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APPLICATION NUMBER:

125544Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sarah Yim, M.D. Supervisory Associate Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) Badrul Chowdhury, M.D, Ph.D. Director, DPARP
Subject	Division Director Summary Review
BLA #	351(k) BLA 125544
Applicant Name	Celltrion, Inc.
Date of Original Submission	August 08, 2014, Complete Response June 8, 2015
Date of Complete Response Submission	October 5, 2015
PDUFA Goal Date	April 5, 2016
Proprietary Name (proposed) / Nonproprietary Name	Inflectra / CT-P13 ¹ , infliximab-dyyb
Dosage Forms / Strength	Sterile lyophilized powder, 100 mg/20mL vial for reconstitution and intravenous injection
Proposed Indication(s)	<ol style="list-style-type: none"> 1. Crohn's Disease (Adult and Pediatric) 2. Ulcerative Colitis (Adult and Pediatric²) 3. Rheumatoid Arthritis 4. Ankylosing Spondylitis 5. Psoriatic Arthritis 6. Plaque Psoriasis
Action:	<i>Approval as a biosimilar to US-licensed Remicade for the same indications (except for pediatric ulcerative colitis because Remicade's indication for pediatric ulcerative colitis is protected by orphan drug exclusivity)</i>

¹ In this document, we 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.

Material Reviewed/Consulted OND Action Package, including:	Names of discipline reviewers
CDTL Review	Nikolay Nikolov, MD
Medical Officer Review	Juwaria Waheed, MD
Biostatistical Review	Primary: Gregory Levin, PhD; Secondary: Ruthanna Davi, PhD; Tertiary: Thomas Permutt, PhD.
Pharmacology Toxicology Review	Primary: Matthew Whittaker, PhD; Secondary: Timothy Robison, PhD
Product Quality Review	Primary: 1 st cycle-Peter Adams, PhD, 2 nd cycle-Cyrus Agarabi, PharmD, PhD; Secondary: Kurt Brorson, PhD; Tertiary: David Frucht, PhD
Product-Immunogenicity	Primary: Will Hallett, PhD; Secondary: Harold Dickensheets, PhD
CMC-Statistical Review	Primary: Meiyu Shen, PhD; Secondary: Yi Tsong, PhD
CMC-Facility and Microbiology	DP: Bo Chi, PhD; DS: Maria Candau-Chacon PhD; Secondary: Patricia Hughes, PhD
Clinical Pharmacology Review	Primary: Lei He, PhD; Secondary: Ping Ji, PhD
OSI	Primary: Anthony Orenca, M.D.; Secondary: Janice Pohlman, MD MPH; Tertiary: Kassa Ayalew MD MPH
OSE/DMEPA	Primary: Teresa McMillan, PharmD; Secondary: Lubna Merchant, MS PharmD

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

1. Introduction

This is the second cycle for the 351(k) biologics license application (BLA) submitted by Celltrion, Inc. for CT-P13, a proposed biosimilar to Remicade (infliximab). The original application, submitted on August 8, 2014, received a complete response (CR) action on June 8, 2015 due to analytical deficiencies that precluded a conclusion that CT-P13 was highly similar to US-licensed Remicade[®]. This was due to residual uncertainty regarding differences in Antibody-Dependent Cellular Cytotoxicity (ADCC) activity and in FcγRIIIa binding. In addition, in the course of the immunogenicity review, differences in sub-visible particulates in the range of 1 to 5 μm in size between CT-P13, US-licensed Remicade and EU-approved Remicade[®] lots used in study 1.4 were observed. Celltrion provided data to address these deficiencies in this Complete Response submission, which is discussed in detail in Section 3 below.

As discussed in the first cycle summary review, Celltrion is seeking licensure of CT-P13 for the same indications previously approved for the reference product, US-licensed Remicade, on the basis of the following:

