FDA Briefing Document

Arthritis Advisory Committee Meeting

February 09, 2016

BLA 125544
CT-P13, a proposed biosimilar to Remicade® (infliximab)

Celltrion

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We bring the 351(k) BLA for CT-P13 with the Applicant's proposed indications to this Advisory Committee to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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1 Introduction

Celltrion has submitted a biologics license application (BLA) under section 351(k) of the Public Health Service Act (PHS Act) for CT-P13[1], a proposed biosimilar to Remicade (infliximab). BLA # 103772 for Remicade was initially licensed by FDA on August 24, 1998, and the BLA is currently held by Janssen Biotech, Inc. US-licensed Remicade is the reference product for Celltrion's 351(k) BLA. Celltrion is seeking licensure of CT-P13 for the same indications as US-licensed Remicade:[2]

1) Crohn's Disease (CD):
    - reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.
    - reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing disease.
2) Pediatric CD:
    - reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely active disease who have had an inadequate response to conventional therapy.
3) Ulcerative Colitis (UC):
    - reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.
4) Pediatric UC[3]:
    - reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely active disease who have had an inadequate response to conventional therapy.
5) Rheumatoid Arthritis (RA) in combination with methotrexate:
    - reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active disease.
6) Ankylosing Spondylitis(AS):
    - reducing signs and symptoms in patients with active disease
7) Psoriatic Arthritis (PsA):
    - reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function.
8) Plaque Psoriasis (PsO):

[1] In this document, FDA generally refers to Celltrion's proposed product by the Celltrion descriptor "CT-P13." FDA has not yet designated a nonproprietary name for Celltrion's proposed biosimilar product that includes a distinguishing suffix (see Draft Guidance on Nonproprietary Naming of Biological Products).
[2] Remicade USPI
[3] 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

- treatment of adult patients with chronic severe (i.e., extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate.

2 Background

Introduction to Regulatory Pathway

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(k) 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." 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 structurally and functionally highly similar to a reference product is anticipated to behave like the reference product in the 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, once the applicant has established that the proposed biosimilar meets the analytical similarity prong of the biosimilarity standard the amount of residual uncertainty remaining with respect to both the structural/functional evaluation and the potential for clinically meaningful differences. Additional data, such as nonclinical and/or clinical data, can then be tailored to address these residual uncertainty(-ies).

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.

The Reference Product

In general, an applicant needs to provide information to demonstrate biosimilarity based on data directly comparing the proposed product with the reference product (US-licensed Remicade).[4] 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 must 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 compare all three products [i.e., the proposed biosimilar product (CT-P13), the reference product (US-licensed Remicade), and the non-US-licensed comparator product (European Union (EU)-approved Remicade)] and is likely to also include bridging clinical PK and/or PD study data for all three products.

[4] The BPCI Act defines the "reference product" as the single biological product licensed under section 351(a) of the PHS Act against which a proposed biosimilar product is evaluated in a 351(k) application (see section 351(i)(4) of the PHS Act).

3 Executive Summary

This is a 351(k) BLA submitted by Celltrion, Inc. for CT-P13, a proposed biosimilar to Remicade (infliximab). Celltrion is seeking licensure of CT-P13 for the same indications previously approved for the reference product, US-licensed Remicade. The application consists of:

- Extensive analytical data intended to support (i) a demonstration that CT-P13 and US-licensed Remicade are highly similar, (ii) 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 and (iii) a justification of the relevance of comparative data generated using the European Union-approved Remicade (EU)-approved Remicade to support a demonstration of the biosimilarity of CT-P13 to US-licensed Remicade.
- A single-dose pharmacokinetic (PK) study (study 1.4) providing a 3-way comparison of CT-P13, US-licensed Remicade, and EU-approved Remicade intended to (i) support PK similarity of CT-P13 and US-licensed Remicade and (ii) provide PK data to justify the relevance of the comparative data generated using EU-approved Remicade to support a demonstration of the biosimilarity of CT-P13 to US-licensed Remicade.
- A comparative clinical study (study 3.1) 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 RA on background methotrexate (MTX), who were randomized 1:1 to CT-P13 or EU-approved Remicade at a dose of 3 mg/kg.
- A supportive 54-week randomized, double-blind, parallel-group study (study 1.1) conducted outside the US in 250 patients with moderate to severe AS who were randomized 1:1 to CT-P13 or EU-approved Remicade at a dose of 5 mg/kg, intended to (i) support PK similarity in a patient population not taking concomitant immunosuppressives, and (ii) provide descriptive assessments of efficacy and safety in a different patient population.
- An assessment of safety and immunogenicity in patients undergoing single transition from EU-approved Remicade to CT-P13 during the open-label extensions (OLE) of study 1.1 and study 3.1.
- A scientific justification for extrapolation of data to support biosimilarity in each of the indications for which Celltrion is seeking licensure, specifically psoriatic arthritis, plaque psoriasis, adult and pediatric ulcerative colitis, and adult and pediatric Crohn's Disease.

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 proposed commercial product. Based on our 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 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 worse safety or immunogenicity profile. This would support 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 demonstration 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 potential 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.

4 Draft Points to Consider

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

Discussion Point 2:
Does the Committee agree that there are no clinically meaningful differences between CT-P13 and US-licensed Remicade in the studied conditions of use (RA and AS)?

Discussion Point 3:
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 (PsA, PsO, adult and pediatric CD, and adult and pediatric UC[5])? If not, please state the specific concerns and what additional information would be needed to support extrapolation. Please discuss by indication if relevant.

Voting Point 1:
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 following indications for which US-licensed Remicade is currently licensed and CT-P13 is eligible for licensure:

a. RA,
b. AS,
c. PsA,
d. PsO,
e. adult CD,
f. pediatric CD, and
g. adult UC?

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

5 Relevant Regulatory History

The development of CT-P13 was conducted entirely outside of the US and was directed towards meeting the product approval requirements of non-US regulatory agencies. During the development of CT-P13, the applicant sought scientific and procedural advice from the European Medicines Agency's Committee for Medicinal Products for Human Use and other non-US regulatory authorities on the quality, nonclinical and clinical development programs. 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 previously approved for US-licensed Remicade in several regions including the EU, South Korea, Japan, and India. In 2014, Health Canada approved CT-P13 for all indications except ulcerative colitis and Crohn's Disease (collectively referred to as inflammatory bowel disease or IBD), with the conclusion that extrapolation of data from the settings of rheumatoid arthritis and ankylosing spondylitis to IBD indications could not be recommended due to residual uncertainty regarding the role and impact of small differences in antibody-dependent cellular cytotoxicity (ADCC) that might have relevance in IBD.[6]

The first interaction with the FDA occurred at a Biosimilar Biological Product Development (BPD) Type 3 meeting held on 10 July 2013 with a second meeting (BPD Type 4) held on 28 April 2014. Additional interactions occurred to discuss the initial Pediatric Study Plan (iPSP). At the BPD Type 3 meeting, FDA provided product quality, non-clinical, and clinical comments, including the following recommendations to the applicant regarding clinical development:

- Demonstrate PK similarity between CT-P13, US-licensed Remicade and EU-approved Remicade based on the following PK variables (AUCinf, Cmax and AUClast).
- Provide a detailed description of the methodology and plans for qualification of the assays that will be used for the detection of anti-drug antibodies.
- Assess safety and immunogenicity in the setting of patients who undergo a single transition from EU-approved Remicade to CT-P13 to provide a descriptive comparison with patients who continue on EU-approved Remicade.

At the BPD Type 4 meeting, general agreement was reached on the proposed format and content of the BLA, including the Agency's expectation of the information needed to support a demonstration of biosimilarity and extrapolation of clinical data to support the demonstration of biosimilarity for each indication for which licensure is sought.

[6] 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

Of note, the FDA previously scheduled an Advisory Committee meeting for March 17, 2015, to discuss this application, but postponed the meeting due to information requests pending with Celltrion (see 80 FR 12823, March 11, 2015).

6 CMC

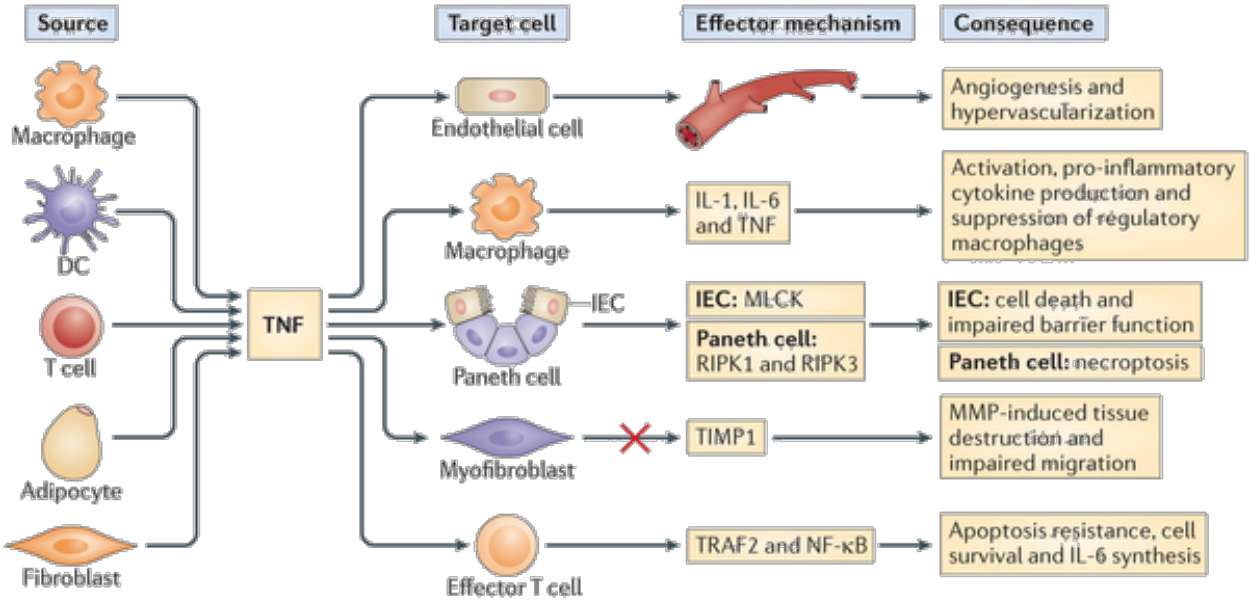
Executive summary

CT-P13 is a proposed biosimilar to US-licensed Remicade. An analytical similarity program was designed utilizing the proposed biosimilar, CT-P13, US-licensed Remicade (the reference product) and EU-approved Remicade. The program had two goals. First, an analytical comparison of the proposed biosimilar to US-licensed Remicade was needed to demonstrate findings consistent with the conclusion that it is "highly similar" to the reference product. Second, a comparison of US-licensed Remicade to EU-approved Remicade was needed to create an analytical bridge to justify the relevance of data generated using EU-approved Remicade as the comparator in some clinical and non-clinical studies. The results of these comparisons show that the three products met the pre-specified criteria for analytical similarity, including statistical criteria for the critical potency bioassay (TNF-α neutralization) and TNF-α binding strength. Thus, a pair-wise analytical comparison of CT-P13 to US-licensed Remicade is consistent with the conclusion that CT-P13 is highly similar to the reference product (US-licensed Remicade). Further, an adequate analytical bridge between EU-approved Remicade, US-licensed Remicade, and CT-P13 was established to justify the relevance of the comparative data generated using EU-approved Remicade to support a demonstration of the biosimilarity of CT-P13 to US-licensed Remicade.

Pathophysiologic Role of TNF-alpha and Mechanisms of Action of Infliximab

Tumor Necrosis Factor (TNF)-α is considered to be a master cytokine critical for the function of the immune system as well as inflammatory responses. It exists in both a soluble and membrane-bound form that can be produced by a range of immune-related or other cell types. The consequences of effector functions of TNF-α are also varied and include tissue destruction, activation of pro-inflammatory cytokines and cell death. Thus, dysregulation of this master pro-inflammatory cytokine can have multiple clinical consequences in diseases like RA or inflammatory bowel disease (IBD).

Figure 1. TNF-α: A "Master Cytokine"



Source: Neurath, 2014[7]

TNF-α exists in both in a 26 kDa membrane bound (mTNF-α) form and a 17 kDa soluble form (sTNF-α), both of which form non-covalently linked homo-trimers. Because both forms are active, signals may be passed locally from cell-to-cell via mTNF:TNF-R interactions, or more distally through release of sTNF. sTNF-α is generated following cleavage by members of a class of metalloproteinases called "sheddases", which include TNF-converting enzyme (TACE, ADAM17) and ADAM 10. While under normal physiological conditions, the concentration of TNF-α found in bodily fluids is almost undetectable, stimulation by external sources can increase concentrations to measurable and sometimes very high levels. Biological responses to TNF-α are mediated through two structurally distinct, cognate TNF receptors, TNF-R1 (p55) and TNF-R2 (p75). These high affinity receptors are present as preassembled trimers on the cell surface. Most cells constitutively express TNF-R1 on their surface; in contrast, TNF-R2 is inducible and expressed preferentially on hematopoietic and endothelial cells.

Infliximab is an IgG1 kappa monoclonal antibody, with a high avidity for TNF-α, both soluble and membrane-bound forms. It functions primarily via the variable region complementary determining region (CDR) surface by binding, neutralizing and sequestering excess sTNF-α produced in local inflammatory disease tissue sites. Another potential variable region-mediated mechanism of action is mediating reverse signaling via binding and cross-linking mTNF on inflammatory cells or induction of

[7] Neurath, M. Nature Reviews Immunology, 2014, 14(5), 329-342.

regulatory macrophages. Finally, there are some potential functions dependent on the Fragment crystallizable region (Fc) part of the antibody that may be important. These include antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) of lysis of mTNF+ inflammatory T-cells or other cells associated with particular disease states. The relative importance of merely sequestering sTNF vs. eliciting other effector functions on mTNF+ cells may vary between disease states. A summary of known and potential (likely or plausible), mechanisms of action of US-licensed Remicade are listed in Table 1.

Table 1. 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[8,9]

CT-P13 Manufacturing

CT-P13 is produced using a mammalian cell line in large scale bioreactor culture followed by a drug substance purification process that includes various steps designed to isolate and purify the protein product. Residual levels of process-related impurities

[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

such as host cell proteins (HCP), host cell DNA (HCDNA) and other process-related impurities specific to the CT-P13 process were evaluated in CT-P13 drug substance. Data were provided that demonstrate that the manufacturing process of CT-P13 drug substance is able to reduce the levels of these impurities to very low levels (e.g., ppm for HCP and pg/mg for HCDNA).

CT-P13 drug product was developed as a lyophilized powder with the same strength, dosage form, and route of administration (100 mg in a 20 mL vial for intravenous infusion) for use in the treatment of the same indications as those approved for US-licensed Remicade. The CT-P13 formulation has the same inactive ingredients as US-licensed Remicade.

The manufacturing process for CT-P13 drug substance was scaled up and optimized during the clinical development program. To rule out the possibility of evolution or drift in product quality over time, Celltrion has provided data to demonstrate equivalent product quality of CT-P13 drug substances that were manufactured over the duration of process development. The drug product manufactured for commercial launch was also shown to be comparable to the drug product manufactured by the clinical process.

The CT-P13 final drug substance and drug product processes are validated, and the resultant product is of a consistent quality. The controls that have been put in place for the manufacture of CT-P13 drug substance and CT-P13 drug product meet regulatory requirements. An assessment of the manufacturing facilities took place in February 20-March 7, 2015, by a team of Agency inspectors. The team verified that the drug substance and drug product sites are acceptable from a good manufacturing practice (GMP) perspective.

Analytical Similarity Assessment

Determining high analytical similarity of CT-P13 to US-licensed Remicade, and establishing the validity of the analytical bridge between CT-P13, US-licensed Remicade, and EU-approved Remicade was accomplished by Celltrion's evaluation and comparison of analytical data from multiple lots of each of the three products. The FDA performed confirmatory statistical analysis of the submitted data, which is presented in further detail later in this section. Overall, 26 lots of CT-P13 drug product (DP), 41 lots of the EU-approved Remicade DP and 45 lots of US-licensed Remicade DP were used for analysis, although not all lots were assessed using each test. Importantly, 13-16 lots of CT-P13 drug product (DP), 13-23 lots of the EU-approved Remicade and 16-27 lots of US-licensed Remicade were used for analysis with critical assays that directly measured the primary mechanism of action of the product, TNF-α binding and neutralization. The number of lots that were analyzed using each assay was chosen by the Applicant, Celltrion, based on their assessment of the variability of the analytical method and availability of material.

The expiration dates of the US-licensed Remicade lots and EU-approved Remicade lots that were analyzed spanned approximately 3 years and 4 years, respectively. The CT-P13 lots that were used for analysis were manufactured between 2010 and 2012.

The analytical comparison of CT-P13 with US-licensed Remicade was used to support the Applicant's contention that CT-P13 is "highly similar to the reference product [US-licensed Remicade] notwithstanding minor differences in clinically inactive components." Pairwise comparisons of CT-P13, US-licensed Remicade, and EU-approved Remicade were used to support an analytical bridge between the three products to justify the relevance of the comparative data generated using EU-approved Remicade from some clinical and non-clinical studies.

The analytical similarity exercise used a comprehensive range of methods listed in Table 2, which included orthogonal methods that measured the same critical quality attribute (CQA) from different perspectives. Many assays were designed to specifically address and measure potential mechanisms of action of infliximab, including Fc-mediated functions. All methods were validated or qualified prior to the time of testing and demonstrated to be suitable for intended use.

