CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION

Application number:	BLA 125544
Supporting document/s:	12 and 42
Applicant's letter date:	11/14/2014 and 10/5/2015
CDER stamp date:	11/14/2014 and 10/5/2015
Product:	INFLECTRA™ (infliximab-dyyb) or CT-P13
Indications:	Crohn's disease, Pediatric Crohn's disease, ulcerative colitis, pediatric ulcerative colitis[1], RA in combination with MTX, ankylosing spondylitis, Psoriatic arthritis, plaque psoriasis
Applicant:	Celltrion, Inc.
Review Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Reviewer:	Matthew Whittaker, Ph.D.
Supervisor/Team Leader:	Timothy Robison, Ph.D.
Division Director:	Badrul Chowdhury, M.D., Ph.D.
Project Manager:	Nina Ton

Template Version: September 1, 2010

[1] This reflects information for Inflectra that Celltrion submitted on August 8, 2014. We note that Remicade's indication for pediatric ulcerative colitis is protected by orphan drug exclusivity expiring on September 23, 2018. See the Orphan Drug Designations and Approvals database at http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm. Accordingly, FDA will not be able to license a proposed biosimilar product for this indication until the orphan exclusivity expires.

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1 Executive Summary

1.1 Introduction

BLA 125544 was initially submitted by Celltrion, Inc. on August 8, 2014 under section 351(k) of the Public Health Service Act (PHS Act) to support registration of INFLECTRA™ (referred to during development as CT-P13) as a proposed biosimilar to US-licensed Remicade® (infliximab). The BLA was re-submitted on October 5, 2015 after addressing Chemistry, Manufacturing and Control (CMC) deficiencies raised by the FDA during the first review cycle (Complete Response June 8, 2015).

Draft labeling for INFLECTRA was submitted on November 14, 2014. The proprietary name used for the CT-P13 drug product in the draft labeling was (b) (4). Celltrion submitted the proposed proprietary name INFLECTRA on November 28, 2014, and withdrew the proprietary name (b) (4) on February 10, 2015. The proprietary name INFLECTRA was granted on November 24, 2015.

US-licensed Remicade® is an intravenously administered product, originally developed by Centocor, Inc. (BLA 103772, 8/24/1998), indicated for the treatment of Crohn's disease, Pediatric Crohn's disease, ulcerative colitis, pediatric ulcerative colitis, RA in combination with MTX, ankylosing spondylitis, psoriatic arthritis and plaque psoriasis. Infliximab is a chimeric human-murine monoclonal IgG1 antibody directed against both soluble and membrane-bound human tumor necrosis factor α (TNFα). It is designed to inhibit TNF receptor mediated functions including cell proliferation, cytokine production, inflammatory cell recruitment, and other inflammatory processes. Celltrion intends to use dosing regimens for Inflectra that are identical to US-licensed Remicade, and seeks approval for all currently approved Remicade indications[1].

The CT-P13 nonclinical development program has been reviewed previously, and judged to be adequate for approval (Nonclinical Review, BLA 125544, May 4, 2015). No new nonclinical information has been submitted since the initial BLA review.

1.2 Brief Discussion of Nonclinical Findings

The language in the nonclinical sections of the labeling (e.g., Established Pharmacological Classification under Indications and Usage in the Highlights of Prescribing Information section and Sections 8.1 & 8.2, 12.1, and 13.1) is generally consistent with the most recent approved labeling for US-licensed Remicade (10/2/15). However, certain references to (b) (4) (INFLECTRA) have been revised to "infliximab products" as appropriate. The reason for this change is the information applies to both the reference product (US-licensed Remicade) and the biosimilar product (CT-P13). The change to "infliximab products" helps to avoid the implication that study results referenced in nonclinical sections of the INFLECTRA labeling are derived from studies conducted with CT-P13.

The initial 351(k) BLA for CT-P13 was pending as of the effective date of the Pregnancy and Lactation Labeling Rule (PLLR, Effective Date: June 30, 2015) and is subject to the PLLR implementation plan. The PLLR implementation plan states that PLLR content in Section 8 of the labeling of such applications must be submitted to FDA by 4 years after the effective date of the final rule (June 30, 2019) or at the time of BLA approval, whichever is later. The format and content of Section 8 of the INFLECTRA labeling need not conform to PLLR guidelines at this time.

1.3 Recommendations

1.3.1 Approvability

INFLECTRA (CT-P13) is recommended for approval from the nonclinical perspective.