- Analytical data intended to support the following purposes:
 - A demonstration that CT-P13 can be manufactured in a well-controlled and consistent manner, leading to a product that is sufficient to meet required quality standards
 - A demonstration that CT-P13 and US-licensed Remicade are highly similar
 - A justification of the scientific relevance of comparative data that were generated using EU³-approved Remicade to a demonstration of biosimilarity.
 - Because the comparative clinical studies in the application utilized EU-approved Remicade, 3-way analytical characterization data from a comparison of CT-P13, US-licensed Remicade, and EU-approved Remicade were utilized to provide a scientific basis (along with pharmacokinetic data) for justifying the relevance of the comparative clinical data between CT-P13 and EU-approved Remicade to the demonstration of biosimilarity between CT-P13 and US-licensed Remicade.
- Study CT-P13 1.4, a single-dose pharmacokinetic (PK) study providing a 3-way comparison of CT-P13, US-licensed Remicade, and EU-approved Remicade. This study is the only clinical study in the original 351(k) BLA submission that included US-licensed Remicade as a comparator. This study serves as the primary basis for:
 - Evaluating the PK similarity of CT-P13 and US-licensed Remicade, and
 - Providing a scientific basis (along with analytical data) for justifying the relevance of comparative clinical data between CT-P13 and EU-approved Remicade as applicable to the demonstration of biosimilarity between CT-P13 and US-licensed Remicade.
- Study CT-P13 3.1, a comparative clinical study intended to demonstrate the similarity in efficacy and safety between CT-P13 and EU-approved Remicade. This is a 54-week, randomized, double-blind, parallel group study conducted outside the US in approximately 600 patients with moderate to severely active rheumatoid arthritis (RA) on background methotrexate (MTX), who were randomized 1:1 to CT-P13 or EU-approved Remicade at a dose of 3 mg/kg.
- The applicant also provided results from Study CT-P13 1.1, which is a 54-week randomized, double-blind, parallel-group study conducted outside the US in 250 patients with moderate to severe Ankylosing Spondylitis (AS) who were randomized 1:1 to CT-P13 or EU-approved Remicade at a dose of 5 mg/kg. This study was intended to support PK similarity in a patient population not taking concomitant immunosuppressives, and also included descriptive assessments of efficacy and safety.
- Open-label extensions (OLE) of Study 1.1 and Study 3.1 were utilized to evaluate the safety of patients transitioning from treatment with EU-approved Remicade to treatment with CT-P13. Patients in the OLE who were on EU-approved Remicade were transitioned to CT-P13, and patients who were on CT-P13 remained on CT-P13.

2. Background

³ EU=European Union

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

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

It is under this relatively new paradigm that Celltrion seeks licensure of CT-P13. The development of CT-P13 was conducted exclusively outside of the US and was geared towards meeting the requirements of non-US regulatory agencies. Much of the clinical development program was ongoing or completed at the time of Celltrion’s first meeting with FDA in July 2013. FDA input in the pre-submission period addressed the purpose and design of the 3-way PK bridging study between CT-P13, EU-approved Remicade and US-licensed Remicade, expectations for safety and immunogenicity data, and expectations regarding the information needed to support proposed extrapolation of existing clinical data to support a demonstration of biosimilarity for other conditions of use not studied.

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

3. Chemistry, Manufacturing, and Controls (CMC)

CT-P13 drug substance (DS) is a chimeric human-murine IgG1 κ monoclonal antibody that binds with high affinity to human TNF α . It is a glycoprotein with 1 N-linked glycosylation site in the CH2 domain of each heavy chain. Each heavy chain consists of 450 amino acids with 11 cysteine residues, and each light chain consists of 214 amino acids with 5 cysteine residues.

All cysteines in the heavy and light chains are involved in either intra- or inter- disulfide bonding. CT-P13 drug substance is a colorless to light yellow and slightly opalescent to opalescent solution and free of foreign particles, with a pH of approximately 7.2. The DS is manufactured at the Celltrion Incheon site in Korea using bioreactor mammalian Sp2/0 transfectoma cell culture and a conventional purification scheme.

The CT-P13 drug product (DP) is formulated as a sterile, white, lyophilized powder in a 20 mL type I borosilicate glass vial with a 20 mm (b) (4) butyl rubber stopper and a 20 mm flip-off seal. Each CT-P13 drug product vial contains 100 mg CT-P13 drug substance as the active ingredient, and sodium dihydrogen phosphate monohydrate, di-sodium hydrogen phosphate dihydrate, sucrose and polysorbate 80 as excipients. Stability data supported the proposed shelf-life of 51 months.