Table 2. Quality Attributes and Methods Used to Evaluate Analytical Similarity of CT-P13, US-licensed Remicade, and EU-approved Remicade

Quality Attribute	Methods
Primary structure	• Peptide mapping with ultraviolet (UV) and mass spectrometry (MS) detection • Amino Acid Analysis • Post-translational modification (MS/MS) • Intact Mass Reduced (LC-MS) • Peptide mapping coupled with tandem mass spectrometry (MS/MS)
Protein content	• UV280
Higher order structure	• Far and Near UV circular dichroism • FTIR • Free thiols • Antibody Array • Liquid chromatography coupled with mass spectrometry (LC-MS)(disulfide bond characterization) • Differential scanning calorimetry
High molecular weight species/aggregates	• Size exclusion chromatography (HPLC) • Size exclusion chromatography (SEC-MALS) • CE-SDS (reduced and non-reduced) • Analytical Ultracentrifugation
Charge	• IEF • IEC-HPLC
Glycosylation	• Oligosaccharide profiling • N-linked Glycan analysis • Sialic Acid analysis • Monosaccharide Analysis
Potency	• *In vitro* TNF-α neutralization assay
Binding assay – TNF	• ELISA • Cell based binding affinity
Binding assay – Fc	• NK cell binding affinity via Fc receptors (in presence of 50% serum or 1% BSA) • FcγRIIIa V and F type binding affinity (SPR) • FcγRIIIb binding affinity (SPR) • FcγRIIa binding affinity (SPR) • FcγRIIb binding affinity (SPR) • FcγRI binding affinity (ELISA) • FcRn binding affinity (SPR) • C1q binding assay (ELISA)

Quality Attribute	Methods
Binding assay	• C1q binding assay (ELISA)
Bioassay/ mechanism of action exploration	• ADCC (PBMC as effectors) • ADCC (NK cells as effectors) • ADCC (LPS-stimulated monocytes as targets) • CDC • Induction of apoptosis by reverse signaling • Inhibition of pro-inflammatory cytokine release by reverse signaling (Caco-2 cells) • Wound healing (closure %) • Inhibition of T Cell proliferation (MLR) • Induction of regulatory macrophages

Primary Structure

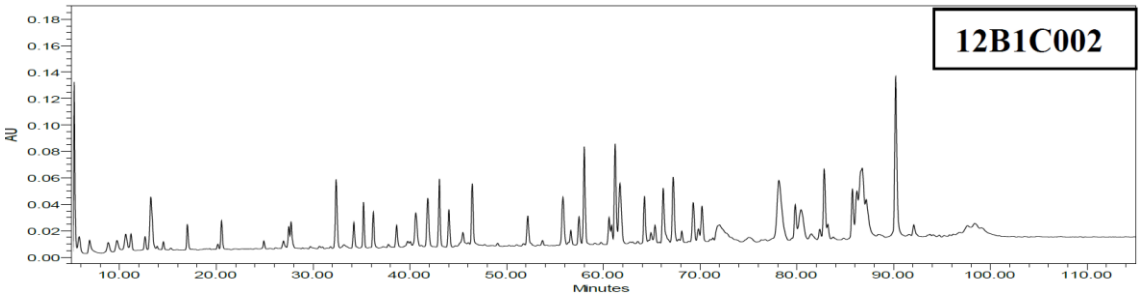
To support a demonstration that the proposed biosimilar product is highly similar to the reference product, it is expected that the expression construct for a proposed biosimilar product will encode the same primary amino acid sequence as its reference product. To achieve this goal, expression constructs were designed to encode a protein sequence that matches the reference product by the CT-P13 production cells. This can be confirmed at the protein level by methods such as N-terminal sequencing, 2-dimensional mass spectroscopy, intact antibody mass spectroscopy and tryptic peptide mapping.

Peptide mapping

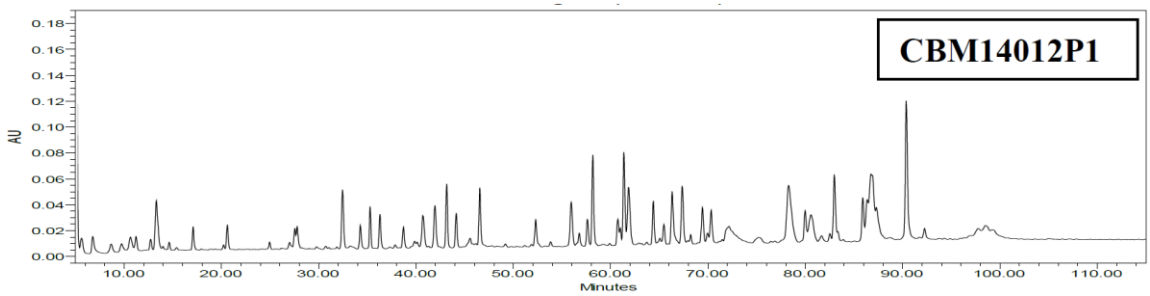
The primary structure of CT-P13, EU-approved Remicade and US-licensed Remicade, as assessed by peptide map data, demonstrated that CT-P13 has a matching chromatographic profile (map) to that of US-licensed Remicade and EU-approved Remicade (see Figure 2 below). No additional peptides or missing peptides were detected in the comparison between the three products. In addition, the applicant established that the intact mass (reduced) was similar for CT-P13, EU-approved Remicade and US-licensed Remicade using LC-MS.

Figure 2. RP-HPLC Chromatograms from the Tryptic Peptide Structural Characterization of CT-P13, US-licensed Remicade, and EU-approved Remicade

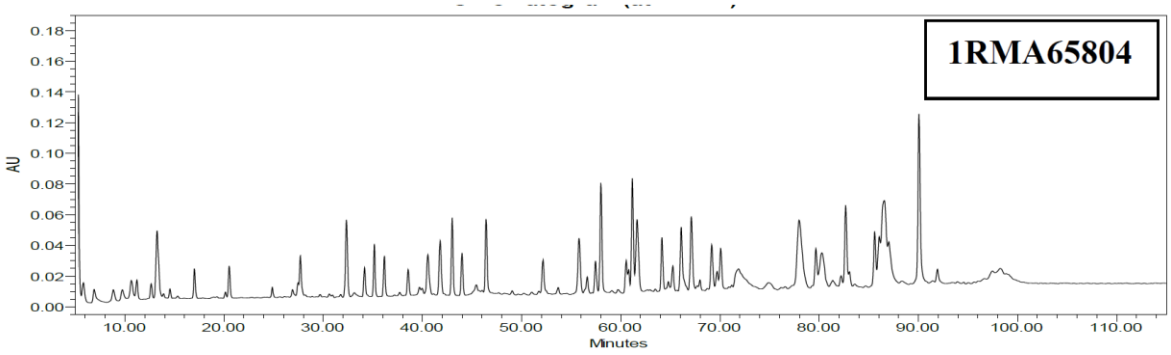
CT-P13



US-licensed Remicade



EU-approved Remicade



Source: Figure excerpted from the Celltrion 351(k) BLA submission

Further primary structure analysis

The N-terminal sequences of the heavy and light chain were determined using peptide mapping in combination with two-dimensional mass spectrometry (MS/MS). The analysis confirmed that first eighteen amino acids of the CT-P13 light chain (i.e., DILLTQSPAILSVSPGER) are identical to the first eighteen amino acids of US-licensed Remicade and EU-approved Remicade. N-terminal sequencing of the CT-P13 heavy chain demonstrated that the first nineteen amino acids i.e.,

EVKLEESGGGLVQPGGSMK) are identical to the first nineteen amino acids of US-licensed Remicade and EU-approved Remicade.

Analysis by mass spectrometry (MS and MS/MS) confirmed the expected presence of eight disulfide bonds in each of the three products.

Protein Content

US-licensed Remicade is filled into 20 mL capacity vials with 100 mg infliximab protein, which is then reconstituted with 10 mL of sterile water for injection (WFI) prior to use. The drug product manufacturing process of CT-P13 was designed to match the protein content of US-licensed Remicade, within reasonable tolerances. A demonstration that protein content matched between vials of US-licensed Remicade and CT-P13 was performed by reconstitution of ten vials from each group in an equal volume of water (10 mL), followed by protein concentration measurement by UV-spectroscopy. The data confirm that total protein amounts in the reconstituted CT-P13 and the reference product met pre-specified acceptance criteria.

Aggregates

Biopharmaceuticals typically contain very low levels of protein aggregates (<1%) which are measured and controlled at lot release. Small amounts of aggregation are present in both CT-P13 and US-licensed Remicade upon reconstitution in water. In the clinical setting, larger particles are removed during patient administration by in-line filters in infusion sets. Aggregation is typically detected and quantified by the size-exclusion chromatography assay (SEC-HPLC). The average level of aggregates in US-licensed Remicade quantified by Celltrion's SEC-HPLC assay was 0.2%, while CT-P13 was 0.6%. These levels of aggregation are consistent with levels seen in other biopharmaceutical products. From a quality standpoint, high levels of aggregation may impact product immunogenicity when infused into patients, but levels below 1% are typical in this class of products. This aspect was also addressed in the immunogenicity assessment and the subvisible particle discussion below.

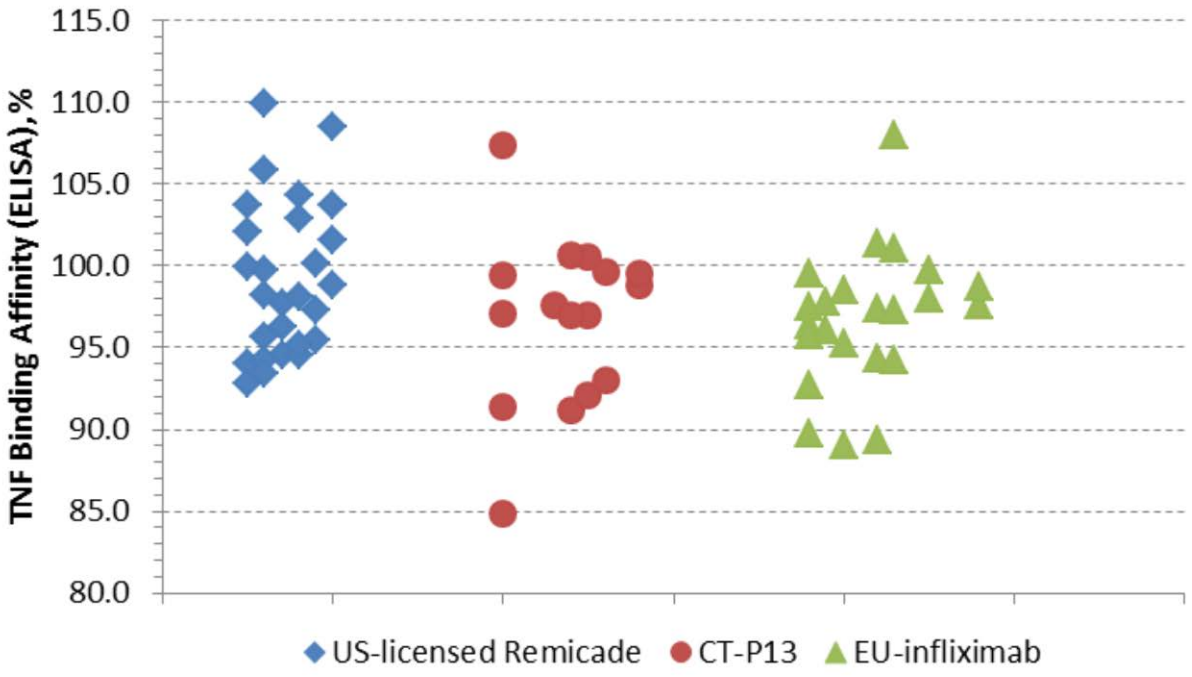
Biological Activity

A number of bioassays were designed and qualified to evaluate potential infliximab functions, including binding and neutralization of TNF-α as well as Fc effector functions. The data are generally reported as a percentage relative to the applicant's in-house CT-P13 reference standard.

TNF-α binding was also assessed using an enzyme linked immunosorbent assay (ELISA). An ELISA is an assay that measures the primary functional activity of infliximab, TNF-α binding. A comparison of the relative binding affinity of CT-P13, EU-approved Remicade and US-licensed Remicade for TNF-α was carried out with 16 to 27 lots of each product. Because of the criticality of this function, these data (see Figure 3)

were subjected to a statistical analysis using equivalence testing. The TNF-α binding affinity (by ELISA) of CT-P13 is statistically equivalent to the TNF-α binding affinity (by ELISA) of US-licensed Remicade if the 90% confidence interval (CI) of the mean difference in TNF-α binding affinity (by ELISA) between CT-P13 and US-licensed Remicade is entirely within an equivalence acceptance criterion calculated from Celltrion's data on US-licensed Remicade. Descriptive statistics for the TNF-α binding Affinity (by ELISA) data of CT-P13, US-licensed Remicade, and EU-approved Remicade are listed in Figure 3.

Figure 3. Comparative Binding Affinity (ELISA) of CT-P13, US-Licensed Remicade, and EU-Approved Remicade to Human TNF-α



Source: FDA analysis of data from Celltrion 351(k) BLA submission

Table 3. Descriptive Statistics for the TNFα Binding Affinity (ELISA) Data of CT-P13, US-licensed Remicade, and EU-approved Remicade

Product	Number of batches	Sample mean, %	Sample standard deviation, %	Min, %	Max, %
CT-P13	16	96.7	5.21	84.9	107.4
US-licensed Remicade	27	99.2	4.69	92.8	109.9
EU-approved Remicade	23	96.8	4.22	89.0	108.0

Source: FDA analysis of data from Celltrion 351(k) BLA submission

The statistical equivalence analyses shown in Table 4 regarding the TNF-α binding affinity (by ELISA) of CT-P13 support the conclusion that CT-P13 is highly similar to that of US-licensed Remicade. Further, these analyses support the analytical component of the scientific bridge between US-licensed Remicade, EU-approved Remicade and CT-P13 to justify the relevance of comparative data generated from clinical and non-clinical studies that used EU-approved Remicade.

Table 4. Equivalence Testing Results for the TNFα Binding Affinity (ELISA) of CT-P13, US-licensed Remicade, and EU-approved Remicade

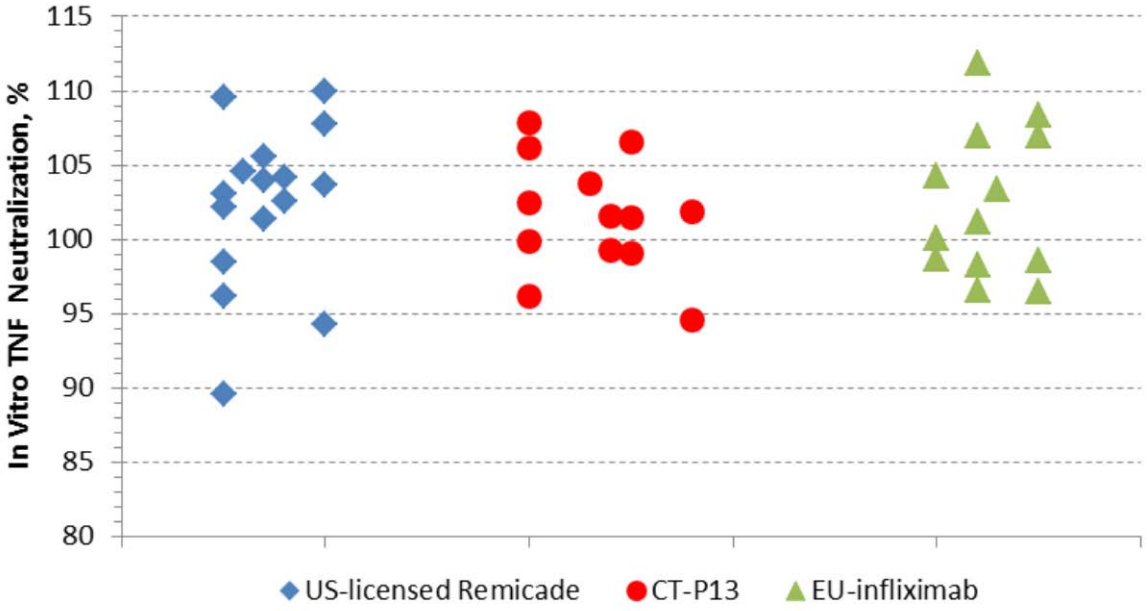
Product	Number of batches	Comparator Product	Number of batches	Equivalent
CT-P13	16	US-licensed Remicade	27	Yes[a]
CT-P13	16	EU-approved Remicade	23	Yes[b]
EU-approved Remicade	23	US-licensed Remicade	27	Yes[c]

Source: FDA analysis of data from Celltrion 351(k) BLA submission
[a] The 90% confidence interval for the mean difference in TNFα binding affinity (ELISA) between CT-P13 and US-licensed Remicade, (-5.09, 0.09)%, falls entirely within the equivalence margin, (-7.04, 7.04)%.
[b] The 90% confidence interval for the mean difference in TNFα binding affinity (ELISA) between CT-P13 and EU-approved Remicade, (-2.60, 2.50)%, falls entirely within the equivalence margin, (-6.34, 6.34)%.
[c] The 90% confidence interval for the mean difference in TNFα binding affinity (ELISA) between EU-approved Remicade and US-licensed Remicade, (-4.58, -0.31)%, falls entirely within the equivalence margin, (-7.04, 7.04)%.

The primary mechanism of action of the three products was also measured using an orthogonal *in vitro* TNF-α neutralization assay. This assay measures the ability to inhibit TNF-α-induced cell death in a mouse fibrosarcoma cell line, WEHI-164 cells. These data (see Figure 4) were also subjected to a statistical analysis using equivalence testing with a 90% confidence interval (CI). The *in vitro* TNF-*α* neutralization activity of CT-P13 is statistically equivalent to the *in vitro* TNF-*α* neutralization activity of US-licensed Remicade if the 90% confidence interval (CI) of the mean difference in the *in vitro* TNF-*α* neutralization activity between CT-P13 and US-licensed Remicade is entirely within an equivalence acceptance criterion calculated from the Applicant's data

on US-licensed Remicade. Descriptive statistics for the *in vitro* TNFα neutralization activity data are listed in Table 5.