1.3.2 Additional Non Clinical Recommendations

Labeling recommendations are provided in Section 1.3.3. There are no other nonclinical recommendations or outstanding issues at this time.

1.3.3 Labeling

The recommended text for the nonclinical sections of the INFLECTRA prescribing information is provided below. Additions are shown as underlined text and deletions are shown in strikeout text.

INDICATIONS AND USAGE

(b) (4) INFLECTRA™ is a tumor necrosis factor (TNF) blocker indicated for:

Crohn's Disease (1.1):

- 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.

Pediatric Crohn's Disease (1.2):

- reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active disease who have had an inadequate response to conventional therapy.

Ulcerative Colitis (1.3):

- 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.

(b) (4)

Rheumatoid Arthritis (1.4) 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.

Ankylosing Spondylitis (1.5):

- reducing signs and symptoms in patients with active disease.

Psoriatic Arthritis (1.6):

- reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function.

Plaque Psoriasis (1.7):

- 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.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B.

It is not known whether (b) (4) infliximab products can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. (b) (4) INFLECTRA should be given to a pregnant woman only if clearly needed. Because infliximab products do (b) (4) not cross-react with TNFα in species other than humans and chimpanzees, animal reproduction studies have not been conducted with (b) (4) infliximab products. No evidence of maternal toxicity, embryotoxicity or teratogenicity was observed in a developmental toxicity study conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse TNFα. Doses of 10 to 15 mg/kg in pharmacodynamic animal models with the anti-TNF analogous antibody produced maximal pharmacologic effectiveness. Doses up to 40 mg/kg were shown to produce no adverse effects in animal reproduction studies.

As with other IgG antibodies, infliximab products cross the placenta (b) (4) Infliximab has been detected in the serum of infants at up to 6 months following birth. Consequently, these infants may be at increased risk of infection, including disseminated infection which can become fatal. At least a 6 month waiting period following birth is recommended before the administration of live vaccines (e.g. BCG vaccine or other live vaccines, such as the rotavirus vaccine) to these infants [see *Warnings and Precautions (5.14)*].

8.2 Nursing Mothers

It is not known whether (b) (4) infliximab products are excreted in human milk or absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for adverse reactions in nursing infants from (b) (4) infliximab products, women should not breast-feed their infants while taking (b) (4) INFLECTRA. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Infliximab products neutraliz (b) (4) the biological activity of TNFα by binding with high affinity to the soluble and transmembrane forms of TNFα and inhibit (b) (4) binding of TNFα with its receptors. Infliximab products do (b) (4) not neutralize TNFβ (lymphotoxin-α), a related cytokine that utilizes the same receptors as TNFα. Biological activities attributed to TNFα include: induction of proinflammatory cytokines such as IL-1 and IL-6, enhancement of leukocyte migration by increasing endothelial layer permeability and expression of adhesion molecules by endothelial cells and leukocytes, activation of neutrophil and eosinophil functional activity, induction of acute phase reactants and other liver proteins, as well as tissue degrading enzymes produced by synoviocytes and/or chondrocytes. Cells expressing transmembrane TNFα bound by infliximab can be lysed *in vitro* or *in vivo*. Infliximab products inhibit (b) (4) the functional activity of TNFα in a wide variety of *in vitro* bioassays utilizing human fibroblasts, endothelial cells, neutrophils, B and T lymphocytes and epithelial cells. The relationship of these biological response markers to the mechanism(s) by which (b) (4) infliximab products exert (b) (4) their clinical effects is unknown. Anti-TNFα antibodies reduce disease activity in the cotton-top tamarin colitis model, and decrease synovitis and joint erosions in a murine model of collagen-induced arthritis. Infliximab products prevent (b) (4) disease in transgenic mice that develop polyarthritis as a result of constitutive expression of human TNFα, and when administered after disease onset, allows eroded joints to heal.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The significance of the results of nonclinical studies for human risk is unknown. A repeat dose toxicity study was conducted with mice given cV1q anti-mouse TNFα to evaluate tumorigenicity. CV1q is an analogous antibody that inhibits the function of TNFα in mice. Animals were assigned to 1 of 3 dose groups: control, 10 mg/kg or 40 mg/kg cV1q given weekly for 6 months. The weekly doses of 10 mg/kg and 40 mg/kg are 2 and 8 times, respectively, the human dose of 5 mg/kg for Crohn's disease. Results indicated that cV1q did not cause tumorigenicity in mice. No clastogenic or mutagenic effects of infliximab were observed in the *in vivo* mouse micronucleus test or the *Salmonella-Escherichia coli* (Ames) assay, respectively. Chromosomal aberrations were not observed in an assay performed using human lymphocytes. It is not known whether infliximab products can impair fertility in humans. No impairment of fertility was observed in a fertility and general reproduction toxicity study with the analogous mouse antibody used in the 6-month chronic toxicity study.