As was discussed in the first cycle reviews, the CMC/product quality review team concluded that the manufacture of CT-P13 was adequate to meet the product quality standards that would ordinarily be expected for approval. Results from most assessments, including those assessing the primary mechanism of TNF binding activity, were considered to be supportive of analytical similarity between CT-P13 and US-licensed Remicade. However, the reviewers concluded there was residual uncertainty at that time regarding differences in ADCC activity and in FcγRIIIa binding and also related to immunogenicity and subvisible particle content. In this submission, Celltrion adequately addressed the CR issues as follows:

CR Comment #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.”*

Response to CR Comment#1:

Celltrion provided results of additional subvisible particulate analysis from 13 CT-P13, US-licensed Remicade, and EU-approved Remicade lots, using two orthogonal methods. The additional testing revealed that levels of subvisible particles varied, but no consistent trend towards more or fewer particles were evident for any of the three products. These data reassured that no quality-related attribute exists that would be expected to increase the antigenicity of CT-P13 over US-licensed Remicade. Additionally, these data suggest the immunogenicity data from single-dose 3-way PK study, Study 1.4, are not founded in a true difference between the products, and are more likely due to variability/random chance. Moreover, additional immunogenicity data from a new clinical study involving patients revealed no increase in immunogenicity in patients receiving CT-P13 vs. US-licensed Remicade after repeated dosing, further mitigating this concern. (See Section 8 immunogenicity subsection below for details.)

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

Response to CR Comment#2:

- a) Celltrion evaluated the ADCC activity of additional lots (13, 22, and 20 lots, respectively) 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 Celltrion’s testing of the reference product, meeting expectations for this product quality attribute to support a demonstration that CT-P13 is “highly similar” to the reference product.
- b) Celltrion also performed an exercise where impurity/variant-enriched CT-P13 preparations were evaluated for ADCC activity and FcγRIIIa binding. The goal of the exercise was to identify and demonstrate control of product quality attributes that underlie ADCC activity with CT-P13. As a result of this exercise, it was determined that FcγRIIIa binding strength correlated with NK-cell mediated ADCC activity. Celltrion agreed to tighten their drug substance specifications for FcγRIIIa binding strength, ensuring that CT-P13 lots will be within the quality range for NK-cell mediated ADCC activity, as determined by testing of multiple lots of the reference product. The Product Quality review team concluded that this, together with the point above, resolves CR issue #2.
- c) Celltrion also provided additional justification that the observed, small differences (~20%) in mean ADCC activity are probably not important for clinical activity. This

information was provided as a follow-up to a position paper (“Extrapolation of CT-P13 Data to Indications for which Licensure is sought”) submitted in the original 351(k) BLA, and included a comprehensive literature search, expert opinion, and a new experimental report on the ADCC activity of gut lamina propria mononuclear cells. FDA’s evaluation, which included an independent FDA review of the pertinent scientific literature, concluded that reverse signaling together with TNF sequestration (antibody activities not dependent on the Fc portion of the molecule) likely predominate in the mechanism of infliximab function for all indications, including IBD. The response also addressed a question raised during a Type 1 meeting on Aug 5, 2015, which pertained to the apparent lack of efficacy or effectiveness only for maintenance treatment by antibodies or fusion proteins lacking or with attenuated Fc effector functions (e.g., Onercept, Enbrel, Cimzia, and CDP571), which suggests a role for intact Fc function and ADCC in IBD indications. Celltrion provided other explanations aside from lack of ADCC activity for the clinical outcome of each of the products referenced above, such as structural features of the biomolecules or inadequate dosing or other aspects of clinical trial design. The Product Quality review team concluded that Celltrion’s justification adequately addressed this aspect of CR comment #2.

In summary, in this second cycle submission, Celltrion has adequately addressed the deficiencies noted in the CR letter of June 8, 2015. Therefore the product quality review team has concluded that CT-P13 and US-licensed Remicade are highly similar and that, if other criteria are met, CT-P13 may be licensed as a biosimilar to US-licensed Remicade.

4. Nonclinical Pharmacology/Toxicology

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

5. Clinical Pharmacology/Biopharmaceutics

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

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

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

Immunogenicity

See Section 8 below.