Figure 4. Biological Activity of CT-P13, US-licensed Remicade, and EU-approved Remicade



Source: FDA analysis of data from Celltrion 351(k) BLA submission

Table 5. Descriptive Statistics for the *in vitro* TNFα Neutralization Activity Data of CT-P13, US-licensed Remicade, and EU-approved Remicade

Product	Number of batches	Sample mean, %	Sample standard deviation, %	Min, %	Max, %
CT_P13	13	101.6	3.92	94.6	107.9
US-licensed Remicade	16	102.3	5.45	89.6	110.9
EU-approved Remicade	13	102.5	4.94	96.5	111.9

Source: FDA analysis of data from Celltrion 351(k) BLA submission

The statistical equivalence analyses shown in Table 6 regarding the *in vitro* TNF-α neutralization activity of CT-P13 support the conclusion that CT-P13 is highly similar to that of US-licensed Remicade. Further, these analyses support the analytical component of the scientific bridge between US-licensed Remicade, EU-approved Remicade and CT-P13 to justify the relevance of comparative data generated from clinical and non-clinical studies that used EU-approved Remicade.

Table 6. Equivalence Testing Results for the *in vitro* TNFα Neutralization Activity of CT-P13, US-licensed Remicade, and EU-approved Remicade

Product	Number of batches	Comparator Product	Number of batches	Equivalent
CT-P13	13	US-licensed Remicade	16	Yes[a]
CT-P13	13	EU-approved Remicade	13	Yes[b]
EU-approved Remicade	13	US-licensed Remicade	16	Yes[c]

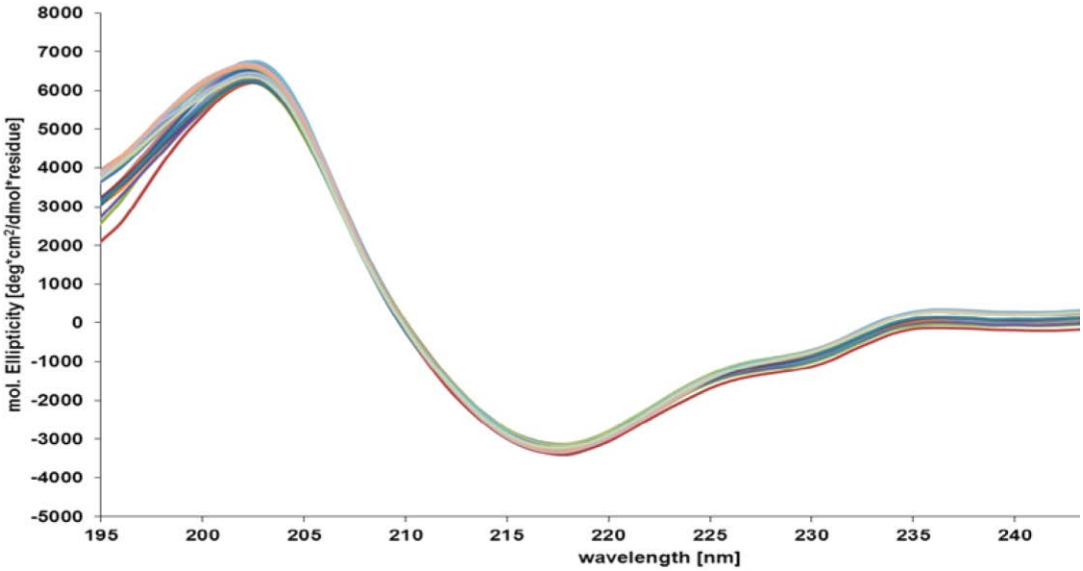
Source: FDA analysis of data from Celltrion 351(k) BLA submission
[a] The 90% confidence interval for the mean difference in the TNFα neutralization activity between CT-P13 and US-licensed Remicade, (-3.79, 2.36)%, falls entirely within the equivalence margin, (-8.18, 8.18)%.
[b] The 90% confidence interval for the mean difference in the TNFα neutralization activity between CT-P13 and EU-approved Remicade, (-3.83, 2.15)%, falls entirely within the equivalence margin, (-7.42, 7.42)%.
[c] The 90% confidence interval for the mean difference in the TNFα neutralization activity between EU-approved Remicade and US-licensed Remicade, (-3.20, 3.45)%, falls entirely within the equivalence margin, (-8.18, 8.18)%.

Higher Order Structure (HOS)

Secondary and tertiary structures of the infliximab products were evaluated by far and near UV circular dichroism (CD), and Fourier Transform Infrared (FTIR) spectroscopy (Table 2). Proper folding is critical for the effective function and serum life of antibodies.

Far and near UV CD spectroscopy provides information regarding secondary (α-helix, β-sheet and random coil structures) and tertiary structure, respectively. Representative Far UV CD spectra, with largely overlapping spectral traces for seven lots each of CT-P13, US-licensed Remicade and EU-approved Remicade are shown in Figure 5. Near UV CD and FTIR spectral trace were similarly overlapping (data not shown).

Figure 5. Far UV CD Spectra for CT-P13, US-licensed Remicade, and EU-approved Remicade



Source: Figure excerpted from the Celltrion 351(k) BLA submission

Process-related Substances and Impurities

The types and levels of process-related substances and impurities in the three products were assessed quantitatively by the methods listed in Table 2. Such substances originate from the complex biological culture system (e.g., HCPs, media components, etc.) or the purification process (e.g., protein A from the initial capture column). The goal in bioprocessing is to remove these inevitable undesirable components of bioreactor cell culture to levels as low as achievable by the downstream purification. The three products all achieved acceptably low levels of residual impurities (data not shown).

Fc function

Antibodies function not only by binding and neutralizing antigens via their antigen binding complementary determining region (CDR) surface, but also by activating or down-modulating other parts of the immune system. An example of down modulation would be antibody-mediated reverse signaling, where antibody cross-linked cells may undergo apoptosis or be inhibited from secreting pro-inflammatory cytokines. In contrast, antibodies can also activate immune effector functions via molecular bridging between the Fc part of the antibody and soluble (e.g. C1q) or cell membrane-bound (e.g. FcγR proteins) molecules. Functions activated in this manner include antibody-dependent cellular cytotoxicity (ADCC), initiated by bridging effector and target cells via Fc-binding receptors on the effector cell surface and complement-dependent cytotoxicity (CDC). In CDC, the complement system is activated by targeting C1q binding to a cell surface, which initiates a biological cascade that ultimately results in pore formation in the target cell membrane.

The Fc- receptors, FcγRI, FcγRII, FcγRIII, FcRn, are diverse in structure and location of cell expression. The predominant Fc receptor type on natural killer (NK) cells is FcγRIII (a or b forms), while other leukocytes express a more broad range. NK cells are highly potent immune cells believed to play a predominant role in the host rejection of both tumor and virally infected cells. Thus, different ADCC effector cells can be recruited based on which Fc receptor is bound.

The binding strength of CT-P13, EU-approved Remicade, and US-licensed Remicade to various Fc receptors was measured. Binding activity was measured either by ELISA assays or surface plasmon resonance (SPR) methodology. Overall, the binding affinities of the three products were highly similar for FcRn, FcγRI and FcγRIIa & b (data not shown).

However, the binding affinity of CT-P13 to the NK expressed FcγRIIIa and b was shifted lower compared to US-licensed Remicade (see Table 7). This was associated with subtle shifts in glycosylation at Asn297 on the heavy chain of the two antibody products detected in the analysis using a HPAEC-PAD chromatography method (e.g., CT-P13 on average had <39% G0F, the predominant form, while US-licensed Remicade & EU-approved Remicade had 41-46% G0F). Glycosylation of antibodies is typically heterogeneous; up to twenty different detectable N-linked glycan forms can exist in an antibody preparation. There are typically predominant species like G0F (no terminal galactoses, with a fucose at the base) or G1F (one terminal galactose, with a fucose). Some types, such as forms with fucose at the base of the biantennary structure, can influence the Fc three dimensional structure to lower the binding affinity to receptors like FcγRIII. The relative levels of minor species like G0 (no terminal galactoses, but no fucose), which were different between CT-P13 (0.7%) and US-licensed Remicade (1.4%), can have an impact on binding to FcγRIII and are important to measure and control in antibody-based biopharmaceuticals. Antibodies produced in mammalian cell culture systems will vary in glycan pattern somewhat from product-to-product, and to a lesser degree, from lot-to-lot. The implications of FcγRIII binding difference between CT-P13 and Remicade vis-à-vis ADCC and product mechanism of action are discussed below.

Table 7. FcγRIIIa Binding (SPR) of CT-P13, US-Licensed Remicade and EU-approved Remicade

Binding (SPR)[a]	CT-P13	EU-Remicade	US-Remicade
FcγRIIIa V type%	101±2.3	126±7.7	127±4.9
FcγRIIIa F type%	103±2.8	126±6.3	124±6.0

Source: FDA analysis of data from Celltrion 351(k) BLA submission
[a]-All data are expressed at % activity relative to a CT-P13 reference standard included in the same assay.

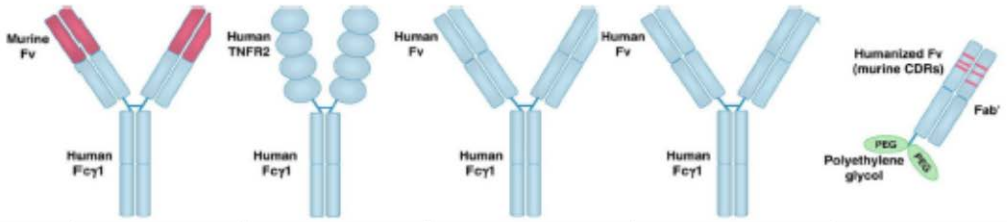
Biological Assays that Address Potential Mechanisms of Action

The main activity of infliximab is believed to be TNF-α binding and sequestration, mediated via the variable region CDR surface. However, other potential mechanisms involving mTNF-α binding exist, such as reverse signaling (discussed below and summarized in Peake et al., 2013.[10] Also, antibodies can mediate effector functions via their Fc portion like ADCC or CDC. In theory, the Fc portion of infliximab could play a role in infliximab function in some indications, as summarized in Table 1.

Antibody-Dependent Cellular Cytotoxicity (ADCC)

When features of the broad class of TNF-α antagonists are examined (Remicade, Enbrel, Humira, Simponi, Cimzia), there is a hint that Fc-related mechanism might be involved. This is summarized in Figure 6 below.

Figure 6. The Role of Fc in the Anti-TNF-α Class Mechanism(s) of Action



	Infliximab	Etanercept	Adalimumab	Golimumab	Certolizumab (pegol)
ADCC	High	Low	High	High	None
CDC	High	Low	High	High	None
RA	Yes	Yes	Yes	Yes	Yes
CD/UC	Yes/Yes	No/NS	Yes/Yes	NS/Yes	Yes#/NS

NS=Not Studied
# approved indication in CD is based on reducing signs and symptoms and maintaining clinical response rather than achieving and maintaining /sustaining remission

Source: FDA summary of existing literature on the topic of Fc functions of TNF-blockers.[11,12,13]

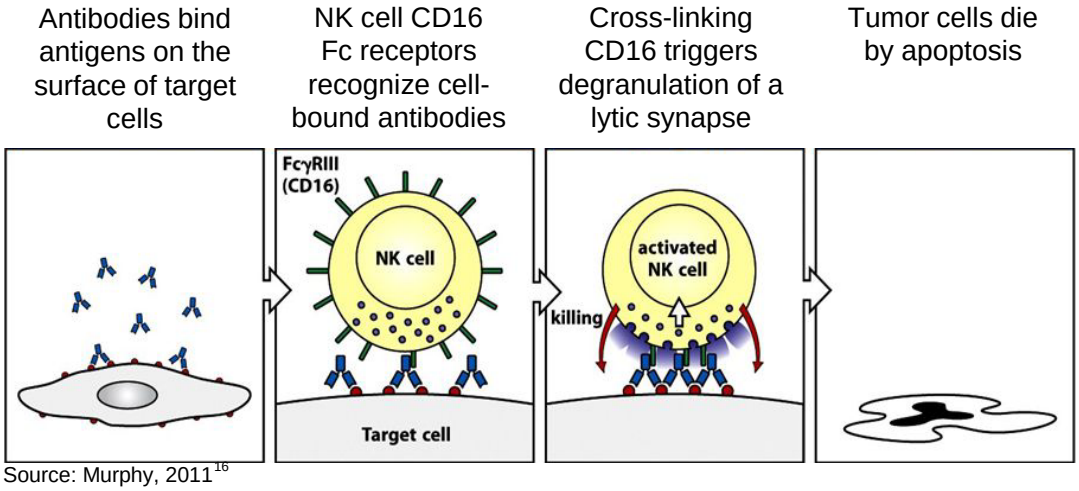
As shown in the third row, all listed TNF-α antagonists have demonstrated efficacy and are approved for the treatment of RA. However, this is not true for all indications as shown in the bottom row, where the efficacy in Crohn's Disease (CD) and ulcerative colitis (UC) has not been demonstrated for all listed TNF-α antagonists. Enbrel (etanercept), which has low ADCC activity, is not approved for treatment of CD or UC.

[10] Peake, S. T. C., et al. Inflammatory bowel diseases, 2013, 19(7), 1546-1555.
[11] Arora, T., et al. Cytokine, 2009 45(2), 124-131.
[12] Kaymakcalan, Z. et al. Clinical immunology, 2009, 131(2), 308-316.
[13] Mitoma, H. et al. Gastroenterology, 2005, 128(2), 376-392.

Published literature supports a lack of efficacy of etanercept in CD based on a small study (N=49) using a dose approved in RA[14]. In addition, Cimzia (certolizumab pegol), which has no ADCC activity, achieved clinical response but not clinical remission achieved by other approved TNF-α antagonists, as summarized in Figure 6. Although it is possible that other factors contributed to this outcome, such as inadequate dosing, it also raises a question as to whether absence of ADCC activity could have played a role.

In theory, ADCC could be involved with the mechanism of action of infliximab by eliminating mTNF+ inflammatory cells like macrophage or T-cells and thereby down modulating disease activity in inflamed sites. ADCC is an immune function where effector cells such as NK cells lyse target cells via antibody bound to the surface of the targets. The antibody Fc portion is able to recruit the effector cells via FcγR:Fc bridging. FcγRIIIa or CD16 is the main form of FcγR on NK cells, a highly potent type of immune cells that target antibody bound tumor or virally infected cells (see Figure 7). While there is no direct *in vivo* or clinical evidence that ADCC plays a role in infliximab efficacy, it is discussed in the literature[15] and was adequately addressed by Celltrion, as discussed below.

Figure 7. ADCC: Proposed Role in Anti-TNF-α Class Mechanism(s) of Action



Source: Murphy, 2011[16]

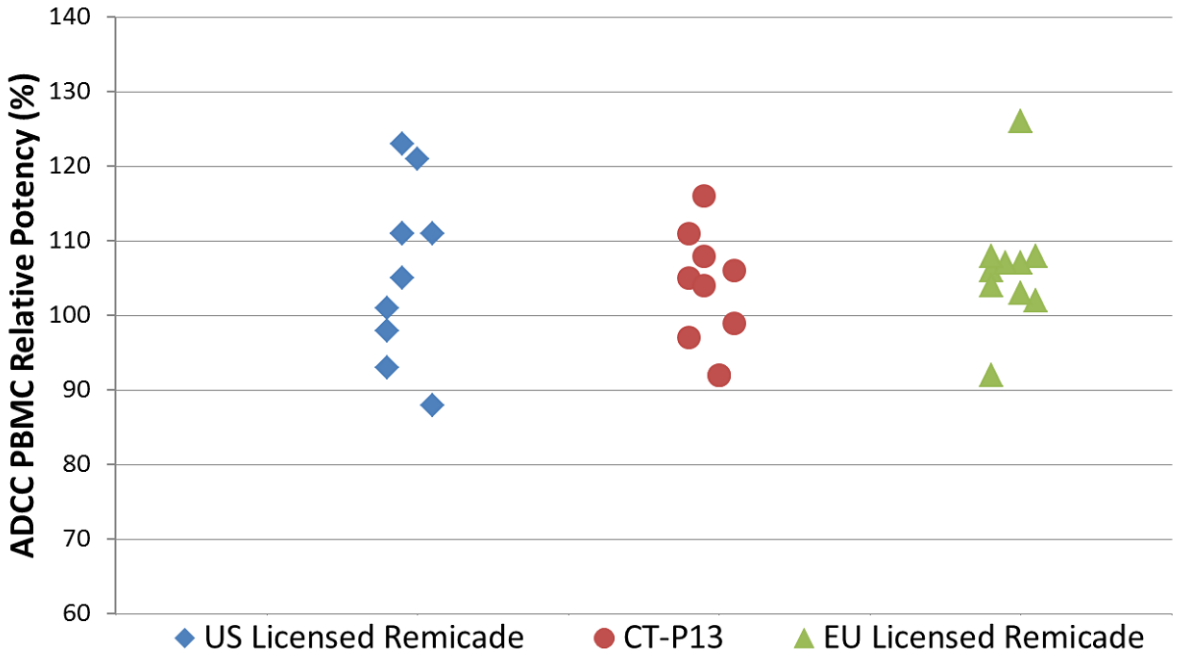
ADCC activity may vary with the strength of the FcγR:Fc bridging, which in turn may be dependent on the glycan composition on the antibody (see discussion above). To fully evaluate the role that ADCC may play in CT-P13 and Remicade function, Celltrion designed a panel of three ADCC assays to compare the activity of CT-P13 with US-licensed Remicade. The three assays used combinations of peripheral blood mononuclear cell (PBMC) or purified NK cells as effectors, and mTNF+ Jurkat cell transfectomas or lipopolysaccharisde (LPS)-activated macrophages as targets. The

[14] Sandborn WJ, Hanauer SB, Katz S, et al. Etanercept for active Crohn's disease: A randomized, double-blind, placebo-controlled trial. Gastroenterology 2001;121:1088–94.
[15] Peake, S. T. C., et al. Inflammatory bowel diseases, 2013, 19(7), 1546-1555.
[16] Murphy, K. Janeway's Immunobiology, 8th Edition, 2011

transfectomas target cells expressed very high levels of mTNF-α, about 20-50 fold that present on activated leukocytes. They found that only using the transfectomas targets were they able to detect ADCC activity with either CT-P13 or US-licensed Remicade.