2 Drug Information

2.1 Drug

Developmental Name: CT-P13

Non-proprietary Name: infliximab-dyyb

Proprietary Name: INFLECTRA

Chemical Name: Chimeric human-murine monoclonal IgG1 antibody directed against soluble and membrane-bound human TNFα

Molecular Formula/Molecular Weight

- 2 Light Chains: $C_{1028}H_{1587}N_{279}O_{337}S_6$ (450 amino acids)
- 2 Heavy Chains: $C_{2203}H_{3411}N_{585}O_{682}S_{16}$ (214 amino acids)

Structure or Biochemical Description: The DNA sequence of CT-P13 was synthesized based on the published amino acid sequence of infliximab. The primary amino acid sequence of CT-P13 is identical to that of infliximab (Figure 1).

Heavy Chain

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1   EVKLEESGGG LVQPGGSMKL SCVASGFIFS NHWMNWVRQS PEKGLEWVAE
51  IRSKSINSAT HYAESVKGRF TISRDDSKSA VYLQMTDLRT EDTGVYYCSR
101 NYYGSTYDYW GQGTTLTVSS ASTKGPSVFP LAPSSKSTSG GTAALGCLVK
151 DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTQT
201 YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP
251 KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN [1]
301 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ
351 VYTLPPSRDE LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV
401 LDSDGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK
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Light Chain

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1   DILLTQSPAI LSVSPGERVS FSCRASQFVG SSIHWYQQRT NGSPRLLIKY
51  ASESMSGIPS RFSGSGSGTD FTLSINTVES EDIADYYCQQ SHSWPFTFGS
101 GTNLEVKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV
151 DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG
201 LSSPVTKSFN RGEC
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[1] Glycosylation site is Asn300 of the heavy chain.

Note: The amino acid sequences were defined according to both protein and gene structure. The letters shown denote the one-letter code for the 20 common amino acids. Variable regions for both heavy and light chains are indicated in normal

Figure 1. Amino acid sequence of CT-P13 (BLA 125544, CTD Module 2, Section 2.3.S)

Pharmacologic Class: Tumor necrosis factor (TNF) blocker.

2.2 Relevant INDs, BLAs and DMFs

Application #	Description	Sponsor	Date
IND 118135	IND application in support of clinical testing of CT-P13	Celltrion, Inc.	10/17/13 (IND submission date)
BLA 103772	BLA application for reference product, Remicade®	Centocor, Inc.	8/24/98 (approval date)

2.3 Drug Formulation

The CT-P13 drug product is provided as a lyophilized powder in 20 ml type I borosilicate glass vials (Table 1). The lyophilizate is reconstituted with 10 ml of sterile water for injection to yield a single dose formulation containing 10 mg/ml infliximab, pH 7.2. (b) (4)

Table 1. Drug product formulation for a single dose of CT-P13.

Ingredient	Quantity/Vial	Function	Grade
CT-P13	100 mg	Active ingredient	In-house
Sucrose	500 mg	(b) (4)	NF/Ph. Eur.
Sodium dihydrogen phosphate monohydrate	2.2 mg		USP
di-Sodium hydrogen phosphate dihydrate	6.1 mg		USP/Ph. Eur.
Polysorbate 80	0.5 mg		NF/Ph. Eur.

USP: United States Pharmacopoeia; NF: National Formulary; Ph. Eur.: European Pharmacopoeia

2.4 Comments on Novel Excipients

There are no novel excipients in the CT-P13 drug product formulation. (b) (4)

2.5 Comments on Impurities/Degradants of Concern

There are currently no impurities or degradants of concern.

2.6 Proposed Clinical Population and Dosing Regimen

The proposed clinical population and dosing regimen for CT-P13 are identical to those of the reference product.