6. Clinical Microbiology

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

7. Clinical/Statistical-Efficacy

The primary comparative clinical study in the development program was Study 3.1, a 54-week, randomized, double-blind, parallel group study conducted outside the US in approximately 600 patients with moderate to severely active rheumatoid arthritis (RA) on background methotrexate (MTX), who were randomized 1:1 to CT-P13 or EU-approved Remicade at a dose of 3 mg/kg. Study 3.1 met its pre-specified primary endpoint, which was a similarity margin of $\pm 15\%$ in the proportion of patients achieving an ACR20 response.⁴ The study was completed prior to interactions with FDA, and the FDA did not agree with the chosen margin beforehand. However, based on FDA's analysis of the data provided, the smaller margin considered optimal by the review team ($\pm 12\%$) would also have been met by the results of Study 3.1. Approximately 60.9% of patients randomized to CT-P13 and 58.9% of patients randomized to EU-approved Remicade remained in the study and achieved an ACR20

⁴An ACR20 Response is defined as a $\geq 20\%$ improvement in tender joint count, swollen joint count and at least 3 of the 5 remaining core set variables of patient global assessment (on visual analog scale [VAS]), physician global assessment on a VAS, patient assessment of pain on a VAS, Health Assessment Questionnaire-Disability Index score, and acute phase reactant (erythrocyte sedimentation rate or c-reactive protein).

response at Week 30, for an estimated absolute difference between treatments of 2.0% (90% CI: -4.6%, +8.7%; 95% CI: -5.8%, +9.9%).

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

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

8. Safety

Safety Overview

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

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

⁵ ASAS20 response is defined as an improvement of at least 20% and an absolute improvement from baseline of at least 1 unit on a 0 to 10 scale in at least 3 of 4 domains: patient global assessment of disease status, patient assessment of spinal pain, function according to the Bath Ankylosing Spondylitis Functional Index (BASFI), morning stiffness as assessed by the last 2 questions of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).

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

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

Regarding overall safety, data from the CT-P13 development program are adequate to support a conclusion that there are no clinically meaningful differences in safety between CT-P13 and EU-approved Remicade; and there is an adequate analytical and PK bridge to support the conclusion that no clinically meaningful differences would be expected between CT-P13 and US-licensed Remicade. Further, the transition data from extension studies 3.2 and 1.3 support the conclusion that safety concerns with transitioning patients from the reference product to CT-P13 would not be anticipated.

Immunogenicity

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

The only immunogenicity data in the original 351(k) BLA submission allowing for a direct comparison of CT-P13 and US-licensed Remicade were the data following single-dose

administration in healthy subjects in PK study 1.4. Immunogenicity samples in the rest of the CT-P13 development program were analyzed using an electrochemiluminescent assay (ECLA), but the ECLA appeared to be more susceptible to interference by circulating drug, so the sponsor developed an ELISA assay with better tolerance to circulating drug and both ECLA and ELISA assays were used for Study 1.4. Using ECLA, at Day 57 following a single dose of 5 mg/kg in healthy volunteers, the ADA rate in Study 1.4 was approximately 14%, 7%, and 3% for CT-P13, EU-approved Remicade, and US-licensed Remicade, respectively. Using ELISA, the incidence of ADA for CT-P13, EU-approved Remicade, and US-licensed Remicade was approximately 27%, 25%, and 11% respectively. All subjects testing positive in the ELISA screening assay in Study 1.4 also tested positive in the neutralizing antibody (NAb) assay and neutralizing antibody titers trended higher in CT-P13 patients compared to patients treated with US-licensed Remicade or EU-approved Remicade. While there are limited publically available data on the comparative immunogenicity of EU-approved Remicade and US-licensed Remicade, the 14% difference observed Study 1.4 appeared to be larger than observed with other publically available data; i.e., in a single-dose 3-way PK study of another product described as a “potential biosimilar to infliximab,” the ADA rates for EU-approved Remicade and US-licensed Remicade were 32.6% and 28.2%, respectively, at Day 85.⁶

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

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

Based on the data in the original 351(k) BLA submission, the clinical and clinical pharmacology review teams concluded that the data in the clinical development program for CT-P13 suggest there were no clinically meaningful differences as a result of immunogenicity to CT-P13, EU-approved Remicade or US-licensed Remicade and that the differences in immunogenicity rates do not rise to the level of a deficiency that would preclude approval.

⁶ ACR Abstract 1501, 2014. Udata C et al., “Immunogenicity Assessment of PF-06438179, a Potential Biosimilar to Infliximab, in Healthy Volunteers.”