Below are data from the ADCC assay using peripheral blood mononuclear cells (PBMC) as effector cells. Celltrion has asserted that PBMC are a complex population of cells that are more physiologically relevant than purified populations like enriched NK cells. PBMC would contain some NK cells, but would also contain other populations that may also serve as effector cells or as regulatory cells that modulate the activity of the co-cultured NK cells. Unlike TNF-α binding, there is uncertainty regarding the criticality of Fc effector function for the infliximab mechanism of action. Thus, tests for Fc functions were not examined for statistical equivalence, rather they were examined with respect to quality range testing defined by Celltrion's data on the reference product as defined by mean plus or minus three standard deviations. In this assay format, 100% of the 13 biosimilar lots fell within the quality range.

Figure 8. ADCC of CT-P13, US-licensed Remicade, and EU-approved Remicade Using PBMC as Effector Cells

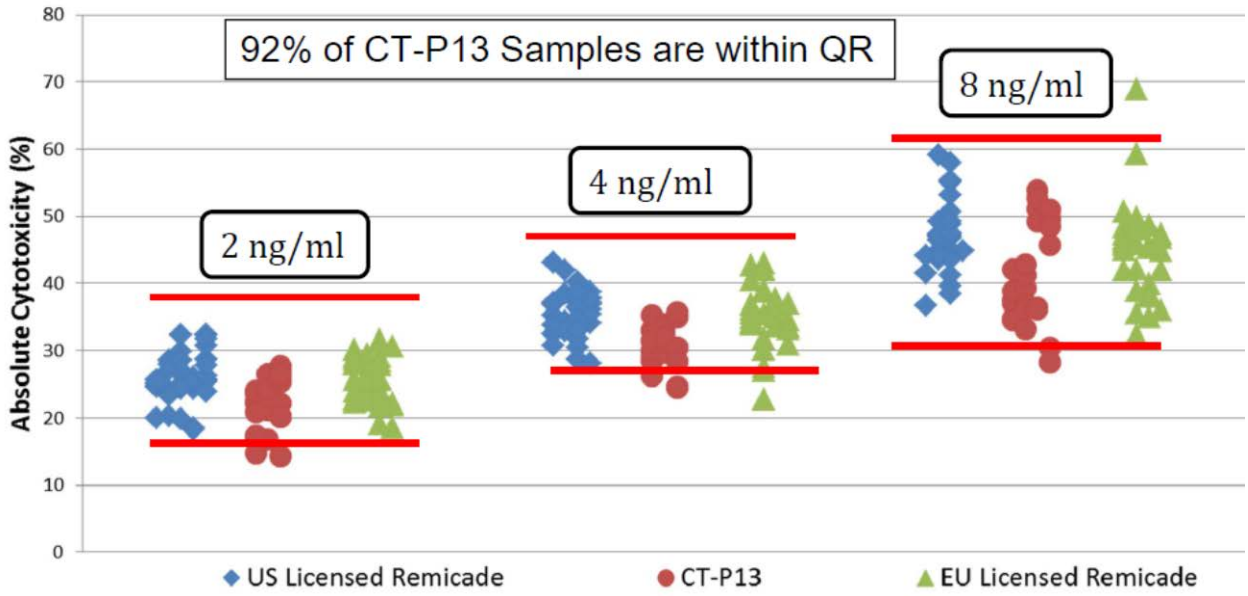


Source: FDA analysis of data from Celltrion 351(k) BLA submission

An orthogonal ADCC assay using enriched NK cells instead of PBMC as effectors was also developed. In theory, this assay could more precisely measure the activity of the effector cell type most likely to mediate ADCC via infliximab, assuming that this activity is occurs or is important for down-modulating inflammation at diseased sites. To ascertain if a dose-response relationship exists; the three antibodies (CT-P13, US-

licensed Remicade, and EU-approved Remicade) were compared for ADCC at three different concentrations. While considerable overlap exists between the lots of the products, a small downward shift, around 20%, is evident in ADCC activity for CT-P13 in this assay format at each concentration. Statistically, >90% of the lots of the proposed biosimilar were within the quality range of the reference product (red bars). The data support a demonstration that CT-P13 is highly similar to US-licensed Remicade because of the largely overlapping data (90% of proposed biosimilar lots were within the quality range (QR) defined by three standard deviations around the mean set by Celltrion's data on the reference product) and the nature of the measured activity (i.e., an Fc function of uncertain importance).

Figure 9. ADCC of CT-P13, US-licensed Remicade, and EU-approved Remicade Using NK Cells as Effector Cells



Source: FDA analysis of data from Celltrion 351(k) BLA submission

Finally, Celltrion developed an ADCC assay format using LPS-stimulated monocytes as target cells and PBMC as effector cells. The goal was to assess CT-P13 and US-licensed Remicade-mediated ADCC of more physiologically relevant target cells than the highly expressing mTNF+ Jurkat cell transfectant. This format detected no lytic activity with either CT-P13 or US-licensed Remicade. This observation led Celltrion to assert that there is low mTNF expression in this more physiologically relevant model for the associated target cell population in IBD, immune cells in the colonic lamina propria. Proving such an assertion would be challenging, and there is uncertainty regarding mTNF levels in the relevant immune cells in IBD colonic lamina propria.[17,18] However, this uncertainty is mitigated by a demonstration that CT-P13 is highly similar to US-

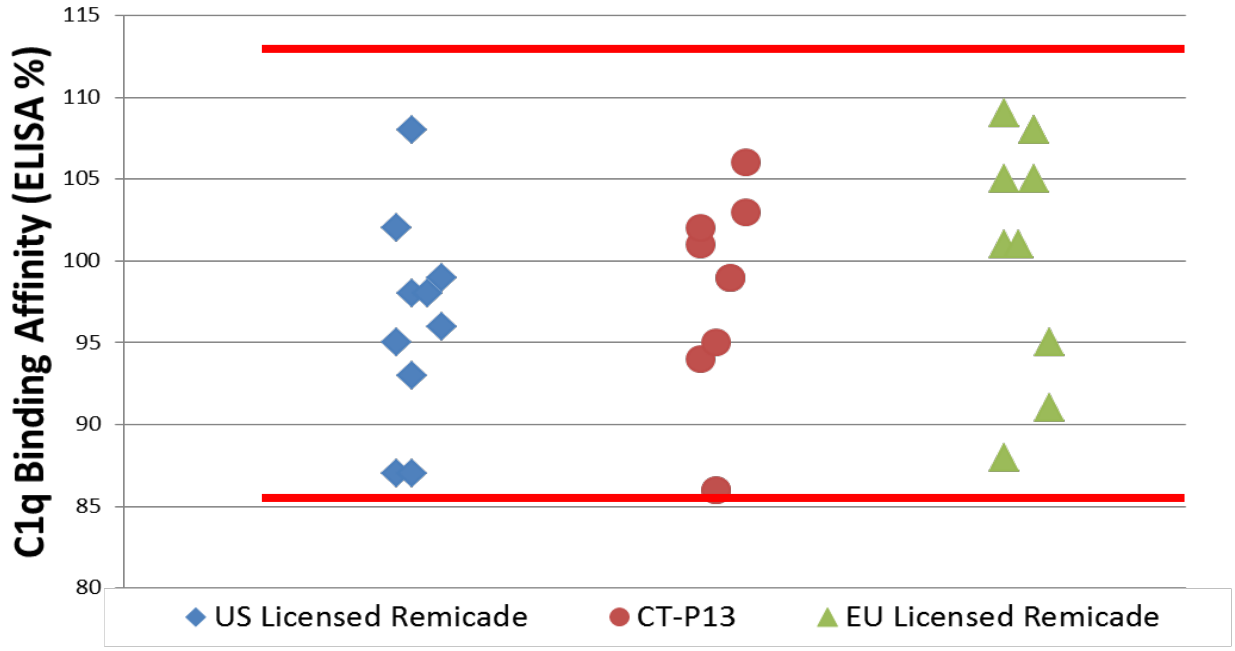
[17] Kamada, N. et. al. Journal of Clinical Investigation, 2008, 118(6), 2269-2280.
[18] Steel, A. W., et. al. Alimentary pharmacology & therapeutics, 2011, 33(1), 115-126.

licensed Remicade because the ADCC activity of CT-P13 is within the quality range set by Celltrion's data on the reference product."

C1q Binding and Complement Dependent Cytotoxicity (CDC)

C1q binding is a precise measure for the initiation of the complement cascade. 100% of the lots of the proposed biosimilar were also within the quality range of Celltrion's data on the reference product, again as defined by the mean values derived from the reference product lots plus or minus three standard deviations. C1q binding is the first step in the activation of the complement system and CDC. There is no direct evidence addressing whether CDC is involved with infliximab function, nor is there direct evidence that it is irrelevant. Data shown in Figure 10 below demonstrated that C1q binding is highly similar between the three product types (red bars are the quality range set by the reference product). Measurement of CDC activity, the downstream outcome of C1q binding, was also overlapping between the three products (data not shown).

Figure 10. C1q Binding Affinity (ELISA) of CT-P13, US-licensed Remicade, and EU-approved Remicade



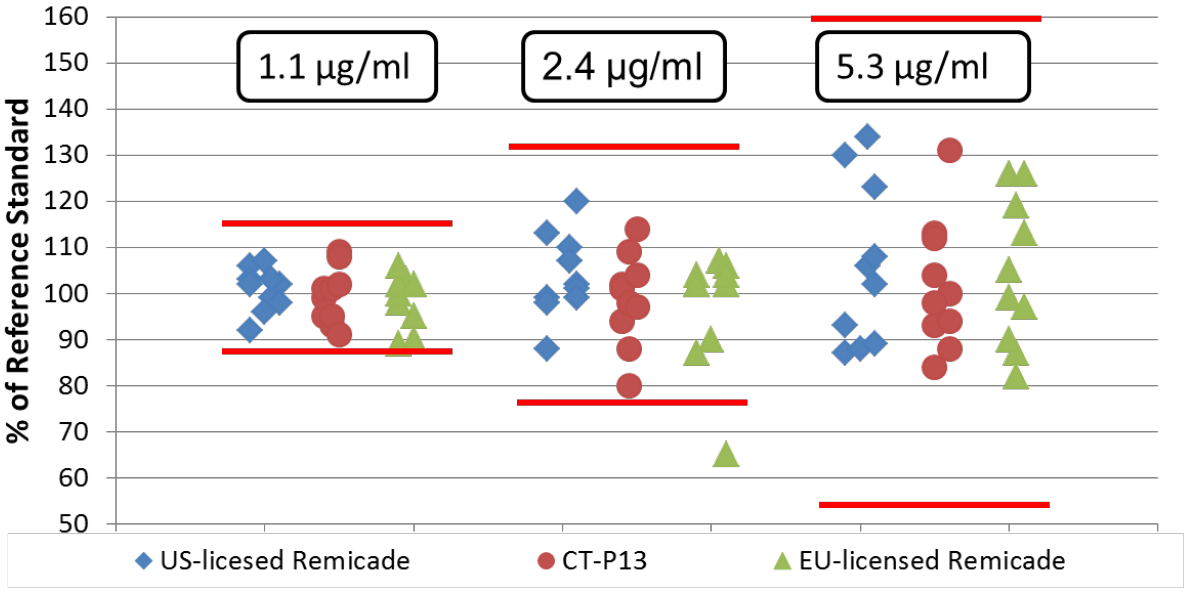
Source: FDA analysis of data from Celltrion 351(k) BLA submission

Reverse Signaling and Apoptosis

Reverse signaling is a cellular feedback that occurs when a molecule that is normally a signaling molecule, like mTNF-α on immune cells (e.g., NK cells and monocytes), is instead bound and/or cross-linked by an antibody transducing a signal back to that cell instead of forward to another cell. In theory, reverse signaling by infliximab can

transduce a signal to mTNF^{+} cells transducing a response like suppression of cytokine release and even apoptosis. There is some published literature that suggests that infliximab may function this way in IBD patients. For example, this contention is supported by studies using *in vivo* immunofluorescent staining of patient colon and/or TUNEL assays of IBD patient biopsies as well as *in vitro* studies using cultured clinical isolates.[19] Celltrion developed three reverse signaling assays, including an *in vitro* reverse signaling assay measuring LPS-induced TNF-α release from PBMCs. Here, three concentrations of the CT-P13 and US-licensed Remicade and EU-approved Remicade were tested for reverse signaling. 100% of the CT-P13 lots were within the quality range set by the US-licensed reference product. CT-P13 and US-licensed Remicade testing results from two other reverse signaling assay formats were found to be overlapping as well.

Figure 11. Reverse Signaling Assay of CT-P13, US-licensed Remicade, and EU-approved Remicade



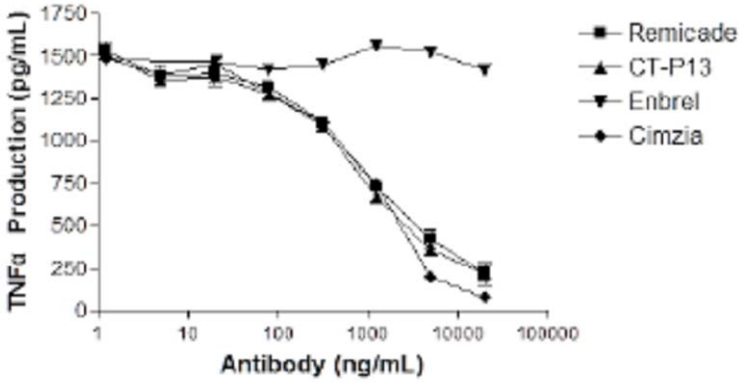
Source: FDA analysis of data from Celltrion 351(k) BLA submission

As discussed above, reverse signaling is described in the literature as potentially important in the mechanism of action of TNF-α antagonists in inflammatory bowel diseases. Additional circumstantial evidence for this contention is provided by the observation that infliximab, adalimumab, and certolizumab pegol (a Fab fragment that lacks an Fc portion, but is pegylated) are able to reverse signal causing cytokine suppression, while etanercept does not[20] (Figure 12 below). Certolizumab, like etanercept, is monomeric and can't cross-link mTNF, but apparently certolizumab binds the mTNF molecule in a way that still delivers a signal. This observation correlates with

[19] Atreya, R., et. al. Nature Medicine, 2014 20(3), 313-318.
[20] Nesbitt, A., Inflammatory bowel diseases, 2007, 13(11), 1323-1332.

anti-IBD activity of the infliximab, adalimumab and certolizumab pegol, but not etanercept.

Figure 12. Reverse Signaling; Suppression of TNF-α Release from LPS-Stimulated PBMCs by Cimzia, Enbrel, CT-P13 and Remicade



Source: Figure excerpted from Celltrion 351(k) BLA submission

Activation of Regulatory Macrophages

Celltrion also developed assays to measure and compare the induction of regulatory macrophage based on the research on this topic.[21] Activities of CT-P13 and Remicade in these semi-quantitative assays were largely overlapping (data not shown).

Sub-Visible Particles

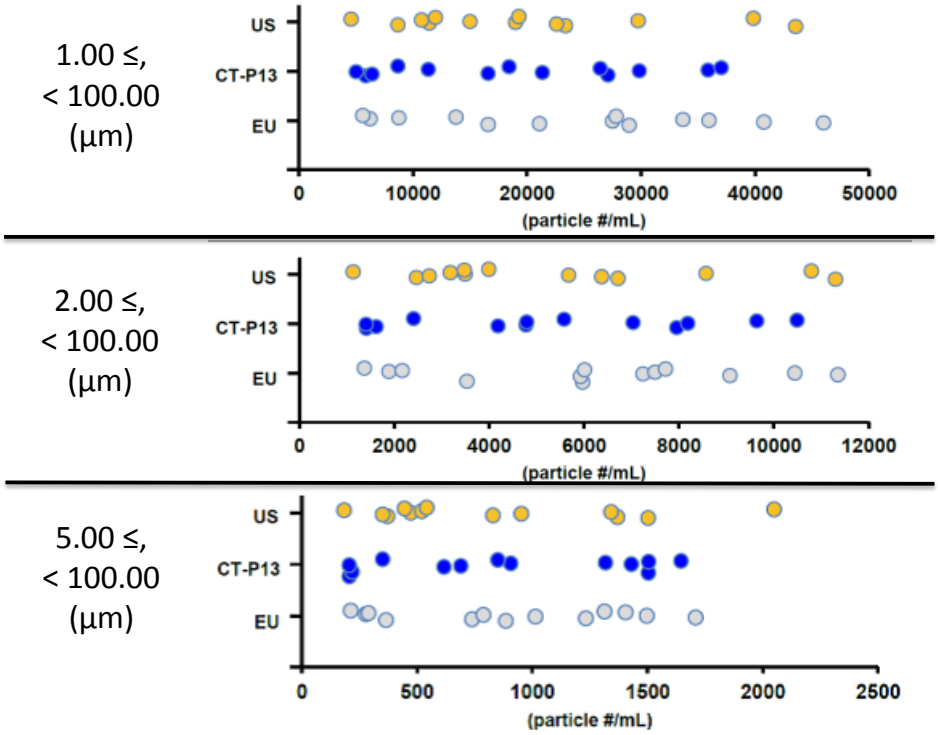
There is a consensus among immunologists that the immune system may be sensitive to particles in the 1 to 25 μm size range. Product-related particles of this size may increase the development of anti-product antibodies. Product-specific immune responses (i.e., anti-Remicade or anti-CT-P13 antibodies) could potentially impact product safety and efficacy[22] and were assessed as part of the CT-P13 development program. This comparison included both clinical data (discussed in greater detail in the section on Immunogenicity below) as well as quality attributes, such as sub-visible particles, that may impact product immunogenicity.

