exclusivity</i>

1. Introduction

This document updates the cross discipline team leader (CDTL) review of the biologics license application (BLA) 125,544 under section 351(k) of the Public Health Service Act (PHS Act) for CT-P13, a proposed biosimilar to US-licensed Remicade (infliximab), which was originally submitted on August 08, 2014 and received a complete response (CR) action on June 08, 2015 due to product quality deficiencies that precluded a conclusion that CT-P13 is highly similar to US-licensed Remicade.

¹ In this document, I generally refer to Celltrion's proposed product by the Celltrion descriptor "CT-P13", which was the name used to refer to this product during development. Subsequently, the nonproprietary name for this proposed product was determined to be "infliximab-dyyb."

² This reflects information for Inflectra that Celltrion submitted on August 8, 2014. We note that Remicade's indication for pediatric ulcerative colitis is protected by orphan drug exclusivity expiring on September 23, 2018. See the Orphan Drug Designations and Approvals database at <http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm>. Accordingly, FDA will not license CT-P13 for this indication until the orphan drug exclusivity expires.

The re-submission was submitted on October 05, 2015, with additional information intended to address the deficiencies identified in the CR letter.

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

2. Background

The BPCI Act

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

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

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

To support a demonstration of biosimilarity, FDA recommends that applicants use a stepwise approach to developing the data and information needed. At each step, the applicant should evaluate the extent to which there is residual uncertainty about the biosimilarity of the

proposed product to the reference product and identify next steps to try to address that uncertainty. The underlying presumption of an abbreviated development program is that a molecule that is shown to be analytically and functionally highly similar to a reference product is anticipated to behave like the reference product in the relevant clinical setting(s). The stepwise approach should start with extensive structural and functional characterization of both the proposed biosimilar product and the reference product, as this analytical characterization serves as the foundation of a biosimilar development program. Based on these results, an assessment can be made regarding the analytical similarity of the proposed biosimilar product to the reference product and the amount of residual uncertainty remaining with respect to both the structural/functional evaluation and the potential for clinically meaningful differences.

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

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

Reference Product

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

Relevant Regulatory History

Celltrion submitted the original 351(k) BLA on August 08, 2014. For detailed discussion on the pertinent pre-submission regulatory history the reader is referred to the CDTL memorandum from the first review cycle. That submission received a complete response (CR) action on June 08, 2015 due to product quality deficiencies that precluded a conclusion that CT-P13 is highly similar to US-licensed Remicade. Specifically, the following was communicated to the applicant as deficiencies precluding approval:

- 1. "You provided data from a limited number of lots showing lower levels of subvisible particulates in the range of 1 to 5 microns in US-licensed Remicade compared to both CT-P13 and EU-approved Remicade. The observed differences may be due to the limited number of lots of CT-P13, US-licensed Remicade and EU-approved Remicade used to perform the analysis. However, these results suggest that analytical differences may exist between US-licensed Remicade and EU-approved Remicade, which, if confirmed, could impact the assessment of the adequacy of the analytical bridge between the three products. To address this concern, provide results of subvisible particulate analysis from an adequate number of additional CT-P13, US-licensed Remicade and EU-approved Remicade lots.*
- 2. You evaluated the analytical similarity of CT-P13 and US-licensed Remicade using a variety of functional assays. Your data generated using a standard NK-cell based killing ADCC assay suggest that CT-P13 has ~20% lower ADCC activity compared to the reference product US-licensed Remicade, which correlates with differences in FcγRIIIa binding. The difference in ADCC leads to residual uncertainty about whether CT-P13 is highly similar to US-licensed Remicade, as the role of ADCC remains uncertain in the clinical activity of the reference product (e.g., in the setting of inflammatory bowel disease). Furthermore, you did not adequately justify the impact of the difference in ADCC on the analytical similarity assessment and did not identify the structural basis underlying this difference. For example, you should determine whether the H2L1 variant that is present at relatively high levels in CT-P13 compared to US-licensed Remicade plays a role in decreasing NK-dependent ADCC activity. On the other hand, the Agency has not excluded the possibility that analysis of additional lots of CT-P13, US-licensed Remicade, and EU-approved Remicade lots could overcome a statistical anomaly due to the analysis of a limited number of lots. To this point, we note that prior differences in glycan patterns were reduced when additional lots of CT-P13, US-licensed Remicade and EU-approved Remicade were analyzed. To address the current deficiency with respect to differences in ADCC activity, we recommend that you repeat the evaluation of ADCC using additional lots to determine whether the ADCC difference you have reported was due to small sample size and decreases when additional lots are evaluated. If the difference in ADCC persists following analysis of additional lots, you should identify and demonstrate control of the product quality attributes that underlie ADCC activity in CTP13 (e.g., glycan pattern, contribution of H2L1 variant, etc.) and provide an adequate justification, including an evaluation of*

the role of ADCC particularly in the setting of inflammatory bowel disease, that the observed difference in ADCC is not relevant to clinical activity.”

In a BPD Type 1 meeting on August 05, 2015, a general agreement was reached between FDA and Celltrion on the data needed to resolve the CR deficiencies. Following this meeting, Celltrion re-submitted the application on October 05, 2015, providing data to address the deficiencies and to support the conclusion that CT-P13 is highly similar to US-licensed Remicade as detailed in the CMC section of this document.

Of note, CT-P13 is approved in several regions outside the U.S. and is marketed under the trade names Inflectra[®] and Remsima[®]. CT-P13 has been approved outside the U.S. for the same indications approved for US-licensed Remicade in several regions including the EU, South Korea, and Japan. In 2014, Health Canada approved CT-P13 for all indications except ulcerative colitis and Crohn’s disease, with the conclusion that extrapolation of data from the settings of rheumatoid arthritis and ankylosing spondylitis to IBD indications was not justified due to questions regarding the possible difference in antibody-dependent cellular cytotoxicity (ADCC) that might have relevance in IBD.³

3. CMC

CMC Reviewer: Peter Adams, Ph.D. and Cyrus Agarabi, Pharm.D., Ph.D.

CMC Team Leader: Kurt Brorson, Ph.D.

CMC Supervisory: David Frucht, M.D., Ph.D.

CMC Statistical Reviewer: Meiyu Shen, Ph.D.

CMC Statistical Supervisor: Yi Tsong, Ph.D.

OBP Director: Steven Kozlowski, M.D.