The indications include:

- RA in combination with methotrexate (moderately to severely active disease)
- Ankylosing Spondylitis (active disease)

- Psoriatic arthritis
- Psoriasis (chronic severe)
- Crohn's disease and Ulcerative colitis in adult and pediatric patients (moderately to severely active disease and inadequate response to conventional therapy)[1]

The US-licensed Remicade dosage recommendation for RA is 3 mg/kg at 0, 2, and 6 weeks then every 8 weeks. The dose can be increased up to 10 mg/kg or treatment can be given as often as every 4 weeks. For Ankylosing Spondylitis, the treatment regimen is 5 mg/kg at 0, 2, and 6 weeks, then every 6 weeks. For all other indications the dosage is 5 mg/kg at 0, 2, and 6 weeks, then every 8 weeks with the provision that in adult Crohn's disease patients, the dose may be increased to 10 mg/kg if patients initially respond but later lose their response.

2.7 Regulatory Background

Notable nonclinical Pharmacology and Toxicology regulatory concerns were limited to the FDA response to a single question raised by Celltrion at a Biosimilar Biological Product Development (BPD) Type 3 meeting held on 7/10/13. Briefly, the Division stated that in vivo studies conducted in mice expressing human TNFα (e.g. Tg197 mice) would have been more informative for assessment of the safety and similarity of CT-P13 relative to US-licensed Remicade. However, additional animal studies beyond those that had already been conducted in SD rats were not recommended based upon the extensive human experience that was available.

CT-P13 has been tested vs. EU-approved Remicade in RA (4 completed studies) and AS patients (2 completed studies) outside of the United States. Study CT-P13 1.4, a single dose (5 mg/kg), 3-way bridging PK study with CT-P13, US-licensed Remicade and EU-approved Remicade, was conducted in healthy subjects.

3 Studies Submitted

3.1 Studies Reviewed

No new nonclinical data has been submitted to the BLA since the time of the initial nonclinical BLA review. The current review includes an evaluation of recommended labeling edits only.

3.3 Previous Reviews Referenced

Pharmacology and Toxicology Review of BLA 125544 dated May 4, 2015.

11 Integrated Summary and Safety Evaluation

11.1 Labeling Evaluation

The language in the nonclinical sections of the proposed INFLECTRA label (e.g. Established Pharmacological Classification under Indication and Usage in the Highlights of Prescribing Information section and Sections 8.1 & 8.2, 12.1, and 13.1) is generally consistent with the labeling for US-licensed Remicade®. However, certain references to (b) (4) (INFLECTRA) have been revised to "infliximab products" as appropriate. The reason for this change is that the information applies to both the reference product (US-licensed Remicade) and the biosimilar product (CT-P13). The change to "infliximab products" also helps to avoid the implication that study results referenced in nonclinical sections of the INFLECTRA labeling are derived from studies conducted with CT-P13.

BLA 125544 was initially submitted on August 8, 2014. The BLA was re-submitted on October 5, 2015 after addressing issues raised by the FDA in a complete response (June 8, 2015). The initial 351(k) BLA for CT-P13 was pending as of the effective date of the PLLR (June 30, 2015) and is subject to the PLLR implementation plan. The PLLR implementation plan states that PLLR content in Section 8 of the labeling of such applications must be submitted to FDA by 4 years after the effective date of the final rule (June 30, 2019) or at the time of BLA approval, whichever is later. The format and content of Section 8 of the INFLECTRA labeling need not conform to PLLR guidelines at this time.

11.2 Labeling Recommendations

The complete labeling recommendations pertaining to nonclinical data in the Prescribing Information for INFLECTRA are presented below. The Sponsor's text is from their draft Prescribing Information dated November 14, 2014. Additions are shown as underlined text and deletions are shown in strikeout text.

INDICATIONS AND USAGE

Sponsor's text

(b) (4)™ is a tumor necrosis factor (TNF) blocker indicated for:

Crohn's Disease (1.1):

- 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.

Pediatric Crohn's Disease (1.2):

- 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.

Ulcerative Colitis (1.3):

- 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.

(b) (4)

Rheumatoid Arthritis (1.5) 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.

Ankylosing Spondylitis (1.6):

- reducing signs and symptoms in patients with active disease.

Psoriatic Arthritis (1.7):

- reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function.

Plaque Psoriasis (1 8):

- 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.

FDA Revised text

(b) (4) INFLECTRA™ is a tumor necrosis factor (TNF) blocker indicated for:

Crohn's Disease (1.1):

- 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.

Pediatric Crohn's Disease (1.2):

- reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active disease who have had an inadequate response to conventional therapy.

Ulcerative Colitis (1.3):

- 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.

(b) (4)

Rheumatoid Arthritis (1.4) 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.

Ankylosing Spondylitis (1.5):

- reducing signs and symptoms in patients with active disease.