Subvisible particles in the 10 to 25 μM range are typically controlled in injectable pharmaceutical products at lot release using compendial light obscuration techniques, which will be used by Celltrion as a control strategy. Celltrion also performed an extensive comparison of CT-P13, US-licensed Remicade and EU-approved Remicade post-reconstitution for proteinaceous particles in the 1-5 μM range, using two analytical

[21] Vos, A. C. W., et al. Gastroenterology, 2011, 140(1), 221-230.
[22] Rosenberg AS, Verthelyi D, Cherney BW. Managing uncertainty: a perspective on risk pertaining to product quality attributes as they bear on immunogenicity of therapeutic proteins. J Pharm Sci. 2012 Oct;101(10):3560-7.

methods, microflow imaging (MFI) and light obscuration (HAIC). Below is the MFI data from this analysis; the orthogonal method of light obscuration yielded similar conclusions (data not shown). As can be seen, there is considerable spread between different product lots, but the data overlapped with no consistent pattern of more or fewer particle levels in any of the three products.

Figure 13. Sub-Visible Particles by MFI



Source: The figure is excerpted from Celltrion 351(k) BLA submission

This observation, in conjunction with the overall protein analytical results from the 3-way analysis, further support the analytical bridge between CT-P13, US-licensed Remicade, and EU-approved Remicade. Moreover, it supports the conclusion that CT-P13 is highly similar to the reference product and confirms the relevance of clinical immunogenicity data from studies using EU-approved Remicade.

Comparative Stability Studies

Celltrion has evaluated comparative stability of CT-P13, US-licensed Remicade and EU-approved Remicade in an accelerated stability trend study. It was conducted at 40°C for three months, with product evaluated for the accumulation of aberrant charge isoforms (IEC-HPLC), fragmentation (CE-SDS), covalent aggregation (CE-SDS) or loss of potency (*in vitro* bioactivity). The stability patterns of the three products were equivalent.

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 totality of evidence 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 FcγRIII 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 nevertheless within the quality range of the reference product. Thus, based on the extensive comparison of the functional, physicochemical, protein and higher order structure attributes, 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 specified 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.

7 Pharmacology/Toxicology

Executive Summary

The CT-P13 nonclinical development program was adequate to support clinical development. Two key nonclinical toxicology/toxicokinetic studies were submitted in support of the BLA: (1) a single dose toxicokinetic (TK) study in Sprague-Dawley (SD) rats comparing CT-P13 vs. EU-approved Remicade and (2) a 2-week toxicity/TK study in SD rats comparing CT-P13 vs. EU-approved Remicade. During pre-submission communications, the Agency acknowledged the limitations of animal studies as infliximab is only active in chimpanzees and advised Celltrion that additional animal

studies were not recommended based upon the available extensive human experience with infliximab.

Collectively, there was no evidence in nonclinical studies conducted in SD rats to indicate potential clinical safety concerns associated with CT-P13 administration. The TK profile of CT-P13 was comparable to that of EU-approved Remicade in SD rats. The pharmacology and animal data submitted to the BLA support a demonstration of biosimilarity (i.e., comparable exposures and safety profile) between CT-P13 and EU-approved Remicade from the nonclinical Pharmacology and Toxicology perspective. There are no outstanding issues from the nonclinical Pharmacology and Toxicology perspective.

Conclusion

In summary, the animal studies submitted, demonstrate the similarity of CT-P13 to EU-approved Remicade in terms of pharmacokinetics. From the perspective of Pharmacology and Toxicology, the results of these animal studies can be taken together with the data from the analytical bridging studies (see CMC section above for details) to support a demonstration that CT-P13 is biosimilar to the reference product US-licensed Remicade. No residual uncertainties have been identified by the discipline.

8 Clinical Pharmacology

Executive Summary

The applicant submitted pharmacokinetic data from two dosing regimens in two 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.

Pharmacokinetic (PK) similarity of CT-P13 to US-licensed Remicade was evaluated in one FDA-recommended pivotal 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 provided PK bridging data, in addition to the analytical bridging data, to scientifically justify the relevance of the comparative data from the clinical development program with EU-approved Remicade to support a demonstration of no clinically meaningful differences to US-licensed Remicade. For additional considerations on the use of data generated using non-US-approved comparator product, refer to section 2, (under “The Reference Product”) above.

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% CIs

for the ratios of geometric mean of AUC_{inf}, AUC_{last}, and C_{max}, within the interval of 80% to 125%), thus establishing the PK component of the scientific bridge to justify the relevance of the comparative data generated using EU-approved Remicade.

In addition, similar PK was demonstrated for CT-P13 and EU-approved Remicade in two different usage scenarios: in patients with RA (3 mg/kg of either product with concomitant use of methotrexate) and in patients with AS study (use of the higher dose of 5 mg/kg, but without concomitant immunosuppressive therapy).

Overall, the submitted clinical pharmacology studies support the demonstration of PK similarity between CT-P13 and US-licensed Remicade and did not raise any new uncertainties in the assessment of biosimilarity of CT-P13 to US-licensed Remicade.

Description of Relevant Clinical Pharmacology Studies

The PK of CT-P13 following IV administration has been characterized in studies using US-licensed Remicade and/or EU-approved Remicade as the comparator product. The summary of each relevant study design is described below.

- Study 1.4 was a randomized, double-blind, three-arm, parallel-group study following a single dose of 5 mg/kg through a 2-hr IV infusion to compare the PK, safety, tolerability, and immunogenicity of CT-P13, EU-Remicade, and US-licensed Remicade in healthy subjects (N=71/arm). The PK endpoints evaluated in this study were AUCinf, AUC0-last, and Cmax.

  As described in the draft guidance for Industry entitled, "Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product,"[12] a single-dose, randomized study is generally the preferred design for PK similarity assessments. A parallel group design is appropriate for infliximab because it has a long half-life and high immune response rate that may affect the PK similarity assessments upon repeated dosing. Additionally, conducting the study in healthy subjects is reasonable as it is more sensitive in evaluating the product similarity due to lack of potentially confounding factors such as underlying and/or concomitant disease and concomitant medications. The 5 mg/kg IV infusion is relevant as it is within the approved dose range of 3 to 10 mg/kg of US-licensed Remicade.

- Study 1.1 was a randomized, double-blind, parallel-group, Phase 1 study following multiple doses of 5 mg/kg through a 2-hr IV infusion to demonstrate the PK similarity at steady state between CT-P13 and EU-approved Remicade in patients with active

[12] Guidance for Industry "Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product." May 2014.
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM397017.pdf

AS (N=125/group). The PK endpoints evaluated in this study were steady state exposure metrics, $AUC_{T,ss}$ and Cmax,ss, between week 22 and 30.

- Study 3.1 was a randomized, double-blind, parallel-group study following multiple doses of 3 mg/kg through a 2-hr IV infusion to demonstrate the similarity in efficacy and safety between CT-P13 and EU-approved Remicade when co-administered with methotrexate in patients with active RA (N=606). Sparse PK samples were collected pre-dose, and at 2 hours (end of infusion) and 3 hours (1 hour after the end of infusion) following each of the multiple doses for PK similarity comparison between CT-P13 and EU-approved Remicade.

Results of Clinical Pharmacology Studies

Study 1.4: Pharmacokinetics Results

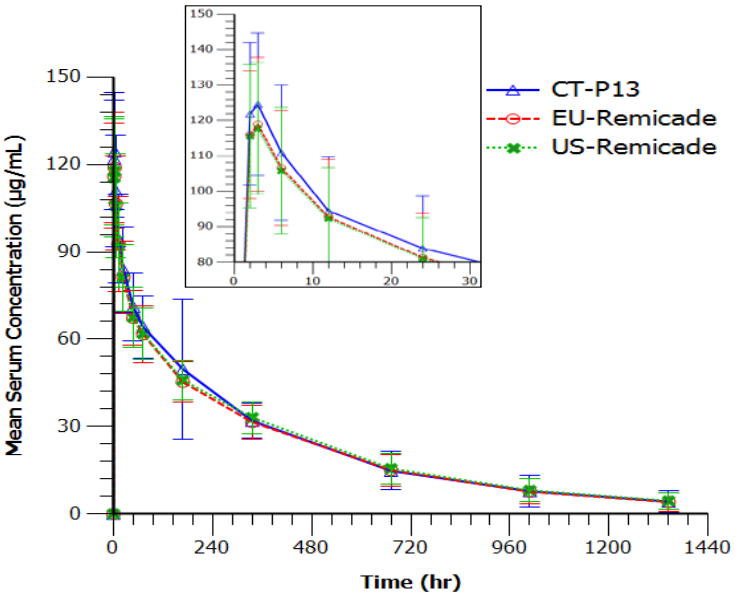
In the dedicated PK study 1.4, the pairwise comparisons of CT-P13, US-licensed Remicade and EU-approved Remicade met the pre-specified acceptance criteria for PK similarity (90% CIs for the ratios of geometric mean of AUCinf, AUClast, and Cmax, within the interval of 80% to 125%) as summarized in Table 8 and depicted in Figure 14. These data establish the PK component of the scientific bridge to justify the relevance of the comparative data generated using EU-approved Remicade to support a demonstration of the biosimilarity of CT-P13 to US-licensed Remicade.

Table 8. PK Analysis of the 3-Way PK Bridging/PK Similarity Study 1.4

Comparison	Parameter	GMR%	90% CI (%)
CT-P13 vs US-licensed Remicade	**Cmax**	105.7	(100.8, 110.8)
	AUC0-t	101.4	(95.1, 108.1)
	AUC0-inf	102.3	(95.1, 110.0)
CT-P13 vs EU-approved Remicade	**Cmax**	106.9	(102.0, 112.1)
	AUC0-t	98.2	(92.3, 104.5)
	AUC0-inf	98.8	(92.1, 106.0)
EU-approved Remicade vs US-licensed Remicade	**Cmax**	100.9	(96.8, 105.8)
	AUC0-t	96.9	(91.7, 102.4)
	AUC0-inf	96.6	(90.4, 103.3)

Source: FDA analysis of data from Celltrion 351(k) BLA submission
CI: confidence interval; GMR: geometric mean ratio

Figure 14. PK Profiles Following a Single IV Dose 5 mg/kg of CT-P13, EU-approved Remicade, or US-licensed Remicade in Healthy Subjects (Study 1.4)



Source: FDA analysis of data from Celltrion 351(k) BLA submission

Study 1.1 Pharmacokinetics Results

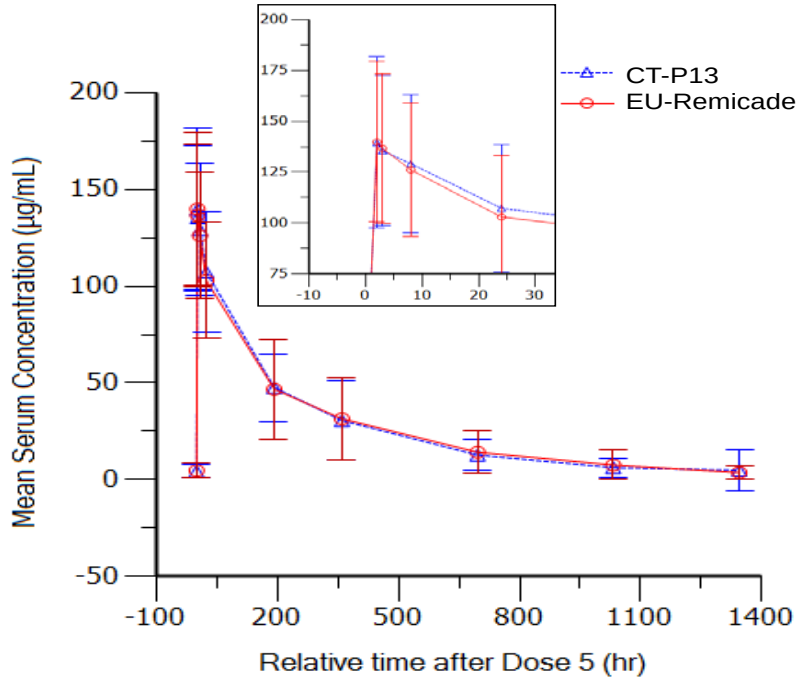
Similar PK, safety, and immunogenicity were demonstrated for CT-P13 and EU-approved Remicade in two different usage scenarios: in patients with RA (3 mg/kg of either product with concomitant use of methotrexate) and in patients with AS study (use of the higher dose of 5 mg/kg, but without concomitant immunosuppressive therapy). In the supporting PK similarity study 1.1 in AS, the 90% CIs for CT-P13 vs. EU-approved Remicade geometric mean ratios of Cmax and AUCtau were contained within the similarity range of 80% –125% as summarized in Table 9 and depicted in Figure 15.

Table 9. PK similarity analysis of Study 1.1 Using Average Bioequivalence Approach

CT-P13 (T) vs EU-approved Remicade (R)						
Parameter	**LSM (T)**	**N**	**LSM (R)**	**N**	**GMR (%)**	**90% CI (%)**
Cmax	149.90	119	144.79	116	103.5	(97.5, 109.9)
AUCss	32155.86	119	30739.38	116	104.6	(94.8, 115.4)

Source: FDA analysis of data from Celltrion 351(k) BLA submission
CI: confidence interval; GMR: geometric mean ratio; The units of Cmax and AUC are µg/mL and µg*hr/mL, respectively

Figure 15. PK Profiles at Steady State between Weeks 22 and 30 Following Multiple IV Doses (5 mg/kg) of CT-P13 or EU-approved Remicade in AS Patients (Study 1.1)

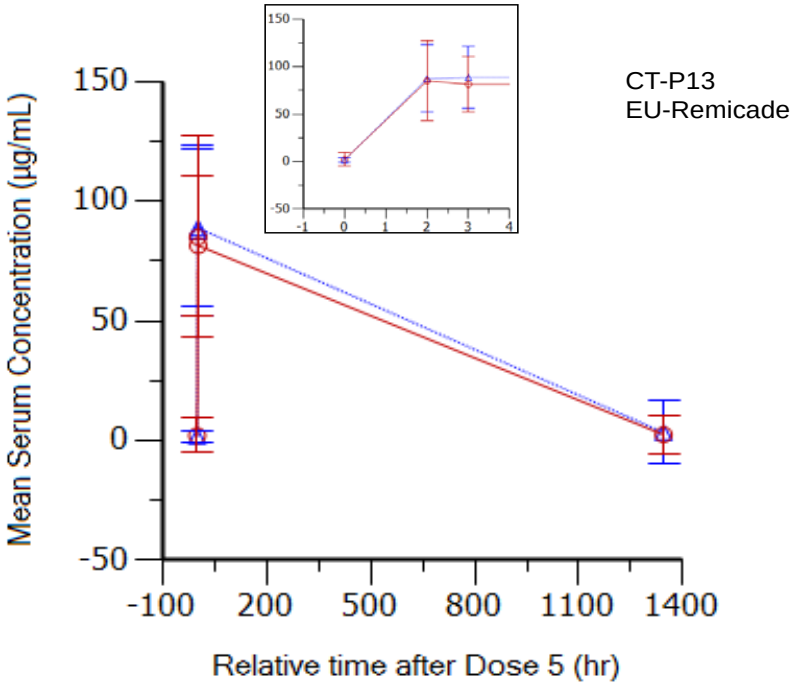


Source: FDA analysis of data from Celltrion 351(k) BLA submission

Study 3.1 Pharmacokinetics Results

In study 3.1, sparse PK samples were collected pre-dose, and at 2 hours (end of infusion) and 3 hours (1 hour after the end of infusion) following each of the multiple IV doses (3 mg/kg) in RA patients. As shown in Figure 16, the concentrations following dose 5 are comparable at each time point between CT-P13 and EU-approved Remicade. The same was observed for all other doses.

Figure 16. PK Profiles between Weeks 22 and 30 Following Multiple IV Dosing (3 mg/kg) of CT-P13 or EU-approved Remicade in RA Patients (Study 3.1)



Source: FDA analysis of data from Celltrion 351(k) BLA submission

Relevance of the PK Data to Indications Not Studied in CT-P13 Program

The PK of CT-P13 is comparable across the various studied populations including healthy subjects and patients with RA and AS. Further, 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.[23] Since similar PK was demonstrated between CT-P13 and US-licensed Remicade as discussed above, a similar PK profile would be expected for CT-P13 in patients with PsA, PsO, adult and pediatric CD, and adult and pediatric UC[24].

Clinical Pharmacology Conclusions

Overall, the submitted clinical pharmacology studies are adequate to:

1) Demonstrate similarity of exposure between CT-P13 and US-licensed Remicade. The PK study 1.4, conducted in healthy subjects, is considered sensitive to

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

detect clinically meaningful differences in exposure among the products. Single-dose PK similarity pre-specified margins were met for the 5 mg/kg dose.

2) Establish the PK component of the scientific bridge to justify the relevance of the comparative data generated using EU-approved Remicade to support a demonstration of the biosimilarity of CT-P13 to US-licensed Remicade.
3) Justify the relevance the PK findings from the CT-P13 clinical program to the other indications for which the applicant is seeking licensure.

In summary, the PK similarity has been demonstrated between CT-P13 and US-licensed Remicade, and the results from the PK studies add to the totality of evidence to support a demonstration of no clinically meaningful differences between CT-P13 and US-licensed Remicade. The PK studies have not raised any new uncertainties in the assessment of biosimilarity of CT-P13 to US-licensed Remicade.

9 Clinical Efficacy and Safety/Statistics

Executive Summary

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 support the relevance of comparative data generated using EU-approved Remicade to support a demonstration of the biosimilarity of CT-P13 to US-licensed Remicade.