The original submission contained analytical similarity data comparing multiple lots of CT-P13 with US-licensed Remicade using methods to assess physicochemical and functional properties of the products. For detailed review of those data, the reader is referred to the CDTL memorandum from the first review cycle. Based on those data, the product quality review team identified deficiencies in the analytical biosimilarity assessment that precluded a determination that CT-P13 is “highly similar” to US-licensed Remicade, as detailed in section Background, *Relevant Regulatory History* above. Thus these deficiencies precluded a demonstration of biosimilarity of CT-P13 to US-licensed Remicade. In this re-submission, Celltrion provided key analytical similarity data needed to resolve these deficiencies. A summary of the analysis of the new data is discussed in this section.

Data to Address Deficiency Comment #1

To address deficiency comment #1, Celltrion provided results of additional subvisible particulate analysis from a large number of additional CT-P13, US-licensed Remicade, and

³ See Summary Basis of Decision on Inflectra by Health Canada, accessed at http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/sbd_smd_2014_inflectra_159493-eng.php.

EU-approved Remicade lots using two orthogonal methods, micro flow imaging (MFI) and light obscuration (HIAC). The additional testing revealed that levels of subvisible particles varied for the three products, but no consistent trend towards more or fewer particles were evident for any of the three products. These results add to the totality of the analytical data supporting the conclusion that CT-P13 is highly similar to US-licensed Remicade. Importantly, these analyses also support the analytical component of the scientific bridge between the three products to justify the relevance of the clinical data, including immunogenicity data, generated using EU-approved Remicade in CT-P13 clinical program. The product quality team concluded, and I agree, that based on this additional information, Celltrion has resolved deficiency comment #1.

Data to Address Deficiency Comment #2

To address deficiency comment #2, Celltrion evaluated the ADCC activity of additional lots of CT-P13, US-licensed Remicade and EU-approved Remicade. The additional analysis revealed that >90% of CT-P13 lots were within the quality range established by testing of the reference product, meeting expectations for a determination of “highly similar” for this product quality attribute. Celltrion has also provided an evaluation of an exercise to identify and demonstrate control of product quality attributes that underlie ADCC activity in CT-P13. As a result of this exercise, it was determined that Fc γ R3a binding strength correlated with NK-cell mediated ADCC activity. To further ensure that CT-P13 lots will be within the quality range for NK-cell mediated ADCC activity, Celltrion agreed with the Agency’s proposal to implement a control strategy for Fc γ R3a binding strength. Celltrion has also provided a justification ADCC is likely not an important mechanism of action for infliximab in any indication, based on their assessment of the scientific and medical literature as well as in-house experimentation. Based on the information submitted by Celltrion, and the Agency’s independent review of the literature, the product quality review team considers ADCC to be a “plausible” mechanism of action of infliximab for which a similarity approach involving a quality range assessment is appropriate. Based on these considerations, ADCC activity between CT-P13 and US-licensed Remicade is highly similar, supporting an overall demonstration that CT-P13 is highly similar to US-licensed Remicade. The product quality team concluded, and I agree, that based on this additional information, Celltrion has resolved deficiency comment #2.

Conclusions on Analytical Similarity Assessment

In summary, the CT-P13 product has been evaluated and compared to the reference product (US-licensed Remicade) and EU-approved Remicade in a battery of bioanalytical and functional assays. The exercise also included assays that addressed each potential mechanism of action. The additional information submitted by Celltrion, when considered along with the data in the original application, supports the conclusion that CT-P13 is highly similar to the reference product. The amino acid sequences of CT-P13 and US-licensed Remicade are identical. A comparison of the secondary and tertiary structures, and the impurity profiles, of CT-P13 and US-licensed Remicade support the conclusion that the two products are highly similar. TNF- α binding and neutralization activities, reflecting the primary mechanism of action of US-licensed Remicade further support a conclusion that CT-P13 is highly similar to the US-licensed Remicade. Some tests indicate that subtle shifts in glycosylation (a-

fucosylation) and Fc γ RIII binding exist and are likely an intrinsic property of the CT-P13 product due to the biological production system. However, when CT-P13 is compared to the reference product, the biological functions that these subtle differences might impact (ADCC) are within the quality range of the reference product. Thus, based on the extensive comparison of the functional, physicochemical, protein and higher order structure attributes, the product quality review team concluded, and I agree, that CT-P13 is highly similar to the reference product, US-licensed Remicade, notwithstanding minor differences in clinically inactive components. Further, the data submitted by Celltrion, support the conclusion that CT-P13 and US-licensed Remicade have the same mechanisms of action for each of the requested indications, to the extent that the mechanisms of action are known or can reasonably be determined.

In addition, the three pairwise comparisons of CT-P13, US-licensed Remicade, and EU-approved Remicade met the pre-specified criteria for analytical similarity. Celltrion provided a sufficiently robust analysis for the purposes of establishing the analytical component of the scientific bridge among the three products to justify the relevance of comparative data generated from clinical and non-clinical studies that used EU-approved Remicade, to support a demonstration of biosimilarity of CT-P13 to the US-licensed reference product.

4. Nonclinical Pharmacology/Toxicology

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

No new pharmacology/toxicology information has been submitted in this re-submission. The relevant pharmacology/toxicology data were submitted and reviewed during the first review cycle. The Pharmacology and Toxicology review team recommended approval of the 351(k) BLA from the nonclinical perspective without the need for additional animal studies. There are no outstanding issues from the nonclinical Pharmacology and Toxicology perspective. I concur with this assessment and recommendations.

5. Clinical Pharmacology/Biopharmaceutics

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

- **General clinical pharmacology/biopharmaceutics considerations**

No new clinical pharmacology information has been submitted in this re-submission. The relevant clinical pharmacology data were submitted and reviewed during the first review cycle and are only summarized in this memorandum below.

Pharmacokinetic (PK) similarity of CT-P13 to US-licensed Remicade was evaluated in one 3-way PK similarity study that compared the PK, safety, tolerability, and immunogenicity of single dose 5 mg/kg of either CT-P13, EU-approved Remicade and US-licensed Remicade in healthy subjects (study 1.4). The study was recommended by the FDA to provide needed PK bridging data, in addition to the analytical bridging data, to scientifically justify the relevance of the comparative data from the clinical development program which used exclusively EU-approved Remicade to support a demonstration of biosimilarity to US-licensed Remicade (for additional considerations on the use of data generated using a non-US-licensed comparator product, refer to Section Background, The Reference Product (above). Additional supportive PK data were provided from two dosing regimens in two distinct patient populations (3 mg/kg in combination with MTX in patients with RA and 5 mg/kg as monotherapy in patients with AS) comparing CT-P13 and EU-approved Remicade, and single dose of 5 mg/kg in healthy subjects comparing CT-P13, EU-approved Remicade, and US licensed Remicade.