However, the product quality team was concerned this difference might be related to difference in subvisible particulates and the product quality immunogenicity team was additionally concerned about differences in binding and neutralizing antibody titers in Study 1.4.

As discussed in Section 3, in this submission, the applicant provided additional data that reassured there were no consistent trends toward a difference in subvisible particulates between CT-P13, EU-approved Remicade, and US-licensed Remicade. The applicant also provided additional interim immunogenicity data from Study 3.4, which is an ongoing 54-week, randomized, double-blind, controlled study in patients with active Crohn's Disease (CD) to evaluate the efficacy, safety, and immunogenicity of CT-P13, US-licensed Remicade, or EU-approved Remicade after multiple doses of 5 mg/kg. Patients were randomized 1:1:1:1 to one of 4 groups—1) CT-P13 only, 2) US-licensed Remicade or EU-approved Remicade (depending on patient location) followed by CT-P13 at Week 30, 3) US-licensed Remicade or EU-approved Remicade only (depending on patient location), or 4) CT-P13 followed by US-licensed Remicade or EU-approved Remicade (depending on patient location) at Week 30. Patients are dosed at Weeks 0, 2, 6, and 14, and then every 8 weeks thereafter through Week 54.

As of September 14, 2015, a total of 109 patients were enrolled and treated and had immunogenicity results 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. At Week 14, using the previously validated ELISA assay, the proportion of patients with positive ADA with CT-P13 was 8/54 (14.8%), with US-licensed Remicade was 5/43 (11.6%), and with EU-approved Remicade was 4/12 (33.3%). These numbers included one patient in the CT-P13 group who was ADA-positive at baseline. These interim data show a small difference of approximately 3% between the CT-P13 and US higher licensed Remicade groups, and are in contrast with the single-dose data from Study 1.4. The proportion of ADA-positive patients in the EU-approved Remicade group is likely to be artifactually high due to the small number of EU-approved Remicade patients evaluated in this study thus far.

In summary, the additional data in this submission on subvisible particulates resolved the concern that there are analytical differences between the products that would cause a difference in immunogenicity. Additional repeat-dose immunogenicity data from Study 3.4 also alleviated the initial concerns about a possible difference in immunogenicity based on single-dose study 1.4. This information supports the conclusion that there are no clinically meaningful differences in immunogenicity between CT-P13 and US-licensed Remicade.

9. Advisory Committee Meeting

An Arthritis Advisory Committee (AAC) meeting was held for this application on February 9, 2016. This meeting included experts in product quality assessment, clinical pharmacology, rheumatology, dermatology, and gastroenterology, as well as patient, consumer, and industry representatives. The Committee discussed the analytical data for CT-P13 and generally agreed

that CT-P13 was highly similar to the reference product, US-licensed Remicade. The Committee also discussed the clinical data with CT-P13 in RA and AS, and generally agreed there were no clinically meaningful differences between CT-P13 and US-licensed Remicade in these indications. The Committee then discussed the scientific justification for extrapolating conclusions of biosimilarity to additional indications that had not been studied. While many panel members agreed that extrapolation was justified, some members expressed reservations about extrapolating conclusions of biosimilarity to the inflammatory bowel disease (IBD) indications. For the voting question, panelists were asked whether they agreed 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, and adult UC). The Committee voted 21 to 3 in favor of licensure of CT-P13 for these indications. Panelists who had reservations wanted to wait for ongoing additional clinical data in IBD.

10. Pediatrics

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

11. Other Relevant Regulatory Issues

- **Inspections:** No issues precluding approval were found on inspection of the manufacturing facilities or of selected clinical sites.
- **Financial Disclosure:** No issues.
- **Exclusivity or Patent Issues:** Celltrion requested licensure for pediatric ulcerative colitis. However, 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/ood/index.cfm>).

12. Labeling

The proprietary name for CT-P13 will be Inflectra. FDA has determined that the use of a distinguishing suffix in the nonproprietary name is necessary to distinguish this product from Remicade (infliximab). The nonproprietary name for CT-P13 will be infliximab-dyyb. 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. 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.

The general approach taken for the Inflectra labeling is to have the labeling incorporate relevant data and information from the current FDA-approved labeling for US-licensed Remicade, with appropriate product-specific modifications. This approach is informed by the consideration that biosimilar product labeling that is consistent with the reference product labeling should more clearly convey FDA's conclusion that the two products are highly similar and there are no clinically meaningful differences.