The FDA evaluation of the comparative clinical data focused on the two 54-week, randomized, double-blind, parallel-group clinical trials that compared the efficacy and safety of CT-P13 and EU-approved Remicade. Study 3.1 was a large comparative clinical study in 606 patients with active RA who had an inadequate response to methotrexate (MTX). Study 1.1 was a clinical study in 250 patients with AS designed to compare PK profiles, with safety and efficacy comparisons as secondary objectives.

In study 3.1, the primary endpoint was the proportion of patients who remained in the study and achieved an American College of Rheumatology 20% (ACR20) response at Week 30. Approximately 60.9% of patients randomized to CT-P13 and 58.9% of patients randomized to EU-approved Remicade were ACR20 responders, for an estimated absolute difference between treatments of 2.0% (90% confidence interval [CI]: -4.6%, +8.7%). The 90% CI successfully ruled out the similarity margin of ±12% that the Agency has determined reasonable. ACR20, ACR50, and ACR70 responses over time, in addition to mean changes from baseline in the components of the ACR composite endpoint, the disease activity score (DAS28), and the radiographic joint score, were also similar between the treatment arms.

In study 1.1, among the subset of randomized patients remaining in the study at Week 30, 70.5% of patients randomized to CT-P13 and 72.4% of patients randomized to EU-approved Remicade achieved an Assessment of SpondyloArthritis International Society 20% (ASAS20) response, for an estimated odds ratio comparing treatments of 0.91 (95% CI: 0.51, 1.62). In a supportive FDA analysis in all randomized patients, 63.2% of patients on CT-P13 and 67.2% on EU-approved 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%). Mean changes from baseline in important patient-reported outcome assessments, including the ASAS components, were also similar between the arms.

Patients who discontinued treatment early were also withdrawn from the clinical studies, leading to substantial dropout: 25% and 16% failed to complete the 54-week double-blind periods in studies 3.1 and 1.1, respectively. The high dropout rates led to substantial missing data in important analyses, such as the evaluations of ACR20 and DAS28 at Week 30 in all randomized patients regardless of adherence in study 3.1. Therefore, we conducted tipping point analyses to explore the sensitivity of results to violations in assumptions about the missing data. Confidence intervals for the differences between CT-P13 and EU-approved Remicade failed to rule out concerning losses in efficacy only under the assumption that patients who dropped out on CT-P13 had much worse outcomes than dropouts on EU-approved Remicade. Given the similar proportions of patients and distributions of reasons for early withdrawal on the two treatment arms, in addition to the similar baseline characteristics between dropouts on the two arms, an assumption of such large differences between the outcomes in dropouts on the two treatments seems implausible. That is, the finding of similar efficacy is highly credible notwithstanding the number of dropouts.

To reliably evaluate whether there are clinically meaningful differences between two products, a comparative clinical study must have assay sensitivity, or the ability to detect meaningful differences between the products, if such differences exist. Historical evidence of sensitivity to drug effects and appropriate trial conduct may be used to support the presence of assay sensitivity and a conclusion that the treatments are similarly effective rather than similarly ineffective. Based on an evaluation of five historical, randomized, placebo-controlled clinical trials of Remicade we concluded that (1) the design of the historical trials were largely similar to that of comparative clinical study 3.1; and (2) there were relatively large and consistent treatment effects across the five historical studies. We did not identify any issues with the quality of study conduct, with the exception of the high rate of study withdrawal. The totality of available information largely supports the assay sensitivity of study 3.1. The collective evidence from the comparative clinical studies is supportive of similar efficacy between CT-P13 and US-licensed Remicade in the studied indications.

The safety analysis of the CT-P13 clinical program in the two studied conditions of use, RA and AS, and in healthy volunteers, has not identified any new safety signals. 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 increase in adverse events or immunogenicity, supporting the safety of the clinical scenario where non-treatment naïve patients transition to CT-P13.

The clinical safety and immunogenicity data using two labeled doses (3 mg/kg and 5 mg/kg) for US-licensed Remicade either as a monotherapy or in combination with methotrexate, in two patient populations showed similar safety profile between CT-P13 and EU-approved Remicade and support the conclusion of no clinically meaningful differences.

The FDA review of the safety, immunogenicity, and efficacy data from the comparative clinical study in patients with RA and the key supportive study in patients with AS support the applicant's contention that there are no clinically meaningful differences between CT-P13 and US-licensed Remicade in the studied indications.

Review

Overview of the Clinical Program

The applicant submitted results from eight completed clinical studies. A summary of the key design features of these studies is provided in Table 10. Study 1.4 (discussed in the section on Clinical Pharmacology above) was a randomized, double-blind, parallel-group, single-dose clinical study in 213 healthy volunteers to compare the PK profiles of CT-P13, EU-approved Remicade, and US-licensed Remicade. Study 3.1 was a randomized, double-blind, parallel-group clinical study to compare the safety and efficacy of CT-P13 and EU-approved Remicade in 606 patients with active RA who had an inadequate response to MTX. Study 3.2 was an open-label, single-arm extension study in 302 RA patients who had completed Study 3.1. Study 1.2 was a randomized, double-blind, parallel- group pilot study to compare CT-P13 and EU-approved Remicade in 19 RA patients in the Philippines. Study 3.3 was a randomized, double-blind, parallel-group study to compare CT-P13 and EU-approved Remicade in 15 RA patients in Russia. Study B1P13101 was a randomized, double-blind, parallel-group clinical study to compare the PK profiles of CT-P13 and EU-approved Remicade in 108 Japanese patients with active RA who had an inadequate response to MTX. Study 1.1 was a randomized, double-blind, parallel-group clinical study to perform PK, safety, and efficacy comparisons of CT-P13 and EU-approved Remicade in 250 patients with AS. Study 1.3 was an open-label, single-arm extension study in 174 AS patients who had completed Study 1.1. There are also a number of ongoing studies.

Study 3.1 in RA was the comparative clinical study in which a comparison of efficacy and safety was the primary objective providing the primary evidence to support the conclusion of no clinically meaningful differences between CT-P13 and US-licensed Remicade. Supportive safety and efficacy data were provided by the rest of the clinical studies, including study 1.1 in a different population of patients with AS using a different dosing regimen approved for US-licensed Remicade.

Table 10. 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: *Efficacy, Safety, PK, Immunogenicity*	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 *PK, Efficacy, Safety, Immunogenicity*	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 *PK, Efficacy, Safety, Immunogenicity*	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: *Efficacy, Safety*	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: *Efficacy, Safety*	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: PK, Safety, Immunogenicity*	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: *Safety, Immunogenicity*	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: *Safety, Immunogenicity*	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
* Study 3.4, discussed only in the section on Immunogenicity below, is an ongoing randomized, double-blind, controlled, post-marketing study in patients with active Crohn's disease (CD), comparing efficacy, safety, and immunogenicity of CT-P13 with US-licensed Remicade and EU-approved Remicade after multiple doses of 5 mg/kg. This study was not a part of the clinical program originally submitted to support the BLA and thus is not discussed in detail in this briefing document.

Brief Description of Efficacy Endpoints

Comparative Clinical Study 3.1 in RA

The prespecified primary efficacy endpoint was the proportion of patients achieving an ACR20 response at Week 30, a well validated outcome measure in RA. In 1995, the American College of Rheumatology (ACR) published a definition of improvement for clinical trials in rheumatoid arthritis, which has since been used in drug development

trials to demonstrate evidence of efficacy for signs and symptoms of RA.[25] The ACR20 response is calculated as a ≥20% improvement in:

- tender joint count (of 68 joints) and
- swollen joint count (of 66 joints) and
- 3 of the 5 remaining ACR core set measures
    - Patient Global Assessment of Arthritis on a visual analog scale (VAS)
    - Physician Global Assessment of Arthritis on a VAS
    - Patient Assessment of Pain on a VAS
    - Patient Assessment of Physical Function (e.g. Health Assessment Questionnaire)
    - Acute Phase Reactant (Erythrocyte Sedimentation Rate or C-reactive protein)

Fifty percent and 70 percent improvement (ACR50 and ACR70) are similarly calculated using these higher levels of improvement.

Secondary efficacy endpoints included the components used to define ACR20 response, time to onset of ACR20 response, the Disease Activity Score in 28 joints (DAS28), EULAR response, ACR50 response, ACR70 response, Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), total van der Heijde radiographic joint score, SF-36 total score, fatigue (SF-36 vitality subscale score), and the number of patients requiring salvage treatments. Most endpoints were evaluated at Weeks 14, 30, and 54.

Discussion on Similarity Margin

The determination of a similarity margin is a critical aspect of the design of the comparative clinical study because it determines the null hypothesis being tested in the primary analysis, i.e., the differences in efficacy that the study will need to rule out at an acceptable significance level.

Study 3.1 had a pre-specified similarity margin of ±15% and was completed prior to Celltrion's interactions with FDA. In response to comments from FDA indicating that the margin was not acceptable, the applicant provided justification for a revised margin of ±13% based on a meta-analysis of historical data from randomized clinical trials of Remicade and the goal of preserving at least 50% of the effect size of the reference product. The Agency does not agree with the applicant's selection of historical trials as, unlike the meta-analysis conducted by the Agency (see Table 11), the applicant did not include one important study (Schiff et al, 2008) in their meta-analysis. The agency believes that a similarity margin of ±12% is more appropriate for this study. The agency's recommendation for a ±12% similarity margin is aimed at weighing the clinical importance of different losses in effect against the feasibility of different study sizes. In a comparative clinical study designed with 90% power to reject absolute differences

[25] DT Felson, et al., Arthritis & Rheum, 1995 June, 38(6):727-735

greater than 12% in magnitude, observed differences larger than approximately 6% will result in failure to establish similarity, as the 90% confidence interval for the estimated difference will not rule out the 12% margin. Therefore, the comparative clinical study will be able to rule out differences in ACR20 response greater than 12% with high (at least 95%) statistical confidence, and will be able to rule out differences greater than around 6% with moderate (at least 50%) statistical confidence. The lower bound of the proposed similarity margin (-12%) also corresponds to the retention of approximately 50% of conservative estimates of treatment effect sizes relative to placebo for Remicade.

Table 11. Meta-analysis of Historical Effect of Remicade on ACR20 Response in Randomized Clinical Trials of Patients with Active RA Despite Treatment with MTX

		MTX+Placebo		MTX+Remicade		
Study	Week	N	ACR20 Response	N	ACR20 Response	Treatment Difference
Maini et al, 1999	30	88	20%	86	50%	30%
Westhoven et al, 2006	22	361	24%	360	55%	31%
Schiff et al, 2008	28	110	42%	165	59%	18%
Zhang et al, 2006	18	86	49%	87	76%	27%
Abe et al, 2006	14	47	23%	49	61%	38%
Meta-Analysis (Fixed Effect[1]): Difference (95% CI)						28.4% (23.6%, 33.3%)
Meta-Analysis (Random Effect[2]): Difference (95% CI)						28.3% (22.6%, 34.1%)

Source: FDA meta-analysis
[1]Based on Mantel-Haenszel weights
[2]Based on DerSimonian-Laird approach

PK and Efficacy Study 1.1 in AS

The primary objective was to demonstrate similar PK at steady state between CT-P13 and EU-approved Remicade which was discussed in the section on Clinical Pharmacology above. Secondary objectives were to compare CT-P13 and EU-approved Remicade with respect to long-term safety and efficacy endpoints. Efficacy endpoints included the Assessment of SpondyloArthritis International Society (ASAS) 20% improvement scale (ASAS20), ASAS40, BASDAI score, Bath Ankylosing Spondylitis Functional Index (BASFI) score, Bath Ankylosing Spondylitis Metrology Index (BASMI) score, chest expansion, and SF-36 total score, assessed at Weeks 14, 30, and 54 (or an end-of-study visit for patients who stopped treatment early). The ASAS20 response is defined as an improvement of at least 20% and an absolute improvement of at least 1 unit on a 0 to 10 scale from baseline in at least 3 of the following domains:

- Patient global assessment of disease status
- Patient assessment of spinal pain
- Function according to BASFI

- Morning stiffness determined using the last 2 questions of BASDAI

Study Conduct

Treatment groups in the studies were generally balanced with respect to demographics and baseline characteristics. None of the study sites was in the US. In study 3.1, the average disease activity score (DAS28 CRP [C-reactive protein]; scale: 0-10) was 5.8, consistent with the target population of patients with moderate-to-severely active RA. Similarly study 1.1 recruited AS patients with moderate-to-severely active disease with an average disease activity score (BASDAI; scale: 0-10) 6.7. The design of the clinical studies was such that subjects who stopped treatment early were also withdrawn from the study and not followed for the rest of the study duration. As a result, there was substantial patient dropout as shown in Table 12, contributing to missing data. The overall proportions of discontinuation and drop out by category, including adverse events or lack of efficacy, were similar between CT-P13 and EU-approved Remicade arms in both study 3.1 and study 1.1. However, to account for the missing data, sensitivity analyses were conducted as detailed in the subsection on *Missing Data* below.

Table 12. Patient Disposition in Controlled Studies 3.1 in RA and 1.1 in AS

	Rheumatoid Arthritis Study 3.1		Ankylosing Spondylitis Study 1.1	
	CT-P13 3mg/kg n (%)	EU-approved Remicade 3mg/kg n (%)	CT-P13 5mg/kg (n=125) n (%)	EU-approved Remicade 5mg/kg n (%)
ITT Population				
• Screened	302 (100)	304 (100)		
• Randomized	300 (99)	302 (99)	125 (100)	125 (100)
• Completed entire study	233 (77)	222 (73)	106 (85)	104 (83)
• Total Discontinued	69 (23)	82 (27)	19 (15)	21 (17)
Primary reason for Discontinuations				
• Lack of efficacy	10 (3)	6 (2)	2 (2)	0
• Adverse event	31 (10)	41 (14)	10 (8)	8 (6)
• Death	0	1 (<1)	0	2 (2)
Other withdrawals				
• Protocol violation	2 (<1)	2 (<1)	0	1 (<1)
• Withdrew consent	16 (5)	21 (7)	3 (2)	6 (5)

Source: FDA analysis of data from Celltrion 351(k) BLA submission

Efficacy Findings

Comparative Clinical Study 3.1

Study 3.1 met its pre-specified primary endpoint. 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 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%). The 90% CI ruled out the margin of ±13% proposed by the applicant, in addition to the margin of ±12% that the Agency has determined reasonable (see *Discussion of Similarity Margin* subsection above).

In a sensitivity analysis using the per-protocol population (patients who completed the study and adhered to the protocol), 73.4% and 70.1% responded on CT-P13 and EU-approved Remicade, respectively, for an estimated difference of 3.3% (90%: -3.4%, +10.0%). The primary analysis was further supported by the mean changes from baseline in the components of the ACR composite endpoint and the disease activity score (DAS28), ACR50 and ACR70 response rates, which were also similar between the arms in all randomized patients who completed the study and the per-protocol population.

While radiographic endpoints are generally not expected for comparative clinical studies in RA, the applicant has included radiographic assessment in study 3.1 using the change from baseline in total van der Heijde radiographic joint score at Week 54. Original analysis of joint damage progression showed a similar decrease in the modified sharp score at Week 54 for CT-P13 compared to EU-approved Remicade in study 3.1 (difference: 2.6; 95% CI: -2.7, 7.9) but the within-group mean changes on the two arms (-28.5 and -31.9) was significantly larger compared to historical studies with Remicade (where the change was closer to zero). The applicant, therefore, conducted a post-hoc re-evaluation of the radiographs from baseline and Week 54 using a similar approach as used in the historical studies with Remicade. In the original assessment, a single reader evaluated a patient's radiographs with knowledge of the chronological order of the images. The re-evaluation utilized two independent readers without knowledge of the order of the radiographs, evaluating paired, rather than individual, radiographs of the patient. Based on that re-evaluation, the average changes on the two arms remained similar, and the within-group changes from baseline were more in line with those of historical trials. However, the fact that a post hoc reassessment was needed precludes definitive conclusion regarding the radiographic data.

Assay Sensitivity and the Constancy Assumption for Study 3.1

To reliably evaluate whether there are clinically meaningful differences between two products, a comparative clinical study must have assay sensitivity, or the ability to detect meaningful differences between the products, if such differences exist. In addition, to reliably evaluate whether the experimental treatment retains a certain proportion of the effect of the reference product versus placebo, the constancy assumption must be reasonable. This is the assumption that estimates of the effect of the reference product from historical, placebo-controlled trials are unbiased for the setting of the comparative clinical study. Based on an evaluation of five historical, randomized, placebo-controlled clinical trials of Remicade, we concluded that (1) the designs of the historical trials were largely similar to that of comparative clinical study

3.1; and (2) there were relatively large and consistent treatment effects across the five historical studies (Table 11). Within-group responses in Study 3.1 were also similar to those of historical trials. It is also important that a study designed to evaluate similarity has quality conduct, because conduct issues such as violations in eligibility criteria, poor adherence, cross-over between arms, or missing data tend to bias results toward the alternative hypothesis of equivalence. We did not identify any issues with the quality of study conduct, with the exception of the high rate of study withdrawal that was previously discussed. Therefore, the totality of available information largely supports the assay sensitivity of Study 3.1, in addition to the constancy assumption.

PK and Efficacy Study 1.1 in AS

The results from the primary PK analysis in study 1.1 were discussed in the section on Clinical Pharmacology above. According to the applicant's planned efficacy analysis in the subset of patients remaining in study 1.1 at Week 30, approximately 70.5% of patients randomized to CT-P13 and 72.4% of patients randomized to EU-approved Remicade achieved an ASAS20 response, for an estimated odds ratio comparing treatments of 0.91 (95% CI: 0.51, 1.62). A supportive FDA analysis in all randomized patients, 63.2% of patients on CT-P13 and 67.2% on EU-approved 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%) indicating similar efficacy in AS using a 5 mg/kg dosing regimen without background immunosuppression.