Conclusions

Overall, the submitted clinical pharmacology studies are adequate to:

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

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

6. Clinical Microbiology

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

No new microbiology information has been submitted in this re-submission. The relevant microbiology data were submitted and reviewed during the first review cycle. The microbiology review team concluded that the drug product is recommended for approval from sterility assurance and product quality microbiology perspective. I concur with this recommendation.

7. Clinical/Statistical- Efficacy

Clinical Primary Reviewer: Juwaria Waheed, M.D.

Statistical Primary Reviewer: Gregory Levin, Ph.D.

Statistical Team Leader: Ruthanna Davi, Ph.D.

The relevant clinical efficacy data were submitted and reviewed during the first review cycle and are only summarized in this memorandum below.

The applicant submitted results from eight completed clinical studies. A summary of the key design features of these studies is provided in Table 1.

Table 1. Key Design Features of CT-P13 Clinical Studies

Protocol Duration (Dates conducted)	Design Objectives	Patient Population Total Number	Treatment Arms	Number per arm
Controlled Studies in Patients				
CT-P13 3.1 (Global, ex-US) 54 weeks (12/10-07/12)	R, DB, PG Comparative Clinical Study: <i>Efficacy, Safety, PK, Immunogenicity</i>	Moderate to Severe RA, MTX-IR N=606	CT-P13 3 mg/kg+ MTX EU-approved Remicade + MTX	n=302 n=300
CT-P13 1.1 (Global, ex-US) 54 weeks (12/10-07/12)	R, DB, PG <i>PK, Efficacy, Safety, Immunogenicity</i>	Moderate to severe AS N=250	CT-P13 5 mg/kg EU-approved Remicade	n=128 n=122
B1P13101 (Japan) 54 weeks (10/11-06/13)	R, DB, PG <i>PK, Efficacy, Safety, Immunogenicity</i>	Moderate to Severe RA, MTX-IR N=108	CT-P13 3 mg/kg+ MTX EU-approved Remicade + MTX	n=51 n=53
CT-P13 1.2 (Philippines) 54 weeks (04/10-08/12)	R, DB, PG Pilot Study: <i>Efficacy, Safety</i>	Moderate to Severe RA, MTX-IR N=19	CT-P13 3 mg/kg+ MTX EU-approved Remicade + MTX	n=9 n=9
CT-P13 3.3 (Russia) 54 weeks (12/12-10/13*)	R, DB, PG Local Registration Study: <i>Efficacy, Safety</i>	Moderate to Severe RA, MTX-IR N=15	CT-P13 3 mg/kg+ MTX EU-approved Remicade + MTX	n=6 n=9
Controlled Studies in Healthy Volunteers				
CT-P13 1.4 Single Dose (10/13-02/14)	R, DB, PG, SD 3-way PK Bridging <i>PK, Safety, Immunogenicity</i>	Healthy volunteers N=213	CT-P13 5 mg/kg EU-approved Remicade 5 mg/kg US-licensed Remicade 5 mg/kg	n=71 n=71 n=71
Extension Studies				
CT-P13 3.2 (~1year) (02/12-07/13)	OLE: <i>Safety, Immunogenicity</i>	RA, Enrolled from controlled study CT-P13 3.1 N=302	CT-P13 maintenance CT-P13 transitioned from EU- approved Remicade	n=158 n=144
CT-P13 1.3 (~1year) (03/12-06/13)	OLE: <i>Safety, Immunogenicity</i>	AS, Enrolled from controlled study CT-P13 1.1 N=174	CT-P13 maintenance CT-P13 transitioned from EU- approved Remicade	n=88 n=86
¹ EU-approved Remicade; ² US-licensed Remicade; *~30-week data; DB: double blind, IR: inadequate responder; MTX: methotrexate, OLE: open label extension, PG: parallel-group, PK: pharmacokinetics, R: randomized, SD: single dose				

Celltrion submitted one comparative clinical study in patients with RA (study 3.1), one key supportive study in patients with AS (study 1.1), and three additional studies in patients with RA that evaluated efficacy and safety endpoints in support of licensure of CT-P13. Of note, the efficacy data are derived from clinical studies using EU-approved Remicade as the

comparator. However, Celltrion has provided a robust analytical and clinical PK bridging data (study 1.4) between US-licensed Remicade and EU-approved Remicade and CT-P13 to justify the relevance of comparative data generated using EU-approved Remicade to support a demonstration of the biosimilarity of CT-P13 to US-licensed Remicade.

For detailed review of the study design, including selection of a similarity margin, study conduct, and efficacy findings, and handling of missing data, the reader is referred to the CDTL memorandum of the first review cycle.

The FDA statistical review team concluded that the applicant has provided statistically robust comparative efficacy data demonstrating similar efficacy between CT-P13 and EU-approved Remicade in patients with moderate-to-severe RA despite methotrexate, using 3 mg/kg dosing on methotrexate background, and in patients with moderate-to-severe AS, using 5 mg/kg dosing monotherapy. The primary analysis was supported by the analysis of key secondary endpoints and sensitivity analyses accounting for the missing data. The FDA statistical and clinical review teams concluded, and I concur, that the results from the CT-P13 clinical program support a conclusion of no clinically meaningful differences between CT-P13 and US-licensed Remicade in the indications studied.

8. Safety

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

- **Safety Update**

This re-submission includes updated clinical safety data from ongoing open-label studies and registries in RA, AS, and IBD. The status and key design features of these studies are summarized in Table 2. The accumulated clinical safety from ongoing registries and observational studies in RA, AS, and IBD, submitted by Celltrion, appears consistent with the safety seen in CT-P13 clinical development program and known safety profile of US-licensed Remicade. No new safety signals have been identified. No new clinical safety information was submitted from the core clinical studies supporting the application. The relevant clinical safety data from those studies were submitted and reviewed during the first review cycle.

Table 2. Ongoing Open-label Studies and Registries using CT-P13

Protocol Duration	Design	Number of Patients
Study 4.2 RA registry in EU and Korea	Observational, cohort study in patients with RA	N=179
Study 4.3 IBD registry in EU and Korea	Observational, cohort study in patients with IBD	N=54
Study 4.4 AS registry in EU and Korea	Observational, cohort study in patients with AS	N=164
Korean Post-Marketing Surveillance (PMS) study in Korea	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: Adapted from Dr. Juwaria Waheed’s clinical review RA: Rheumatoid Arthritis, EU: European Union, IBD: Inflammatory Bowel Disease, AS: Ankylosing Spondylitis		

- **Immunogenicity**

Clinical Pharmacology Reviewer: Lei He, Ph.D.

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

Clinical Primary Reviewer: Juwaria Waheed, M.D.

Immunogenicity Reviewer: William Hallett, Ph.D.