Psoriatic Arthritis (1.6):

- reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function.

Plaque Psoriasis (1.7):

- 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.

The proprietary name was updated to INFLECTRA. Celltrion's proposed Established Pharmacologic Class (EPC) of "tumor necrosis factor (TNF) blocker" is consistent with the FDA EPC Text Phrase for infliximab.

(b) (4)

8. USE IN SPECIFIC POPULATIONS

Sponsor's text

8.1 Pregnancy

Pregnancy Category B. It is not known whether (b) (4) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. (b) (4) should be given to a pregnant woman only if clearly needed. Because infliximab do (b) (4) not cross-react with TNFα in species other than humans and chimpanzees, animal reproduction studies have not been conducted with (b) (4) No evidence of maternal toxicity, embryotoxicity or teratogenicity was observed in a developmental toxicity study

conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse TNFα. Doses of 10 to 15 mg/kg in pharmacodynamic animal models with the anti-TNF analogous antibody produced maximal pharmacologic effectiveness. Doses up to 40 mg/kg were shown to produce no adverse effects in animal reproduction studies.

As with other IgG antibodies, (b) (4) crosses the placenta (b) (4) [see *Warnings and Precautions (5.14)*].

8.3 Nursing Mothers

It is not known whether (b) (4) is excreted in human milk or absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for adverse reactions in nursing infants from (b) (4) women should not breast-feed their infants while taking (b) (4) A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

FDA Revised text

8.1 Pregnancy

Pregnancy Category B.

It is not known whether (b) (4) infliximab products can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. (b) (4) INFLECTRA should be given to a pregnant woman only if clearly needed. Because infliximab products d (b) (4) not cross-react with TNFα in species other than humans and chimpanzees, animal reproduction studies have not been conducted with (b) (4) infliximab products. No evidence of maternal toxicity, embryotoxicity or teratogenicity was observed in a developmental toxicity study conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse TNFα. Doses of 10 to 15 mg/kg in pharmacodynamic animal models with the anti-TNF analogous antibody produced maximal pharmacologic effectiveness. Doses up to 40 mg/kg were shown to produce no adverse effects in animal reproduction studies.

As with other IgG antibodies, infliximab products cross the placenta (b) (4) Infliximab has been detected in the serum of infants at up to 6 months following birth. Consequently, these infants may be at increased risk of infection, including disseminated infection which can become fatal. At least a 6 month waiting period following birth is recommended before the administration of live vaccines (e.g. BCG vaccine or other live vaccines, such as the rotavirus vaccine) to these infants [see *Warnings and Precautions (5.14)*].

8.2 Nursing Mothers

It is not known whether (b) (4) infliximab products are excreted in human milk or absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for adverse reactions in nursing infants from (b) (4) infliximab products, women should not breast-feed their infants while taking (b) (4) INFLECTRA. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

The format and content of Section 8 were not changed as the labeling for this BLA is not required to comply with the content requirements of the PLLR at this time.

The language in Section 8 is generally consistent with the language in the most recent approved reference product labeling (10/2/15). However, certain references to (b) (4) (INFLECTRA) have been revised to "infliximab products". These changes help to avoid the implication that study results are derived from studies conducted with CT-P13. References to clinical administration of the drug product (b) (4) were changed to INFLECTRA to reflect the proprietary name change that was granted on November 24, 2015.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Sponsor's text

Infliximab neutralizes the biological activity of TNFα by binding with high affinity to the soluble and transmembrane forms of TNFα and inhibit (b) (4) binding of TNFα with its receptors. Infliximab do (b) (4) not neutralize TNFβ (lymphotoxin-α), a related cytokine that utilizes the same receptors as TNFα. Biological activities attributed to TNFα include: induction of proinflammatory cytokines such as IL-1 and IL-6, enhancement of leukocyte migration by increasing endothelial layer permeability and expression of adhesion molecules by endothelial cells and leukocytes, activation of neutrophil and eosinophil functional activity, induction of acute phase reactants and other liver proteins, as well as tissue degrading enzymes produced by synoviocytes and/or chondrocytes. Cells expressing transmembrane TNFα bound by infliximab can be lysed *in vitro* or *in vivo*. Infliximab inhibit (b) (4) the functional activity of TNFα in a wide variety of *in vitro* bioassays utilizing human fibroblasts, endothelial cells, neutrophils, B and T lymphocytes and epithelial cells. The relationship of these biological response markers to the mechanism(s) by which (b) (4) exert (b) (4) clinical effects is unknown. Anti-TNFα antibodies reduce disease activity in the cotton-top tamarin colitis model, and decrease synovitis and joint erosions in a murine model of collagen-induced arthritis. Infliximab prevent (b) (4) disease in transgenic mice that develop polyarthritis as a result of constitutive expression of human TNFα, and when administered after disease onset, allows eroded joints to heal.