Missing Data

As noted in the subsection on *Study Conduct* above, a substantial proportion of subjects dropped out of studies 3.1 and 1.1 due primarily to study design where subjects who discontinued treatment early were not followed for the duration of the study. To investigate the impact of these missing data on the primary analysis, the FDA statistical review team conducted tipping point analyses to explore the sensitivity of results to violations in assumptions about the missing data (i.e., to various missing-not-at-random assumptions). Confidence intervals for the differences between CT-P13 and EU-approved Remicade failed to rule out concerning losses in efficacy only under the assumption that patients who dropped out on CT-P13 had much worse outcomes than dropouts on EU-approved Remicade. Given the similar proportions of patients and distributions of reasons for early withdrawal on the two treatment arms, in addition to the similar baseline characteristics between dropouts on the two arms, an assumption of such large differences between the outcomes in dropouts on the two treatments seems implausible. Therefore, these tipping point sensitivity analyses largely support the findings of the key efficacy analyses in Study 3.1 (data not shown).

In summary, 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 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.

Analysis of Safety in CT-P13 Clinical Program

Adequacy of the safety database

Safety data were derived from the comparative clinical study in RA (study 3.1), PK studies in AS (study 1.1) and healthy volunteers (HVs) (study 1.4) and long-term extension studies (LTE study 3.2 in RA, LTE study 1.3 in AS). The safety database was comprised of 803 subjects, of whom over 600 were exposed to CT-P13 for at least 1 year and 230 for at least 2 years, and 213 healthy volunteers exposed to single doses of CT-P13. Patients with RA received 3 mg/kg CT-P13 or EU-approved Remicade in combination with methotrexate and folic acid and patients with AS received 5 mg/kg CT-P13 or EU-approved Remicade, for over one year. Healthy subjects received a single dose of 5 mg/kg CT-P13, EU-approved Remicade or US-licensed Remicade.

Data from extension studies 3.2 and 1.3 were also analyzed to assess additional risks, if any, in safety and immunogenicity resulting from a single transition from EU-approved Remicade to CT-P13 (denoted as EU-Remi→CT-P13 in the tables) to address the safety of the clinical scenario where non-treatment naïve patients transition to CT-P13.

Of note, the majority of the safety data are derived from clinical studies using the EU-approved Remicade. However, Celltrion has provided robust comparative analytical data and clinical PK bridging data (study 1.4) between the US-licensed and EU-approved Remicade to justify the relevance of comparative data, including safety data generated using EU-approved Remicade to support a demonstration of the biosimilarity of CT-P13 to US-licensed Remicade.

Overall, the safety database is adequate to provide a reasonable comparative safety assessment, using two approved dosing regimens in two distinct patient populations, to support a determination of no clinically meaningful differences between CT-P13 and US-licensed Remicade.

Overview of Safety

No new safety signals were identified in the CT-P13 group compared to the known adverse event profile of US-licensed Remicade. The incidence of adverse events, serious adverse events, adverse events of special interest, and death are summarized in Table 13. The overall incidences of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and AEs leading to discontinuation, infections, infusion-

related reactions and anaphylaxis, were similar between CT-P13 and the comparator products.

Table 13. Overview of Deaths, SAEs, and Events of Interest in Studies 3.1 in RA, 1.1 in AS, and 1.4 in Healthy Volunteers

	Rheumatoid Arthritis Study 3.1		Ankylosing Spondylitis Study 1.1		Healthy Volunteers Study 1.4		
	CT-P13 3mg/kg (n=302)	EU-Remi 3mg/kg (n=300)	CT-P13 5mg/kg (n=128)	EU-Remi 5mg/kg n=122)	CT-P13 5mg/kg (n=71)	EU-Remi 5mg/kg (n=71)	US-Remi 5mg/kg (n=71)
Total # of TEAEs # of pts with ≥1 TEAE, n (%)	732 213 (71)	738 211 (70)	362 95 (74)	375 82 (67)	67 37 (42)	28 21 (30)	54 33 (46)
Total # of SAEs # of pts with ≥1 SAE, n (%)	49 42 (14)	39 3 (10)	12 10 (8)	11 8 (7)	1 1 (1)	1 1 (1)	0 0
TEAEs leading to discontinuation # of pts (%)	40 33 (11)	52 47 (16)	12 11 (9)	9 9 (7)	0	0	0
Infections, n # of pts with ≥1 infection, n (%)	237 127 (42)	231 137 (46)	91 55 (43)	107 49 (40)	18 18 (25)	12 12 (17)	26 24 (34)
Serious Infections (SIE), n # of pts with ≥ 1SIE, n (%)	13 13 (4)	8 7 (2)	2 2 (2)	4 3 (3)	0	0	0
Infusion-related reactions (IRR) # of pts with IRR, n (%)	12 10 (3)	11 11 (4)	0 0	4 4 (3)	0	0	0
Anaphylaxis, n (%)	6 (2)	4 (1)	1 (<1)	3 (2)	0	0	0
Death, n	0	1	1	1	0	0	0
Source: FDA analysis of data from Celltrion 351(k) BLA submission EU-Remi: EU-approved Remicade; US-Remi: US-licensed Remicade; SAE: serious adverse event; TEAE: treatment-emergent adverse events							

Death

As of the original BLA submission, a total of 4 deaths were reported in the CT-P13 clinical development program, two in each CT-P13 and EU-approved Remicade groups. Details of each case are summarized below by study and treatment group:

- Study 3.1, EU-approved Remicade: A 59-year-old female patient with a long-standing history of hypertension and RA died of sudden death after 379 days on treatment. The cause of death was unknown.
- Study 3.2, CT-P13 maintenance group: A 44-year-old male patient with RA died after 578 days of treatment following appendectomy with peritonitis. The cause of death was suspected peritonitis, and multiorgan failure.
- Study 1.1, EU-approved Remicade: A 38-year-old patient died in a car accident.
- Study 1.1, CT-P13: A 25-year-old patient died in a car accident as a passenger.

Nonfatal Serious Adverse Events (SAE)

The proportion of patients who experienced at least one SAE was similar between the two treatment groups, CT-P13 and EU-approved Remicade, during the controlled period of clinical studies as detailed in Table 13 above. The most frequently reported SAEs were infections and infusion-related reactions and were similar between both treatment groups. SAEs across the system organ classes (SOCs) showed a similar distribution with minor numerical differences between each group. There was no notable difference

in the incidence of SAEs following a single transition of RA and AS patients from EU-approved Remicade to CT-P13 in the extension studies. The different SOCs of SAEs or the pattern of SAEs in the studies comparing CT-P13 and EU-approved Remicade was consistent with the known safety profile of the reference product, US-licensed Remicade.

Discontinuations due to Adverse Events

The proportion of patients discontinuing due to an adverse event was similar between CT-P13 and EU-approved Remicade as detailed in Table 13 above. Infections were the most common reason for discontinuation in studies 3.1 and 1.1 (approximately 3% in the CT-P13 groups compared to 5% in the EU-approved Remicade groups). Infusion-related reactions, and drug hypersensitivity, including anaphylaxis, were the next leading cause of treatment discontinuation in the same studies (with combined rates of approximately 3% in CT-P13, and 5% in the EU-approved Remicade groups). In the extension studies 1.3 and 3.2, generally fewer patients discontinued therapy after a single transition from EU-approved Remicade to CT-P13 than those who continued on CT-P13. Adverse events of infections and infusion-related reactions and hypersensitivity are discussed in further detail in separate sections below.

Adverse Events of Special Interest (AESI)

For AESI, which included infections, serious infections, pneumonia, active tuberculosis (TB), latent TB, infusion related reactions, anaphylactic reactions, serious hepatobiliary events, drug induced liver injury, malignancy and lymphoma, Celltrion provided pooled analyses of crude percent rates and exposure-adjusted incidence rates. To account for the differences in the study designs, e.g. study patient populations and dosing regimens, FDA conducted supplementary analysis of the safety data from the core studies (studies 3.1 and 1.1 and their long-term extension studies 3.1 and 1.3) of the study-specific estimated differences between groups with respect to adverse events of special interest. Of note, electronic datasets for the Japanese study B1P13101 were not submitted as they were not accessible to Celltrion as discussed at the BPD Type 4 meeting, and were not included in this integrated analysis. Table 14 provides a summary of the comparative analysis of AESI during the controlled studies 3.1 in RA and 1.1 in AS. The relative risk of an AESI comparing CT-P13 and EU-approved Remicade was calculated based on DerSimonian-Laird random effects meta-analysis, and there were no significant differences between the treatment groups (although the confidence intervals for the relative risks of the more rare events are quite wide). Similar analysis for the extension studies 3.2 in RA and 1.3 in AS, summarized in Table 15, show that the risk of an AESI was also similar between patients who underwent a single transition from EU-approved Remicade to CT-P13 and those who continued CT-P13 treatment.

Table 14. Adverse Events of Special Interest - Controlled Studies 3.1 in RA and 1.1 in AS

	Rheumatoid Arthritis Study 3.1				Ankylosing Spondylitis Study 1.1				Integrated RR [3] (95% CI)
	CT-P13 (N=302)		EU-approved Remicade (N=300)		CT-P13 (N=128)		EU-approved Remicade (N=122)		
	n (%) [1]	Rate [2]	n (%) [1]	Rate [2]	n (%) [1]	Rate [2]	n (%) [1]	Rate [2]	
Latent TB	28 (9)	9.3	26 (9)	8.6	10 (8)	7.3	6 (5)	4.6	1.2 (0.7, 1.8)
Active TB	3 (1)	0.9	0	0.0	2 (2)	1.4	1 (1)	0.7	3.2 (0.5, 20.4)
Infection	127 (42)	53.8	137 (46)	60.4	55 (43)	52.5	49 (40)	48.4	1.0 (0.8, 1.1)
Serious Infection	13 (4)	4.2	7 (2)	2.2	2 (2)	1.4	3 (3)	2.2	1.4 (0.6, 3.5)
Pneumonia	8 (3)	2.5	5 (2)	1.6	2 (2)	1.4	0	0.0	1.8 (0.6, 5.1)
Malignancy and Lymphoma	3 (1)	0.9	4 (1)	1.3	2 (2)	1.4	0	0.0	1.2 (0.2, 5.7)
Infusion-related Reaction	30 (10)	9.8	43 (14)	14.8	11 (9)	8.2	15 (12)	11.8	0.7 (0.5, 1.0)
Vascular disorder	25 (8)	8.3	16 (5)	5.3	4 (3)	2.9	1 (1)	0.7	1.7 (0.9, 3.0)
Cardiac disorder	5 (2)	1.6	12 (4)	3.9	5 (4)	3.6	6 (5)	4.6	0.6 (0.3, 1.2)
Opportunistic Infection	4 (1)	1.3	6 (2)	1.9	0	0.0	2 (2)	1.5	0.6 (0.2, 1.8)

Source: FDA safety analysis of data from Celltrion 351(k) BLA submission
[1] Number of patients with event (percent)
[2] Incidence rate of first event per 100 person-years
[3] Relative risk of event (95% confidence interval) comparing CT-P13 with EU-approved Remicade based on DerSimonian-Laird random effects meta-analysis of results from Studies 1.1 and 3.1
[4] Definitions of Adverse Events of Special Interest:
Latent TB: All preferred terms with latent tuberculosis or Mycobacterium tuberculosis complex test
Active TB: All preferred terms with tuberculosis not classified as latent TB
Infection: All events in infections and infestations system organ class
Serious Infection: All events in infections and infestations system organ class classified as serious
Pneumonia: All preferred terms with pneumonia, bronchopneumonia, lobar pneumonia, or lower respiratory tract infection
Malignancy and Lymphoma: All preferred terms with cancer, carcinoma, lymphoma, neoplasm, or Myeloproliferative disorder
Infusion-related Reaction: Defined in the section on Infusion-Related Reactions and Drug Hypersensitivity
Vascular Disorder: All events in vascular disorders system organ class
Cardiac Disorder: All events in cardiac disorders system organ class
Opportunistic Infection: All preferred terms with Herpes zoster, Oesophageal candidiasis, Oral candidiasis, or Varicella

Table 15. Adverse Events of Special Interest - Extension Studies 3.2 in RA and 1.3 in AS

	Rheumatoid Arthritis Study 3.2				Ankylosing Spondylitis Study 1.3				Integrated RR[3] (95% CI)
	CT-P13 → CT-P13 (N=159)		EU-Remi →CT-P13 (N=143)		CT-P13 → CT-P13 (N=90)		EU-Remi → CT-P13 (N=84)		
	n (%)[1]	Rate[2]	n (%)[1]	Rate[2]	n (%)[1]	Rate[2]	n (%)[1]	Rate[2]	
Latent TB	11 (7)	5.0	7 (5)	3.4	5 (6)	4.1	7 (8)	5.3	1.0 (0.3, 3.2)
Active TB	0	0.0	0 (0.0)	0.0	1 (1)	0.8	1 (1)	0.7	1.1 (0.1, 16.9)
Infection	50 (31)	32.3	47 (33)	34.9	23 (26)	25.4	29 (35)	30.5	1.1 (0.9, 1.5)
Serious Infection	4 (3)	1.7	3 (2)	1.4	2 (2)	1.5	1 (1)	0.7	0.7 (0.2, 2.6)
Pneumonia	1 (1)	0.4	0	0.0	0	0.0	0	0.0	NA
Malignancy and Lymphoma	1 (1)	0.4	4 (3)	1.9	1 (1)	0.8	0	0.0	1.7 (0.1, 18.6)
Infusion-related Reaction	11 (7)	5.0	4 (3)	1.9	7 (8)	5.7	6 (7)	4.5	0.6 (0.3, 1.4)
Vascular disorder	4 (3)	1.7	3 (2)	1.4	3 (3)	2.3	2 (2)	1.4	0.8 (0.3, 2.4)
Cardiac disorder	1 (1)	0.4	1 (1)	0.5	4 (4)	3.2	3 (4)	2.1	0.9 (0.2, 3.2)
Opportunistic Infection	1 (1)	0.4	1 (1)	0.5	1 (1)	0.8	1 (1)	0.7	1.1 (0.2, 7.7)

Source: FDA safety analysis of data from Celltrion 351(k) BLA submission
[1] Number of patients with event (percent)
[2] Incidence rate of first event per 100 person-years
[3] Relative risk of event (95% confidence interval) comparing transition from EU-approved Remicade to CT-P13 with CT-P13 maintenance based on DerSimonian-Laird random effects meta-analysis of results from Studies 1.3 and 3.2
[4] Definitions of Adverse Events of Special Interest:
Latent TB: All preferred terms with latent tuberculosis or Mycobacterium tuberculosis complex test
Active TB: All preferred terms with tuberculosis not classified as latent TB
Infection: All events in infections and infestations system organ class
Serious Infection: All events in infections and infestations system organ class classified as serious
Pneumonia: All preferred terms with pneumonia, bronchopneumonia, lobar pneumonia, or lower respiratory tract infection
Malignancy and Lymphoma: All preferred terms with cancer, carcinoma, lymphoma, neoplasm, or Myeloproliferative disorder
Infusion-related Reaction: Defined in the section on Infusion-Related Reactions and Drug Hypersensitivity
Vascular Disorder: All events in vascular disorders system organ class
Cardiac Disorder: All events in cardiac disorders system organ class
Opportunistic Infection: All preferred terms with Herpes zoster, Oesophageal candidiasis, Oral candidiasis, or Varicella

Infections

In the CT-P13 clinical development program, the overall incidence and types of infections were similar between CT-P13 and EU-approved Remicade. During the controlled periods of the CT-P13 clinical studies, 15/430 (3.4%) patients treated with CT-P13, compared to 10/422 (2.4%) patients treated with EU-approved Remicade experienced serious infection. This difference was driven by numerical imbalance in cases of TB and pneumonia as discussed below.

Active tuberculosis (TB)

In the controlled studies 5 cases of active TB were reported in CT-P13 treated patients (3 in RA, and 2 in AS) compared to 1 case of active TB in the EU-approved Remicade group in an AS patient. Two additional cases were reported during the extension study

1.3 in AS, one in a patient who continues CT-P13 and one in a patient who underwent a single transition from EU-approved Remicade to CT-P13. Two cases of active TB were also reported in the supportive study 1.2 in the Philippines. Most of the cases occurred in endemic areas. Of note, three patients from Philippines (Study 3.1 – 1 patient; and study 1.2 – 2 patients) treated with CT-P13 received a clinical diagnosis of TB based on investigator's judgment without a histopathological or microbiological confirmation of presence of M. tuberculosis in clinical samples. Tuberculosis is a well-recognized safety risk with TNF inhibition, including with infliximab. The slight numerical imbalance in the incidence of TB between CT-P13 and EU-approved Remicade is likely to reflect a chance finding. Furthermore, the numerical imbalance in the cases of active TB between the two treatment groups cannot be explained by known analytical or functional differences between the molecules.

Pneumonia

During the controlled safety period in studies 3.1 and 1.1, 10 cases of pneumonia (8 in RA and 2 in AS patients, respectively) were reported in CT-P13 treated subjects (2%) compared to 5 cases of pneumonia (RA patients only) in the EU-approved Remicade group (1%). Only one case of pneumonia was reported in the extension studies that occurred in the CT-P13 maintenance group in the RA study. The numerical differences between the two treatment groups were small and this imbalance was not observed in the Japanese RA study B1P13101 where 2 patients developed pneumonia in the CT-P13 group (4%) versus 4 patients in the EU-approved Remicade group (8%). Serious infections, including pneumonia, are a well-recognized safety risk with TNF inhibition, including with infliximab.

Overall, the incidence and pattern of infections observed in the CT-P13 clinical program are consistent with the safety profile of the US-licensed Remicade and do not indicate a new safety concern. The observed numerical imbalance in active TB and pneumonia do not indicate a clinically meaningful difference between CT-P13 and US-licensed Remicade.