Immunogenicity Team Leader (acting): Harold Dickensheets, Ph.D.

An application submitted under section 351(k) of the PHS Act must contain, among other things, information demonstrating that the biological product is biosimilar to a reference product based upon data derived from “a clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product.”¹⁰ Consistent with these provisions, immunogenicity was assessed prospectively in CT-P13 clinical program using a validated ELISA method (study 1.4) and ECLA assay (studies 1.4, 1.1, and 3.1). These data were reviewed and discussed in the CDTL memorandum from the first review cycle and are only summarized below.

In the controlled studies (studies 1.1 in AS and 3.1 in RA), the rates of immunogenicity, assessed as the proportion of anti-drug antibody (ADA) positive patients, at all time points, were similar between the CT-P13 and EU-Remicade treatment groups. In the two extension

¹⁰ Section 351(k)(2)(A)(i)(I)(cc) of the PHS Act.

studies (studies 1.3 in AS and 3.2 in RA), the rates of ADA positivity were also similar between patients who underwent a single transition from EU-approved Remicade to CT-P13 and those who remained on CT-P13, providing re-assurance that non-treatment-naïve patients could be transitioned safely to CT-P13. Of note, the RA patients had concomitant immunosuppression with methotrexate, and the AS patients were not on any background immunosuppressive therapies. Overall, assessment of anti-drug antibody incidence at multiple time points in clinical study populations reflects the proposed chronic administration of CT-P13. In both CT-P13 and EU-approved Remicade groups, the ADA formation had similar impact on exposure, efficacy parameters, and immune-mediated safety outcomes including infusion reactions and anaphylaxis indicating that the ADA formation does not differentially impact safety or efficacy between patients treated with CT-P13 and EU-approved Remicade.

As noted in the reviews of the first review cycle, in the only completed study comparing immunogenicity of CT-P13 with US-licensed Remicade, some numerical differences were seen in the incidence and titer of ADA formation. Screening assay ADA titers were overlapping between US-licensed and EU-approved Remicade, but trended higher (though still overlapping) with CT-P13. All of the screening assay positive ADAs were confirmed to be neutralizing antibodies. The neutralizing antibody titers were also numerically higher when CT-P13 was compared to either US-licensed Remicade or EU-approved Remicade. However, no assay-related or subject-related factors could be identified to explain the reported differences. Detailed review of the potential product-related factors that could have contributed to the observed differences in ADA formation in study 1.4 identified a relatively higher content of subvisible particulates (1 to 5 µm) in CT-P13 compared to US-licensed Remicade lots used in study 1.4 which was the foundation for the deficiency comment #1 (see section Background, *Relevant Regulatory History* above) precluding approval during the first review cycle. In this re-submission, Celltrion has adequately addressed this deficiency as discussed in section CMC above.

To supplement the immunogenicity information from study 1.4 (single dose of the same products in healthy subjects) and to alleviate concerns about the lower immunogenicity rates observed in subjects who received US-licensed Remicade compared to those who received either CT-P13 or EU-approved Remicade in study 1.4, during the review of this re-submission, Celltrion submitted interim clinical immunogenicity data from an ongoing randomized, controlled study 3.4 in patients with Crohn's disease. This study was not a part of the clinical program originally submitted to support the 351(k) BLA, therefore the study is discussed in more detail below. Study 3.4 is an ongoing randomized, double-blind, controlled 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. 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: US-licensed Remicade or EU-approved Remicade followed by CT-P13 at Week 30,
- Group 3: US-licensed Remicade or EU-approved Remicade only,

- Group 4: CT-P13 followed by US-licensed Remicade or EU-approved 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 3. At baseline, all patients were ADA negative except 1 patient 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.

Table 3. 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

Analysis of Immunogenicity in CT-P13 Clinical Program

As discussed above, numerical imbalances in the incidence and titer of ADA were seen between CT-P13 and US-licensed Remicade in study 1.4. In evaluating the significance of these imbalances, I considered the following:

- The imbalance in ADA incidence and antibody titers seen in study 1.4 was not associated with a difference in PK.
- The low incidence of immunogenicity with US-licensed Remicade (3% by ECLA or 11% by ELISA) in study 1.4 is not consistent with the published data (Udata et al 2014) comparing US-licensed Remicade and EU-approved Remicade, which showed similarly high immunogenicity after a single-dose (28% and 33% ADA positive, respectively) in healthy volunteers and the 10 to 50% immunogenicity rates reported in the US-licensed Remicade USPI. This raises questions about whether study 1.4 results might be an artifact of sampling a limited range of US-licensed Remicade lots.
- Given that a scientific bridge has been established to justify the relevance of clinical data generated using EU-approved Remicade:
 - Using the same ECLA assay, the apparent differences in immunogenicity between CT-P13 and EU-approved Remicade observed in study 1.4 (14.3% vs 7%, respectively) were not consistent with the similar immunogenicity rates between the two products at all time points in the larger clinical studies 3.1 and 1.1 where two distinct patient populations, RA and AS, were administered two different approved dosing regimens (either 3 mg/kg of study product on the background of methotrexate or a monotherapy of 5 mg/kg of study product, respectively).
 - The ADA formation impacted safety and efficacy similarly in CT-P13 and EU-approved Remicade treated patients in clinical studies 3.1 and 1.1.
 - Immunogenicity and hypersensitivity reactions did not appear to increase after a single transition from EU-approved Remicade to CT-P13 in studies 3.2 and 1.3.
- As discussed in the CMC section, the analyses of product quality attributes that could potentially result in higher immunogenicity, such as subvisible particles, support the conclusion that CT-P13 is highly similar to US-licensed Remicade and confirm the relevance of clinical immunogenicity data from comparative studies using EU-approved Remicade.
- The interim analysis of immunogenicity from the ongoing study 3.4 indicates comparable incidence of ADA formation between CT-P13 and US-licensed Remicade in patients with IBD treated with 5 mg/kg dosing regimen.

In light of these additional contextual pieces, I do not believe that the results of study 1.4 are likely to represent clinically meaningful differences between US-licensed Remicade and CT-P13. Therefore, there are sufficient data supporting similar immunogenicity between CT-P13, EU-approved Remicade, and US-licensed Remicade and that immunogenicity data adds to the totality of the evidence to support a demonstration of no clinically meaningful differences between CT-P13 and US-licensed Remicade.