FDA Revised text

Infliximab products neutraliz (b)(4) the biological activity of TNFα by binding with high affinity to the soluble and transmembrane forms of TNFα and inhibi (b)(4) binding of TNFα with its receptors. Infliximab products do (b)(4) not neutralize TNFβ (lymphotoxin-α), a related cytokine that utilizes the same receptors as TNFα. Biological activities attributed to TNFα include: induction of proinflammatory cytokines such as IL-1 and IL-6, enhancement of leukocyte migration by increasing endothelial layer permeability and expression of adhesion molecules by endothelial cells and leukocytes, activation of neutrophil and eosinophil functional activity, induction of acute phase reactants and other liver proteins, as well as tissue degrading enzymes produced by synoviocytes and/or chondrocytes. Cells expressing transmembrane TNFα bound by infliximab can be lysed *in vitro* or *in vivo*. Infliximab products inhibit (b)(4) the functional activity of TNFα in a wide variety of *in vitro* bioassays utilizing human fibroblasts, endothelial cells, neutrophils, B and T lymphocytes and epithelial cells. The relationship of these biological response markers to the mechanism(s) by which (b)(4) infliximab products exert (b)(4) their clinical effects is unknown. Anti-TNFα antibodies reduce disease activity in the cotton-top tamarin colitis model, and decrease synovitis and joint erosions in a murine model of collagen-induced arthritis. Infliximab products prevent (b)(4) disease in transgenic mice that develop polyarthritis as a result of constitutive expression of human TNFα, and when administered after disease onset, allows eroded joints to heal.

References to (b)(4) in the context of mechanism of action were revised to "infliximab products" because the information applies to both US-licensed Remicade and INFLECTRA.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Sponsor's text

The significance of the results of nonclinical studies for human risk is unknown. A repeat dose toxicity study was conducted with mice given cV1q anti-mouse TNFα to evaluate tumorigenicity. CV1q is an analogous antibody that inhibits the function of TNFα in mice. Animals were assigned to 1 of 3 dose groups: control, 10 mg/kg or 40 mg/kg cV1q given weekly for 6 months. The weekly doses of 10 mg/kg and 40 mg/kg are 2 and 8 times, respectively, the human dose of 5 mg/kg for Crohn's disease. Results indicated that cV1q did not cause tumorigenicity in mice. No clastogenic or mutagenic effects of infliximab were observed in the *in vivo* mouse micronucleus test or the *Salmonella-Escherichia coli* (Ames) assay, respectively. Chromosomal aberrations were not observed in an assay performed using human lymphocytes. It is not known whether infliximab can impair fertility in humans. No impairment of fertility was observed in a fertility and general reproduction toxicity study with the analogous mouse antibody used in the 6-month chronic toxicity study.

FDA Revised text

The significance of the results of nonclinical studies for human risk is unknown. A repeat dose toxicity study was conducted with mice given cV1q anti-mouse TNFα to evaluate tumorigenicity. CV1q is an analogous antibody that inhibits the function of TNFα in mice. Animals were assigned to 1 of 3 dose groups: control, 10 mg/kg or 40 mg/kg cV1q given weekly for 6 months. The weekly doses of 10 mg/kg and 40 mg/kg are 2 and 8 times, respectively, the human dose of 5 mg/kg for Crohn's disease. Results indicated that cV1q did not cause tumorigenicity in mice. No clastogenic or mutagenic effects of infliximab were observed in the *in vivo* mouse micronucleus test or the *Salmonella-Escherichia coli* (Ames) assay, respectively. Chromosomal aberrations were not observed in an assay performed using human lymphocytes. It is not known whether infliximab products can impair fertility in humans. No impairment of fertility was observed in a fertility and general reproduction toxicity study with the analogous mouse antibody used in the 6-month chronic toxicity study.

The results of all nonclinical studies described in this section are relevant to the reference product as well as INFLECTRA. For this reason, the reference to the effect of "infliximab" on impairment of fertility was changed to "infliximab products". Section 13.1 did not include any direct references to INFLECTRA.