13. Decision/Action/Risk Benefit Assessment

- **Regulatory Action**

The action on this application will be Approval.

- **Assessment of Biosimilarity**

Section 351(i) of the PHS Act defines the terms “biosimilar” or “biosimilarity” to mean that “the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components” and that “there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product” (see section 351(i)(2) of the PHS Act). In this submission, Celltrion provided data and information to address the residual uncertainty surrounding FcγRIII binding/ADCC activity and subvisible particulates, leading the product quality review team to conclude that CT-P13 is highly similar to US-licensed Remicade, on the basis of the additional data in this submission. The additional data on subvisible particulates and repeat-dose immunogenicity data with CT-P13 and US-licensed Remicade reassured that apparent differences in immunogenicity observed in the single-dose 3-way PK study were not reflective of analytical differences between the products. Therefore, in addition to supporting analytical similarity, these data supported the ability to bridge between EU-approved Remicade and US-licensed Remicade and provide a scientific justification (along with the 3-way PK data) for the relevance of comparative data with EU-approved Remicade to a demonstration of biosimilarity to US-licensed Remicade. Therefore, based on the data available in this application, the statutory standards for biosimilarity have been met, and the application may be approved.

Extrapolation

The applicant sought licensure for all the indications for which US-licensed Remicade is licensed. To support extrapolation of data acquired in RA and AS to support biosimilarity in the other conditions of use, the applicant provided a scientific justification. FDA's Division of Gastroenterology and Inborn Errors Products (DGIEP) and the Division of Dermatology and Dental Products (DDDP) performed a collaborative review of the available data/justification supporting extrapolation of biosimilarity and licensure for the indications under their purview.

Infliximab binds to both soluble and transmembrane TNF, and its primary mechanism of action (MOA) is direct binding of TNF and blocking of TNF receptor-mediated biological activities. The scientific literature indicates that this MOA is the primary MOA in RA, AS, psoriatic arthritis, and psoriasis and is a likely mechanism of action in inflammatory bowel disease (IBD) as well. However reverse signaling via binding to transmembrane TNF is also a likely mechanism of action in IBD, and mechanisms such as complement-dependent cytotoxicity (CDC), ADCC, and induction of regulatory macrophages (in mucosal healing) may also play a role in IBD.

One of the main concerns raised by the data in the original submission was the approximately 20% lower ADCC activity in CT-P13 compared to US-licensed Remicade, leading to residual uncertainty about whether CT-P13 is highly similar to US-licensed Remicade, and uncertainty regarding whether extrapolation was justified for the indications where ADCC could play a role (i.e., IBD). In this submission, the applicant provided sufficient analytical similarity data to support a conclusion that CT-P13 and US-licensed Remicade are highly similar and have the same mechanisms of action for each of the requested indications, to the extent that the mechanisms of action are known or can be reasonably be determined. This includes resolution of the residual uncertainty regarding ADCC, as discussed in Section 3 above.

Other information supporting extrapolation includes:

- The similar pharmacokinetics (PK) of CT-P13 and US-licensed Remicade would not be expected to be different between the studied populations and the other populations.
- Immunogenicity was assessed in the usage scenarios with or without concomitant immunosuppressives (RA and AS respectively) and the immunogenicity in other populations would not be expected to be different. Interim immunogenicity data from Study 3.4 in Crohn's Disease (CD) patients also reassures that immunogenicity with CT-P13 and US-licensed Remicade would be expected to be similar in IBD patients.
- Finally, available safety data support similarities in adverse reactions across the licensed indications of US-Remicade, suggesting a difference in safety profile would not be expected with CT-P13 across different indications.

Although the applicant submitted available data from their post-marketing experience with IBD patients in Norway and from Study 3.4 in CD, these data have many limitations and definitive conclusions cannot be drawn. Nevertheless, based on analytical similarity, PK similarity, clinical data in RA and AS, and justifications based on MOA and other factors, no clinically meaningful differences between CT-P13 and US-licensed Remicade are expected in the other indications for which US-licensed Remicade is approved. Therefore, we conclude that CT-P13 may be approved as a biosimilar to US-licensed Remicade (b) (4) for which CT-P13 is eligible for licensure.

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

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

Not applicable.

- **Comments for Action Letter**

None.

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/s/

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04/05/2016

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