- **Overall Conclusion on Safety and Immunogenicity**

The review team and I are in agreement that the currently submitted safety data and analyses are adequate to inform the conclusion of no clinically meaningful differences between CT-P13 and EU-approved Remicade in patients with RA and AS. The submitted safety and

immunogenicity data and analyses using two dosing regimens (3 mg/kg and 5 mg/kg) either as a monotherapy or in combination with methotrexate, in two distinct patient populations, are adequate to support the conclusion of no clinically meaningful differences between CT-P13 and US-approved Remicade in patients with RA and AS. The safety database submitted for CT-P13 is adequate to provide a reasonable descriptive comparison between the two products. The analysis of the data indicates a safety profile of CT-P13 similar to that of US-licensed Remicade. There were no notable differences between CT-P13 and EU-approved Remicade in treatment-emergent adverse events, serious adverse events, adverse events leading to discontinuations, and deaths between the treatment groups. A numerical imbalance in serious infections, driven by several cases of tuberculosis and pneumonia, was observed in the controlled studies. The differences were small, and serious infections, including tuberculosis, are well-recognized risks with TNF-inhibition as indicated in the Boxed Warning for this class of biological products. No cases of drug-induced liver injury were reported in CT-P13 clinical program. No new safety signals have been identified. The FDA safety analysis is in agreement with the applicant's. The accumulated clinical safety from ongoing registries and observational studies in RA, AS, and IBD, submitted by Celltrion, appears consistent with the safety seen in CT-P13 clinical development program and the known safety profile of US-licensed Remicade. The clinical safety and immunogenicity data support the conclusion that no clinically meaningful differences exist between CT-P13 and US-licensed Remicade in terms of the safety, purity, and potency of the product.

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

Celltrion seeks licensure for the same indications for which US-licensed Remicade is licensed (listed in Introduction section above). The CT-P13 clinical program however, provides clinical efficacy and safety data primarily from clinical studies in patients with RA and AS. Therefore, in this memorandum, the considerations for extrapolation of data to support biosimilarity to the other indications for which Celltrion is seeking licensure (PsA, PsO, adult and pediatric CD, and adult and pediatric UC), reflect the collaborative review among multiple review disciplines and subject matter experts, including review teams from DGIEP and DDDP.

The Agency has determined that it may be appropriate for a biosimilar product to be licensed for one or more additional conditions of use (e.g., indications) for which the reference product is licensed, based on data from a clinical study(ies) performed in only one condition of use. This concept is known as extrapolation. As described in the Guidance for Industry: "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009", if a biological product meets the statutory requirements for licensure as a biosimilar product under section 351(k) of the PHS Act based on, among other things, data derived from a clinical study or studies sufficient to demonstrate safety, purity, and potency in an appropriate condition of use, the applicant may seek licensure for one or more additional conditions of use for which the reference product (i.e., US-licensed

Remicade) is licensed.⁴ The applicant would need to provide sufficient scientific justification for extrapolating clinical data to support a determination of biosimilarity for each condition of use for which licensure is sought.

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

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

As a scientific matter, the FDA has determined that differences between conditions of use with respect to the factors described above do not necessarily preclude extrapolation. A scientific justification should address these differences in the context of the totality of the evidence supporting a demonstration of biosimilarity. Consistent with the principles outlined in the above FDA guidance, Celltrion has provided a justification for the proposed extrapolation of clinical data from studies in RA and AS to each of the other indications approved for US-licensed Remicade, as summarized in this section.

First, Celltrion has provided data to demonstrate that CT-P13 is highly similar to US-licensed Remicade based on extensive analytical characterization data. Celltrion has also provided clinical pharmacokinetics, and efficacy, safety, and immunogenicity data in an approved indication, in this case, clinical data in both RA and AS, to demonstrate that no clinically meaningful differences exist between CT-P13 and US-licensed Remicade.

Further, I considered the following additional points in the scientific justification for extrapolation of data to support biosimilarity in the indications for which Celltrion is seeking licensure (PsA, PsO, adult and pediatric CD, and adult and pediatric UC) include:

- No notable differences were observed in PK parameters for US-licensed Remicade in CD patients, as compared to patients with other conditions of use, including RA and PsO. Additionally, PK characteristics were similar between pediatric and adult patients with CD or UC following the administration of 5 mg/kg US-licensed Remicade.⁵ Since similar PK was demonstrated between CT-P13 and US-licensed Remicade in healthy subjects and between CT-P13 and EU-approved Remicade in two different usage scenarios, i.e., in patients with RA receiving 3 mg/kg infliximab with concomitant use of methotrexate and in patients with AS receiving 5 mg/kg but without concomitant

⁴Guidance for Industry “Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009”, April 2015

<http://www.fda.gov/downloads/Drugs/Guidances/UCM273001.pdf>

⁵Remicade USPI

immunosuppressive therapy, (please refer to the Clinical Pharmacology section of this document for details), a similar PK profile would be expected for CT-P13 in patients with PsA, PsO, adult and pediatric CD, and adult and pediatric UC.

- In general, immunogenicity of the US-licensed Remicade was affected primarily by the use of concomitant immunosuppressive therapy across different indications rather than by patient population, and the results were influenced by the type of immunoassay used. In PsA, PsO, adult and pediatric CD, and adult and pediatric UC, the recommended dose is 5 mg/kg. Infliximab is used without methotrexate in PsO and may be used with or without concomitant immunosuppression in PsA, CD and UC. These usage scenarios were assessed in Celltrion's RA study (concomitant use of methotrexate) and Celltrion's AS study (use of the higher dose of 5 mg/kg, but without concomitant immunosuppressive therapy). As stated previously in this document, the Agency has concluded that there is sufficient data to support similar immunogenicity between CT-P13, EU-approved Remicade, and US-licensed Remicade, and that there are no notable differences in immunogenicity among these products. Furthermore, an interim analysis of the ongoing post-marketing study in patients with CD showed similar incidence of ADA formation between CT-P13 and US-licensed Remicade in patients following the administration of 5 mg/kg dosing regimen (please refer to the Immunogenicity section of this document for details). Accordingly, similar immunogenicity would be expected for patients with PsA, PsO, adult and pediatric CD, and adult and pediatric UC, receiving CT-P13.
- The mechanism(s) of action (MOA) relevant to the extrapolation of data to support biosimilarity in specific indications are discussed below.

Table 4. Known and Potential (Likely or Plausible) Mechanisms of Action of US-licensed Remicade in the Licensed Conditions of Use

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

Source: FDA summary of existing literature on the topic of mechanisms of action of US-licensed Remicade^{6,7}

Extrapolation of Data to Support Biosimilarity in PsO, PsA

The primary MOA of infliximab is direct binding and blocking of TNF receptor-mediated biological activities (see Table 4 above). Infliximab binds to both soluble (s) and transmembrane (tm) TNF, thus blocking TNF binding to its receptors TNFR1 and TNFR2 and the resulting downstream pro-inflammatory cascade of events. The scientific literature indicates that this MOA is the primary MOA in RA, AS, PsA, PsO. The data provided by Celltrion showed similar TNF binding and potency to neutralize TNF-α, supporting the demonstration of analytical similarity pertinent to this MOA.