(b) (4)

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11.3 Overall Recommendations

BLA 125544 is recommended for approval from the nonclinical perspective. There are no outstanding nonclinical issues and no further nonclinical studies are recommended.

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/s/

MATTHEW T WHITTAKER
03/28/2016

TIMOTHY W ROBISON
03/28/2016
I concur

Pharmacology and Toxicology Secondary Review for BLA 125544

TO: BLA 125544 (Inflectra [referred to as CT-P13 during development] as a biosimilar to US-licensed Remicade® [infliximab])

FROM: Timothy W. Robison, Ph.D., D.A.B.T.
Pharmacology and Toxicology Team Leader
Division of Pulmonary, Allergy, and Rheumatology Products

DATE: May 8, 2015

BLA 125544 was submitted by Celltrion, Inc. on August 8, 2014 under section 351(k) of the Public Health Service Act (PHS Act) to support registration of Inflectra (referred to as CT-P13 during development) as a biosimilar to US-licensed Remicade® (infliximab). Remicade® is an intravenously administered product, originally developed by Centocor, Inc. (BLA 103772, August 24, 1998), indicated for the treatment of Crohn's disease, Pediatric Crohn's disease, ulcerative colitis, pediatric ulcerative colitis[1], RA in combination with MTX, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis.

Dr. Matthew Whittaker's review dated May 4, 2015 focused on two nonclinical toxicology/toxicokinetic studies submitted in support of a demonstration of biosimilarity of CT-P13 to US-licensed Remicade: (1) a single dose toxicokinetic (TK) study in Sprague-Dawley rats comparing CT-P13 vs. EU-approved infliximab and (2) a 2-week toxicity/TK study in Sprague-Dawley rats comparing CT-P13 vs. EU-approved infliximab. Celltrion established an adequate scientific bridge to justify the relevance of these comparative data obtained using EU-approved infliximab to support a demonstration of biosimilarity to the US licensed reference product.

I concur with Dr. Whittaker's review dated May 4, 2015 that recommended approval of CT-P13 from the nonclinical Pharmacology and Toxicology perspective. However, a review of labeling was deferred at this time due to Chemistry, Manufacturing and Control (CMC) deficiencies that will lead to a Complete Response for the application.

Nonclinical studies conducted by Centocor Biotech, Inc. in support of initial approval of the innovator product (U.S. licensed Remicade®) established that infliximab cross-reacted with TNFα from human and chimpanzee only. There was no activity with TNFα derived from dog, baboon, rhesus or cynomolgus monkey, pig-tail macaque, marmoset, cotton-top tamarin, pig, rabbit, rat, or mouse. Celltrion conducted a similar study in which neither CT-P13 nor EU-approved infliximab exhibited specific binding to TNFα derived from mouse, rat, dog, pig, or rhesus monkey (See Dr. Whittaker's review for further details).

[1] This reflects information for Inflectra that Celltrion submitted on August 8, 2014. We note that the indication for pediatric ulcerative colitis is protected by orphan drug exclusivity expiring on September 23, 2018. See the Orphan Drug Designations and Approvals database at http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm.

Celltrion chose to conduct nonclinical studies with CT-P13 in the Sprague-Dawley rat despite that the rat was not a pharmacologically relevant species. At a BPD Type 3 meeting held on July 10, 2013, the Division stated that *in vivo* studies conducted in mice expressing human TNFα (e.g., Tg197 mice) would have been more informative for assessment of the safety and similarity of CT-P13 relative to US-licensed Remicade. However, additional animal studies were not recommended based upon the extensive human experience that was available with CT-P13.

Recommendation: From the nonclinical perspective, approval of the application is recommended. A review of labeling will be done at a later date.

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/s/

TIMOTHY W ROBISON
05/08/2015
See Dr. Matthew Whittaker's primary review dated May 4, 2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION

Application number:	BLA 125544
Supporting document/s:	1
Applicant's letter date:	8/8/2014
CDER stamp date:	8/8/2014
Product:	CT-P13
Indications:	Crohn's disease, Pediatric Crohn's disease, ulcerative colitis, pediatric ulcerative colitis[1], RA in combination with MTX, ankylosing spondylitis, Psoriatic arthritis, plaque psoriasis
Applicant:	Celltrion, Inc.
Review Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Reviewer:	Matthew Whittaker, Ph.D.
Supervisor/Team Leader:	Timothy Robison, Ph.D.
Division Director:	Badrul Chowdhury, M.D., Ph.D.
Project Manager:	Nina Ton

Template Version: September 1, 2010

Disclaimer
Except as specifically identified, all data and information discussed below and necessary for approval of BLA 125544 are owned by Celltrion, Inc. or are data for which Celltrion, Inc. has obtained a written right of reference.