Vascular Disorders

Small numerical differences were reported in the Vascular Disorders SOC driven by hypertension. Overall, 19 (4%) and 11 (3%) patients reported hypertension in the CT-P13 and EU-approved Remicade groups, respectively, in the controlled studies 1.1 and 3.1. The majority of the adverse events were mild or moderate and were explained by higher baseline incidence of hypertension in CT-P13 group. Among patients with no baseline hypertension, the incidence of new onset hypertension was similar between CT-P13 and EU-approved Remicade treated patients. This imbalance was not associated with differences in major cardio-vascular outcomes in the CT-P13 clinical program where 2 cases of myocardial infarction were reported in each treatment group.

Infusion-Related Reactions and Drug Hypersensitivity

Infusion-related reactions were defined as: (1) Hypersensitivity, drug hypersensitivity, anaphylactic shock, anaphylactic reaction or infusion-related reaction with a possible, probable or definite relationship to study medication, or (2) TEAE term related to hypersensitivity or infusion-related reactions with a possible, probable or definite relationship to study medication, or (3) Signs and/or symptoms related to hypersensitivity or infusion-related reactions for which the TEAE start date matches an infusion date and classified as "possible, probable or definite" relationship to study drug. In the CT-P13 controlled studies 1.1 and 3.1, 41/430 (10%) patients in the CT-P13 group and 58/422 (14%) patients in the EU-approved Remicade group experienced infusion-related reaction or drug hypersensitivity. Importantly, the incidence of such reactions did not increase after patients underwent a single transition from EU-approved Remicade to CT-P13 (10/227 or 4%) compared to patients who continued on CT-P13 (18/249 or 7%) in studies 3.2 and 1.3.

Anaphylaxis

Based on pre-submission discussions and recommendations by the Agency, Celltrion conducted analyses of the safety database to identify cases of anaphylaxis defined by the criteria described by Sampson et al. (2006).[26] In the CT-P13 controlled studies 1.1 and 3.1, 7/430 (1.6%) patients in the CT-P13 group and 7/422 (1.7%) patients in the EU-approved Remicade group experienced anaphylaxis. Importantly, there were no cases of anaphylaxis in patients who underwent a single transition from EU-approved Remicade to CT-P13 in the extension studies 3.2 and 1.3.

The analysis of the overall incidence of infusion-related reaction or drug hypersensitivity, including anaphylaxis, indicate that a single transition of non-treatment naïve patients to CT-P13 is not likely to result in clinically significant reactions. These results are also consistent with the similar incidence of anti-drug antibodies between patients who transitioned from EU-approved Remicade to CT-P13 compared to patients who continued on CT-P13 in the same extension studies 3.2 and 1.3 as detailed in subsection Immunogenicity below.

Common AEs

Adverse events in the Infections and Infestations SOC were the most common adverse events in the CT-P13 development program with event rates similar between CT-P13 and the comparator products. The most frequently reported infections included nasopharyngitis, upper respiratory tract infection, latent tuberculosis (latent TB), and urinary tract infection. Adverse events in the Investigations SOC, ALT and AST elevations, were the next most common adverse events, followed by Gastrointestinal SOC with diarrhea, abdominal pain and nausea, and Nervous System SOC with

[26] Sampson HA et al, J Allergy Clin Immunol. 2006 Feb;117(2):391-7

headache and dizziness, with similar incidence rates across all treatment groups in the controlled periods of the studies. The common adverse event profile remained consistent during the long-term extension studies 1.3 and 3.2, and similar between subjects who underwent a single transition from EU-approved Remicade to CT-P13 and those who continued on CT-P13.

Laboratory Abnormalities, Vital Signs and Electrocardiograms (ECGs)

Cases of CTCAE Grade 3 and 4 cytopenia, ALT and AST abnormalities were reported sporadically in the CT-P13 clinical studies with similar rates between CT-P13 and the comparator products. The distribution of laboratory findings, vital signs and electrocardiogram (ECGs) findings was balanced between the CT-P13 and EU-approved Remicade groups. No new or unexpected laboratory findings were reported in CT-P13 clinical program.

Immunogenicity

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] Immune responses against therapeutic biological products are a concern because they can negatively impact the drug's pharmacokinetics, safety, and efficacy. Unwanted immune reactions to therapeutic biological products are mostly caused by antibodies against the drug (anti-drug antibodies; ADA). Therefore, immunogenicity assessment for therapeutic biological products focuses on measuring ADA.

In the context of the development program for CT-P13, immunogenicity was assessed using a validated ELISA method (study 1.4) and ECLA assay (studies 1.4, 1.1, and 3.1). The percentage of patients who test positive for ADA is dependent on the sensitivity and specificity of the assay and may also be influenced by other factors such as timing of sample collection and concomitant immunosuppressive medications. The incidence rates of ADA formation in CT-P13 clinical program are summarized in Table 16 by assay and time point of assessment.

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

Table 16. Comparison of Immunogenicity Across CT-P13 Clinical Studies (Study 1.4 in Healthy Subjects, Study 1.1 in Patients with AS, and Study 3.1 in Patients with RA)

Assay	Timepoint	Study 1.4 in Healthy Subjects (5 mg/kg single dose)			Study 1.1 in AS (5 mg/kg at week 0, 2, 6, and then q8w to week 54)		Study 3.1 in RA (3 mg/kg at week 0, 2, 6, and then q8w to week 54)		Study 1.3 in AS (5 mg/kg q8w)		Study 3.2 in RA (3 mg/kg q8w)	
		CT-P13 (N=70)	EU (N=71)	US (N=70)	CT-P13 (N=125)	EU (N=125)	CT-P13 (N=302)	EU (N=304)	CT-P13 to CT-P13 (N=90)	EU to CT-P13 (N=84)	CT-P13 to CT-P13 (N=159)	EU to CT-P13 (N=143)
ECLA	Predose	2 (2.8%)	1 (1.4%)	1 (1.4%)	2 (2%)	1 (<1%)	9 (3%)	6 (2%)	2 (2%)*	1 (<1%)*	7 (4%)*	4 (3%)*
	Week 8	10 (14.3%)	5 (7%)	2 (2.9%)	--	--	--	--	--	--	--	--
	Week 14	--	--	--	11 (9%)	13 (11%)	69 (23%)	70 (23%)	--	--	--	--
	Week 30	--	--	--	32 (25%)	25 (20%)	122 (40%)	122 (40%)	--	--	--	--
	Week 54	--	--	--	25 (20%)	28 (23%)	124 (41%)	108 (36%)	--	--	--	--
	Week 78	--	--	--	--	--	--	--	21 (23%)	25 (30%)	71 (44%)	66 (46%)
	Week 102	--	--	--	--	--	--	--	21 (23%)	23 (27%)	64 (40%)	64 (45%)
ELISA	Predose	4 (5.6%)	0	1 (1.4%)	--	--	--	--	--	--	--	--
	Week 8	19 (26.8%)	18 (25.4%)	8 (11.4%)	--	--	--	--	--	--	--	--

Source: FDA analysis of data from Celltrion 351(k) BLA submission
*reflects the incidence of ADA positivity at the screening/predose visit in index clinical studies 1.1 and 3.1 of the patients who enrolled in the extension studies 1.3 and 3.2

Immunogenicity Results from Study 1.4

Study 1.4 is the only completed study comparing immunogenicity of CT-P13 with US-licensed Remicade, and evaluated immunogenicity after a single dose of 5 mg/kg. This study enrolled 213 healthy volunteers with 71 subjects in each treatment group: CT-P13, EU-approved Remicade and US-licensed Remicade. While the study met its primary objective of demonstrating PK similarity between the three products, some numerical differences were seen in the incidence and titer of ADA formation (Table 16):

- ADA positives by ELISA: CT-P13 19/71 patients (27%), EU-approved Remicade – 18/71 patients (25%) and US-licensed Remicade – 8/71 patients (11%). The ELISA was used to re-analyze the samples in this study because ECLA had a higher degree of drug interference
- ADA positives by ECLA (used in the rest of the clinical program): CT-P13 10/71 patients (14%), EU-approved Remicade – 5/71 patients (7%) and US-licensed Remicade – 2/71 patients (3%)

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.

Overall, the observed differential ADA formation in study 1.4 did not impact the PK similarity among the three products as shown in Table 8 and Figure 14 above. To further investigate the potential clinical impact of the observed ADA differences, the FDA clinical pharmacology review team examined the relationship between ADA and exposure parameters. The numerical differences in ADA titers did not appear to impact the PK similarity between these three treatment groups. Looking at the ADA positive subgroup alone, the 90% confidence interval (IC) of geometric mean ratios for AUC0-t and AUC0-inf were within the acceptance range of 80-125% for all three comparisons, as shown in Table 17. While the 90% CI of Cmax was slightly high in this subgroup, this is probably a statistical anomaly and unlikely to be related to ADA formation, which would be expected to decrease exposure, if anything.

Table 17. Analysis of PK Parameters in Study 1.4 in the ADA Positive Subgroup

Parameter	LSM (T)	N	LSM (R)	N	GMR Ratio (%)	90% CI (%)
CT-P13 (T) vs US-licensed Remicade (R)						
Cmax	127.88	19	107.08	8	119.4	(103.8, 137.4)
AUC0-t	25778.23	19	26308.54	8	98.0	(83.6, 114.8)
AUC∞	26241.01	19	27220.39	8	96.4	(81.6, 113.9)
CT-P13 (T) vs EU-approved Remicade (R)						
Cmax	127.88	19	123.66	18	103.4	(92.4, 115.7)
AUC0-t	25778.23	19	26274.80	18	98.1	(85.9, 121.1)
AUC∞	26241.01	19	26561.97	18	98.8	(86.2, 113.3)
EU-approved Remicade (T) vs US-licensed Remicade (R)						
Cmax	123.66	18	107.08	8	115.5	(101.7, 131.1)
AUC0-t	26274.80	18	26308.54	8	99.9	(82.9, 120.3)
AUC∞	26561.97	18	27220.39	8	97.6	(80.3, 118.5)

Source: FDA analysis of data from Celltrion 351(k) BLA submission
CI: confidence interval; GMR: geometric mean ratio

In support of the similar immunogenic potential of CT-P13 compared to US-licensed Remicade and EU-approved Remicade, the applicant provided experimental data showing that ADA to EU-approved Remicade from IBD patients cross-react similarly with US-licensed Remicade and CT-P13 by ELISA, indicating the three products have similar immune-dominant epitopes, consistent with a similar immunogenic potential. These data also suggest that the immune response difference observed in study 1.4 is not likely to be assay-related.

Immunogenicity Results from Study 3.1 and Study 1.1

Infliximab is known to be immunogenic and the development of anti-infliximab antibodies may have implications for both safety and efficacy. To examine the impact of immunogenicity on comparative safety and efficacy, ADAs were measured at pre-specified time points throughout the controlled clinical studies 3.1 and 1.1, and the extension studies 3.2 and 1.3. Using ECLA assay, in studies 3.1 in RA and 1.1 in AS patients, the rates of immunogenicity, assessed as the proportion of anti-drug antibody (ADA) positive patients, were similar between the CT-P13 and EU-approved Remicade treatment groups for the duration of the studies with nearly all being neutralizing antibodies. In the two extension studies 3.2 and 1.3, 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. Further, the impact of immunogenicity on safety and efficacy in the controlled studies was similar between CT-P13 and EU-approved Remicade. As expected, the incidence of infusion related reactions was higher in ADA-positive compared to ADA-negative patients, as summarized in Table 18. However, within each ADA subpopulation there were no notable differences between CT-P13 and EU-approved Remicade.

Table 18. Incidence of Infusion-related Reactions and Anaphylaxis by ADA Status-Controlled Studies (All-Randomized Population)

		Rheumatoid Arthritis Study 3.1		**Ankylosing Spondylitis Study 1.1**		**Total**	
	ADA Seroconversion Subgroup	CT-P13 3mg/kg (n=302)	EU-Remi 3mg/kg (n=300)	CT-P13 5mg/kg (n=128)	EU-Remi 5mg/kg n=122)	CT-P13 (n=430)	EU-Remi (n=422)
Infusion Related Reaction	ADA +	23/169 (14%)	35/164 (21%)	6/44 (14%)	11/39 (28%)	29/213 (14%)	46/203 (23%)
	ADA -	7/133 (5%)	8/135 (6%)	5/84 (6%)	4/83 (5%)	12/217 (6%)	12/218 (6%)
Anaphylaxis	ADA +	4/169 (2%)	2/164 (1%)	1/44 (2%)	3/39 (8%)	5/213 (2%)	5/203 (3%)
	ADA -	2/133 (2%)	2/135 (2%)	0/84	0/83	2/217 (1%)	2/218 (1%)

Source: FDA analysis of data from Celltrion 351(k) BLA submission
ADA-anti-drug antibodies

Similarly, in the comparative clinical study 3.1, lower proportions of patients achieved ACR20 response in the ADA-positive subgroups as shown in Table 19. However, within each ADA subpopulation there were no notable differences between CT-P13 and EU-approved Remicade.

Table 19. ACR20 Responder Rates by ADA Status in Study 3.1 (All-Randomized Population)

ADA Seroconversion Subgroup	Treatment	ACR20 Response Rate		
		Week 14	Week 30	Week 54
ADA Positive	CT-P13 3mg/kg	38/69 (55%)	74/121 (61%)	77/123 (63%)
	EU-Remicade 3mg/kg	38/70 (54%)	75/123 (61%)	65/109 (60%)
ADA Negative	CT-P13 3mg/kg	148/202 (73%)	106/129 (83%)	95/112 (85%)
	EU-Remicade 3mg/kg	135/202 (67%)	100/132 (76%)	90/111 (81%)

Source: FDA analysis of data from Celltrion 351(k) BLA submission
ADA-anti-drug antibodies

Collectively, these data indicate that the ADA formation does not differentially impact safety or efficacy between patients treated with CT-P13 and EU-approved Remicade.

Interim Immunogenicity Results from Study 3.4

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

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

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

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

The summary of immunogenicity data is shown in Table 20. At baseline, all patients were ADA negative except 1 patients in CT-P13 group. At Week 14, the number of patients with positive ADA was 8/54 (14.8 %), 5/43 (11.6 %) and 4/12 (33.3 %) at Week 14 in the CT-P13 treatment group, US-licensed Remicade group, and EU-approved Remicade group, respectively. This interim analysis shows the incidence of ADA formation was similar between CT-P13 and US-licensed Remicade in patients with IBD treated with 5 mg/kg dosing regimen. In this interim analysis, the ADA incidence was numerically higher in patients treated with the EU-approved Remicade, likely due to the small sample size of this subgroup.

Table 20. 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, the Agency considered the following:

- The imbalance in ADA incidence and antibody titers seen in study 1.4 was not associated with a difference in PK (Table 17).
- 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.
- 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) (see Table 16).
- 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 (see Table 18 and Table 19).
- 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 1.2 (see Table 16).
- As discussed in the CMC section above, 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, the Agency does not believe that the results of study 1.4 are likely to represent real or 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 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 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 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.

10 Considerations for Extrapolation of Biosimilarity

Celltrion seeks licensure for all 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.

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, such as RA in Celltrion's program. 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 potential exists for that product to be licensed for one or more additional conditions of use for which the reference product (i.e., US-licensed Remicade) is licensed.[27] The applicant needs to provide sufficient

[27] Guidance for Industry "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009", April 2015

scientific justification for extrapolation, which 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 addressed in a scientific justification for extrapolation do not necessarily preclude extrapolation. 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 believes CT-P13 is highly similar to US-licensed Remicade based on extensive analytical characterization data, similar clinical pharmacokinetics, and similar efficacy, safety, and immunogenicity in an approved indication; in this case, clinical data in both RA and AS.

Further, the additional points considered 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[28]) 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.[29] Since similar PK was demonstrated between CT-P13 and US-licensed Remicade (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

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444661.pdf

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

[29] Remicade USPI

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 21. (Same as Table 1) 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[30,31]

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 21 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, it is reasonable to extrapolate conclusions regarding similar efficacy and safety of CT-P13 and US-licensed Remicade to PsA and PsO.

[30] 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
[31] Tracey D et al., "Tumor necrosis factor antagonist mechanisms of action: A comprehensive review", Pharmacology & Therapeutics 117 (2008) 244–279

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

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.[32] 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 21 may play a role.[33] 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 21. 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 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 the reference product.
- The mechanism of action of TNF inhibitors in treating IBD is complex and, as summarized in Table 21, 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), while the possible ADCC difference between CT-P13 and US-licensed Remicade is small. 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

[32] 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
[33] Tracey D et al., "Tumor necrosis factor antagonist mechanisms of action: A comprehensive review", Pharmacology & Therapeutics 117 (2008) 244–279

response, clinical remission) lack discriminative capacity to assess the effect of small differences in ADCC and FcγRIII binding.

Therefore, based on the above considerations, it is reasonable to extrapolate conclusions regarding similar efficacy and safety of CT-P13 and US-licensed Remicade to IBD.

In aggregate, the evidence indicates that the extrapolation of biosimilarity to the indications for which Celltrion is seeking licensure (PsA, PsO, adult and pediatric CD, and adult and pediatric UC[34]), may be scientifically justified.

11 Summary

The conclusion of the comparison of the structural and functional properties of the clinical and commercial product lots of CT-P13 and US-licensed Remicade was that they were highly similar, notwithstanding minor differences in clinically inactive components.

Celltrion provided extensive analytical and clinical pharmacology bridging data to scientifically justify the relevance of data obtained using EU-approved Remicade to a demonstration of biosimilarity of CT-P13 to the US-licensed reference product.

The submitted clinical pharmacology studies are adequate to (1) support the demonstration of PK similarity between CT-P13 and US-licensed Remicade, (2) establish the PK component of the scientific bridge to justify the relevance of the data generated using EU-approved Remicade, (3) justify the relevance of the PK findings from the CT-P13 clinical program to the same indications for which US-licensed Remicade is licensed.

The results of the clinical development program indicate that the Celltrion's data would meet the requirement for a demonstration of "no clinically meaningful differences" between CT-P13 and the US-licensed reference product 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 worsening safety or

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

immunogenicity. This would support 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 the applicant 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.

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

12 References

References are listed as footnotes throughout the document.