Therefore, based on the above considerations, the DDDP review team concluded, and I agree, that the scientific justification for extrapolating the clinical data supports a finding of biosimilarity for CT-P13 and US-licensed Remicade to PsO.

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

⁶ Oikonomopoulos A et al., “Anti-TNF Antibodies in Inflammatory Bowel Disease: Do We Finally Know How it Works?”, *Current Drug Targets*, 2013, 14, 1421-1432

⁷ Tracey D et al., “Tumor necrosis factor antagonist mechanisms of action: A comprehensive review”, *Pharmacology & Therapeutics* 117 (2008) 244–279

TNF plays a central role in the pathogenesis of the IBD indications (adult and pediatric ulcerative colitis, and adult and pediatric Crohn's Disease), and TNF inhibition is important in treating the diseases, as evidenced by the efficacy of the approved TNF monoclonal antibodies, but the detailed cellular and molecular mechanisms involved have not been fully elucidated.⁸ However, the available scientific evidence suggests that for TNF inhibitors in IBD, in addition to binding and neutralization of sTNF, other MOA, listed in Table 4 may play a role.⁹ Binding to sTNF and tmTNF involves the Fab region of the antibody, while the other plausible mechanisms of action involve the Fc region of the molecule.

As outlined in the CMC section above, Celltrion provided experimental data supporting a conclusion that CT-P13 and US-licensed Remicade are highly similar based on extensive structural and functional analytical characterization. Further, Celltrion addressed each of the known and potential mechanisms of action of US-licensed Remicade listed in Table 4. As noted in the CMC section above, there were small differences between CT-P13, US-licensed Remicade, and EU-approved Remicade in glycosylation (a-fucosylation), FcγRIII binding, and some NK-based ADCC assays.

In considering whether the apparent fractional FcγRIII binding/ADCC differences between CT-P13 and US-licensed Remicade may translate into a clinically meaningful difference in IBD, the Agency has considered the following:

- The biological functions that the subtle FcγRIII binding differences might impact, namely ADCC, are within the quality range of Celltrion's data on US-licensed Remicade.
- The mechanism of action of TNF inhibitors in treating IBD is complex and, as summarized in Table 4, ADCC is only one of the several plausible mechanisms of action. It is noteworthy that products without any ADCC capability have been approved for the treatment of patients with Crohn's Disease (i.e. certolizumab). The possible ADCC difference between CT-P13 and US-licensed Remicade is small, and Celltrion has also provided data to demonstrate analytical similarity in all the other potential mechanisms of action of infliximab in IBD.
- The historical IBD clinical trial design, including those for Remicade, often utilized doses and timing of primary endpoint assessments that are in the therapeutic plateau, and thus clinical outcome measures (e.g., clinical response, clinical remission) lack discriminative capacity to assess the effect of small differences in ADCC and FcγRIII binding.

Therefore, based on the above considerations, the DGIEP review team concluded, and I agree, that the scientific justification for extrapolating the clinical data supports a

⁸ Oikonomopoulos A et al., "Anti-TNF Antibodies in Inflammatory Bowel Disease: Do We Finally Know How it Works?", *Current Drug Targets*, 2013, 14, 1421-1432

⁹ Tracey D et al., "Tumor necrosis factor antagonist mechanisms of action: A comprehensive review", *Pharmacology & Therapeutics* 117 (2008) 244-279

finding of biosimilarity for CT-P13 and US-licensed Remicade to IBD conditions of use.

In aggregate, my conclusion is that the evidence indicates that the extrapolation of clinical data to the additional indications for which Celltrion is seeking licensure (PsA, PsO, adult and pediatric CD, and adult and pediatric UC¹⁰), is scientifically justified and supports licensure of CT-P13 as a biosimilar product to US-licensed Remicade (b) (4).
CT-P13 is eligible for licensure for certain indications (PsA, PsO, adult and pediatric CD, and adult UC).

10. Advisory Committee Meeting

An Advisory Committee (AC) meeting was determined to be necessary to obtain independent expert advice on issues related to analytical similarity assessment and extrapolation to non-studied indications. The AC meeting was scheduled for March 17, 2015. However, due to information requests pending with Celltrion the AC was postponed.¹¹ Since then, the Applicant has adequately addressed these requests and the AC meeting was convened on February 09, 2016. The following is a brief summary of the questions to the committee and surrounding discussions. The reader is also referred to the full transcript of the meeting that is available at:

<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM490414.pdf>

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?

Committee Discussion: Overall, the committee indicated that CT-P13 does seem to be highly similar to the reference product. One panel member expressed that there is uncertainty about the glycoform differences and the effect on fragment crystallizable (Fc) receptors and antibody-dependent cellular cytotoxicity (ADCC). There were also questions raised regarding the missing data in the clinical studies and how that may impact the result from the clinical studies. One member stated that there are some analytical differences in the products (e.g. average levels of aggregates or charge isoforms). The member was unsure if they were clinically inactive components in terms of impact on clinical outcome, but noted that they were at levels comparable to other biotechnology products. Another panel member stated that with some of the highly complex assays, it would have been nice to have actual values rather than just averaged or normalized results. Please see the transcript for details of the committee discussion.

¹⁰ Remicade's indication for pediatric ulcerative colitis is protected by orphan drug exclusivity expiring on September 23, 2018. Accordingly, FDA will not license CT-P13 for this indication until the orphan drug exclusivity expires.

¹¹ <https://www.gpo.gov/fdsys/pkg/FR-2015-03-11/pdf/2015-05527.pdf>

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))?

Committee Discussion: In general, the committee indicated that there were no clinically meaningful differences between CT-P13 and US-licensed Remicade in the studied conditions of use (RA and AS). One committee member raised a question about the similarity margin used. Other committee members stated that despite the evidence, there is still uncertainty about multiple switching between the biosimilar and the reference product from both the patient and provider perspectives. Please see the transcript for details of the committee discussion.

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)¹²)? If not, please state the specific concerns and what additional information would be needed to support extrapolation. Please discuss by indication if relevant.

Committee Discussion: The overall consensus of the committee was that there was adequate scientific justification to support extrapolation of the data from comparative clinical studies in RA and AS to support a determination of biosimilarity of CT-P13 for the additional indications. However, there was some reservation amongst the committee relating to extrapolation of the data to Crohn's Disease, Ulcerative Colitis and specifically pediatric Ulcerative Colitis due to the limited clinical data in these indications. Some committee members suggested that additional clinical trials should be done in these populations, while others pointed out that the point of the 351(k) approval pathway would be compromised if these additional studies were required. Several committee members stated that the benefits of extrapolation to society as a whole, in terms of access, were worth the perceived risks of extrapolation. Please see the transcript for details of the committee discussion.

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)?

Vote Result: Yes = 21 No = 3 Abstain = 0

¹² 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 license CT-P13 for this indication until the orphan exclusivity expires.

- 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.

Committee Discussion: The majority of the committee voted “Yes”, agreeing that based on the totality of the evidence, CT-P13 should receive licensure as a biosimilar product for each of the indications for which it is eligible. The committee as a whole stated that the total package showed a large number of analytical techniques proving that the threshold for highly similar had been met. One committee member noted that even though there are some residual concerns with extrapolation, it was worth taking the risk to provide new products that may reduce the cost of bringing drugs to the market and in turn may have a reduced cost to patients since the evidence of biosimilarity was compelling. The 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.

11. Pediatrics

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

Under the Pediatric Research Equity Act (PREA), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable. Section 505B(m) of the FD&C Act added by section 7002(d)(2) of the Affordable Care Act, provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a “new active ingredient” for purposes of PREA, and a pediatric assessment is required unless waived or deferred..

Following revisions to the initial pediatric study plan (iPSP), based on Agency’s feedback, Celltrion submitted an agreed iPSP to address the PREA requirements for each of the indications for which they are seeking licensure, as detailed below:

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

[REDACTED]

The applicant has also submitted requests for waiver of the requirement to submit a pediatric assessment for (1) patients ages 2 to < 4 years old because CT-P13 does not represent a meaningful therapeutic benefit over existing

therapies and is not likely to be used in a substantial number of pediatric patients with the condition and (2) patients < 2 years old because condition is rare in this age group and such studies would be impossible or highly impracticable.

- Ankylosing Spondylitis (AS), Psoriatic Arthritis (PsA): The applicant has submitted requests for waiver of the requirement to submit a pediatric assessment for juvenile AS and juvenile PsA because the studies would be impossible or highly impracticable due to the difficulty of making specific diagnoses of juvenile PsA or juvenile AS in the pediatric age range.
- Crohn's Disease (CD), Pediatric CD, Ulcerative Colitis (UC), (b) (4): With this 351(k) BLA, Celltrion proposed that the pediatric assessment is fulfilled for pediatric CD (b) (4) patients 6 years of age and older, by satisfying the statutory requirements for showing biosimilarity and providing an adequate scientific justification for extrapolating the pediatric information from the reference product to CT-P13. (b) (4)

The applicant has also requested a waiver of the requirement to submit a pediatric assessment for pediatric CD (b) (4) patients younger than 6 years of age because such studies are impossible or highly impracticable. As a scientific matter, DGIEP has determined that, based on recent epidemiologic data, a pediatric assessment for pediatric CD (b) (4) patients should be conducted in patients 2 years and older, as opposed to previously recommended cut-off of 6 years of age and older. DGIEP however, acknowledges that in this case, dedicated pediatric studies in pediatric CD (b) (4) patients in only ages 2 to 5 years old would be impossible or highly impracticable due to the low incidence of the disease in this pediatric age group.

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

The CT-P13 pediatric study plan was discussed at the Pediatric Review Committee (PeRC) meeting on April 29, 2015 during the first review cycle and on February 24, 2016 for this re-submission. The PeRC agreed that the pediatric assessment is complete for (b) (4). PeRC also recommended granting the requested waiver of the requirement to submit a pediatric assessment for pediatric CD (b) (4) patients 2 to 5 years old because dedicated pediatric studies in this age group, for this product, would be

impossible or highly impracticable due to the low incidence of the disease in this pediatric age group. The PeRC also agreed with the proposal to grant the other waivers discussed above.

12. Other Relevant Regulatory Issues

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

13. Labeling

- **Proprietary name**

The initially proposed proprietary name for CT-P13 was (b) (4). This name has been reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) and by the Office of Prescription Drug Promotion (OPDP, formerly the Division of Drug Marketing and Advertising) and was found to be conditionally acceptable. Subsequently, on November 27, 2014, the applicant proposed a second proprietary name, Inflectra. The applicant clarified that

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

- **Non-proprietary/Proper name**

FDA has determined that the use of a distinguishing suffix in the nonproprietary name for Celltrion's Inflectra product is necessary to distinguish this proposed product from Remicade (infliximab). As explained in FDA's draft Guidance for Industry, Nonproprietary Naming of Biological Products,¹³ FDA expects that a nonproprietary name that includes a distinguishing suffix will facilitate safe use and optimal pharmacovigilance of biological products. FDA advised Celltrion to provide proposed suffixes in accordance with the draft guidance.

On November 17, 2015, Celltrion submitted a list of suffixes, in their order of preference, to be used in the nonproprietary name of CT-P13 along with supporting analyses to demonstrate that the proposed suffixes satisfy the factors described in section V of the draft guidance. The DMEPA review concluded, and I agree, that Celltrion's proposed suffix "-dyyb" (infliximab-dyyb) is acceptable and should be reflected in the product label and labeling accordingly.

Of note, FDA's determination does not constitute or reflect a decision on a general naming policy for biological products, including biosimilars. FDA issued draft guidance on Nonproprietary Naming of Biological Products in August 2015, and the Agency is carefully considering the comments submitted to the public docket as we move forward in finalizing the draft guidance.¹⁴ As a result, the nonproprietary name is subject to change to the extent that it is inconsistent with any general naming policy for biological products established by FDA. Were the name to change, FDA intends to work with Celltrion to minimize the impact this would have to its manufacture and distribution of this product.

¹³ See the FDA draft guidance for industry on Nonproprietary Naming of Biological Products (August 2015). When final, this guidance will represent FDA's current thinking on this topic. The guidances referenced in this document are available on the FDA Drugs guidance Web page at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf>

¹⁴ FDA has received several citizen petitions directed to the nonproprietary naming of biosimilar products. The citizen petition submitted by Johnson & Johnson requests that FDA require biosimilar products to bear nonproprietary names that are similar to, but not the same as, those of their reference products or of other biosimilars (see Docket No. FDA-2014-P-0077). The citizen petitions submitted by the Generic Pharmaceutical Association and Novartis request that FDA require biosimilar products to be identified by the same nonproprietary name as their reference products (see Docket Nos. FDA-2013-P-1153 and FDA-2013-P-1398). Although FDA is designating a proper name that contains a distinguishing suffix for Inflectra, FDA is continuing to consider the issues raised by these citizen petitions, the comments submitted to the corresponding public dockets, and comments submitted to the dockets for the draft guidance for industry Nonproprietary Naming of Biological Products (August 2015) and the proposed rule, Designation of Official Names and Proper Names for Certain Biological Products (80 FR 52224), with respect to establishing a general naming convention for biological products.

- **Physician labeling**

The applicant proposed labeling that incorporated relevant data and information from the labeling of US-licensed Remicade. In addition, the applicant proposed inclusion in:

- (1) Section 6.1, Adverse Reactions: [REDACTED] (b) (4)
- (2) Section 12.3, Pharmacokinetics:
 - Study description and pharmacokinetic data from study 1.4 in healthy volunteers, and
 - A summary statement on pharmacokinetic data from studies 3.1 in RA, [REDACTED] (b) (4)
- (3) Section 14, Clinical Studies:
 - Study description and efficacy results, including clinical response, radiographic response, and physical function from study 3.1 in RA
 - Study description [REDACTED] (b) (4) and efficacy results from study 1.1 in AS in Section 14, Clinical Studies.

If approved, CT-P13 will be the second biosimilar product on the US market. As such, its labeling was reviewed by the Agency in the context of an evolving policy on labeling for biosimilar products. A biosimilar product is not required to have the “same” labeling as its reference product, and the Agency recommends that biosimilar product labeling incorporate relevant data and information from the reference product labeling, with appropriate product-specific modifications. The CT-P13 review team considered that the format and content of labeling for CT-P13 should be consistent with the current Remicade labeling, with appropriate product-specific modifications, based on the following considerations:

- A conclusion that CT-P13 is a biosimilar to US-licensed Remicade.
- US-licensed Remicade PLR labeling is scientifically accurate and provides sufficient information to ensure the safe and effective use of the product.
- A similar approach was taken with the labeling of Zarxio, the first FDA-approved biosimilar product.

The Office of New Drugs (OND) Labeling Development Team has noted areas of the US-licensed Remicade labeling that may not be consistent with current general labeling recommendations and provided recommendations for the CT-P13 labeling to be optimized for clarity or organization.

Acknowledging these recommendations, the CT-P13 labeling will be consistent with the content and format of the current FDA-approved labeling for US-licensed Remicade, with appropriate product-specific modifications (such as nomenclature differences and omission of certain data and information [REDACTED] (b) (4)). This approach is informed by the consideration that biosimilar product labeling that is consistent with the reference product labeling should more clearly convey the Agency’s conclusion that the two products are highly similar and there are no clinically meaningful differences. Further, because the objectives of a 351(k) application are to establish biosimilarity and not to independently establish safety of effectiveness of the product, inclusion in the proposed labeling of the

(b) (4) is not warranted and will not be included. Of note, these product-specific data for CT-P13 were presented at the Arthritis Advisory Committee on February 09, 2016¹⁵ and FDA’s review of these data will be publically available after licensure as part of the FDA “action package” for the public to review.

As discussed above in the DMEPA review and recommendations, the proprietary name “Inflectra”, and the non-proprietary name “infliximab-dyyb” should be reflected in the product labeling as appropriate.

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

As discussed above.

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

As discussed above in the DMEPA review and recommendations, the proprietary name “Inflectra”, and the non-proprietary name “infliximab-dyyb” should be reflected in the product carton and immediate container label as appropriate.

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

The applicant proposed a Patient labeling/Medication guide closely tracking that of US-licensed Remicade. The proprietary name “Inflectra” and the non-proprietary name “infliximab-dyyb” should be reflected in the product Patient labeling/Medication guide as appropriate.

14. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

I recommend approval of the 351(k) BLA 125,544 for CT-P13 to receive licensure as a biosimilar product to US-licensed Remicade for each of the following indications for which US-licensed Remicade is currently licensed and CT-P13 is eligible for licensure: RA, AS, PsA, PsO, adult CD, pediatric CD, and adult UC.

- **Totality of the Evidence**

Celltrion submitted comparative analytical data on the CT-P13 lots used in clinical studies intended to support a demonstration of biosimilarity (“clinical product lots”) and on the

¹⁵<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/ucm481975.htm>

proposed commercial product. The Applicant has adequately addressed the deficiencies identified from the first review cycle. Based on the review of the data provided, Celltrion's comparative analytical data for CT-P13 demonstrates that it is highly similar to the reference product (US-licensed Remicade) notwithstanding minor differences in clinically inactive components.

Celltrion used a non-US-licensed comparator (European Union-approved Remicade (EU-approved Remicade)) in some studies intended to support a demonstration of biosimilarity to the US-licensed reference product. Accordingly, Celltrion was required to scientifically justify the relevance of that data by establishing an adequate scientific bridge between EU-approved Remicade, the US-licensed reference product and CT-P13. Review of an extensive battery of test results provided by Celltrion confirmed the relevance of comparative clinical and non-clinical data with EU-approved Remicade to support conclusions of biosimilarity to US-licensed Remicade.

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

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

In considering the totality of the evidence, the data submitted by Celltrion show that CT-P13 is highly similar to US-licensed Remicade, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between CT-P13 and US-licensed Remicade in terms of the safety, purity, and potency of the product, to support the conclusion that CT-P13 is biosimilar to the US-licensed Remicade in the studied indications of RA and AS.

The applicant has also provided an extensive data package to address the scientific considerations for extrapolation of data to support biosimilarity to other conditions of use and licensure of CT-P13 for each of the seven indications for which US-licensed Remicade is currently licensed and for which CT-P13 is eligible for licensure. Further, the applicant has provided data that support the conclusion that CT-P13 and US-licensed Remicade have the

same mechanisms of action for each of the requested indications, to the extent that the mechanisms of action are known or can reasonably be determined.

This 351(k) BLA was discussed at an Arthritis Advisory Committee on February 09, 2016 as detailed in section Advisory Committee Meeting above. The committee agreed (21 “Yes”, vs 3 “No”) 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 following indications for which US-licensed Remicade is currently licensed and CT-P13 is eligible for licensure: RA, AS, PsA, PsO, adult CD, pediatric CD, and adult UC.

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

In August 2011, FDA released Remicade from its previously approved Risk Evaluation and Management Strategy (REMS) and determined that “maintaining the Medication Guide as part of the approved labeling is adequate to address the serious and significant public health concern and meets the standard in 21 CFR 208.1” (see August 1, 2011, letter, available at Drugs@FDA). Accordingly, at this time, a Medication Guide for patients, which is included in CT-P13 labeling, is appropriate, should CT-P13 be approved as a biosimilar.

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

Not applicable.

- **Recommended Comments to Applicant**

None

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

/s/

NIKOLAY P NIKOLOV
04/05/2016