Any information or data necessary for approval of BLA 125544 that Celltrion, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or

[1] This reflects information for Inflectra that Celltrion submitted on August 8, 2014. We note that the indication for pediatric ulcerative colitis is protected by orphan drug exclusivity expiring on September 23, 2018. See the Orphan Drug Designations and Approvals database at http://www.accessdata fda.gov/scripts/opdlisting/oopd/index.cfm.

publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of BLA 125544.

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1 Executive Summary

1.1 Introduction

BLA 125544 was submitted by Celltrion, Inc. on August 8, 2014 under section 351(k) of the Public Health Service Act (PHS Act) to support registration of Inflectra (referred to as during development as CT-P13) as a biosimilar to US-licensed Remicade® (infliximab). Remicade® is an intravenously administered product, originally developed by Centocor, Inc. (BLA 103772, 8/24/1998), indicated for the treatment of Crohn's disease, Pediatric Crohn's disease, ulcerative colitis, pediatric ulcerative colitis[1], RA in combination with MTX, ankylosing spondylitis, psoriatic arthritis and plaque psoriasis. Infliximab is a chimeric human-murine monoclonal IgG1 antibody directed against both soluble and membrane-bound human tumor necrosis factor α (TNFα). It is designed to inhibit TNF receptor mediated functions including cell proliferation, cytokine production, inflammatory cell recruitment, and other inflammatory processes. Celltrion intends to use dosing regimens for Inflectra that are identical to US-licensed Remicade, and to obtain approval for all currently approved Remicade indications.

The two key nonclinical toxicology/toxicokinetic studies submitted in support of a demonstration of biosimilarity of CT-P13 to US-licensed Remicade include: (1) a single dose toxicokinetic (TK) study in Sprague-Dawley (SD) rats comparing CT-P13 vs. EU-approved infliximab and (2) a 2-week toxicity/TK study in SD rats comparing CT-P13 vs. EU-approved infliximab. Celltrion established an adequate scientific bridge to justify the relevance of these comparative data obtained using EU-approved infliximab to support a demonstration of biosimilarity to the US-licensed reference product.

1.2 Brief Discussion of Nonclinical Findings

The CT-P13 nonclinical development program has been reviewed previously, and judged to be adequate to support clinical development (IND 118135, Nonclinical review, 11/12/13). 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 considered to be reasonably comparable to that of EU-approved infliximab in SD rats. The pharmacology and animal data submitted to the BLA demonstrate the similarity (i.e., comparable achieved exposures and similar safety) between CT-P13 and EU-approved infliximab from the nonclinical Pharmacology and Toxicology perspective.

1.3 Recommendations

1.3.1 Approvability

CT-P13 is recommended for approval from the nonclinical Pharmacology and Toxicology perspective. However, labeling will be deferred at this time due to Chemistry, Manufacturing and Control (CMC) deficiencies that will lead to a Complete Response for the application.

1.3.2 Additional Nonclinical Recommendations

There are no nonclinical Pharmacology and Toxicology recommendations or outstanding issues at this time.

2 Drug Information

2.1 Drug

Developmental Name: CT-P13

Trade Name: Inflectra

Chemical Name: Chimeric human-murine monoclonal IgG1 antibody directed against soluble and membrane-bound human TNFα

Molecular Formula/Molecular Weight

- 2 Light Chains: $C_{1028}H_{1587}N_{279}O_{337}S_6$ (450 amino acids)
- 2 Heavy Chains: $C_{2203}H_{3411}N_{585}O_{682}S_{16}$ (214 amino acids)

Structure or Biochemical Description: The DNA sequence of CT-P13 was synthesized based on the published sequence of infliximab. The primary amino acid sequence of CT-P13 is identical to that of infliximab (Figure 1).

	Heavy Chain
1	EVKLEESGGG LVQPGGSMKL S**C**VASGFIFS NHWMNWVRQS PEKGLEWVAE
51	IRSKSINSAT HYAESVKGRF TISRDDSKSA VYLQMTDLRT EDTGVYY**C**SR
101	NYYGSTYDYW GQGTTLTVSS *ASTKGPSVFP LAPSSKSTSG GTAALG**C**LVK*
151	*DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTQT*
201	*YI**C**NVNHKPS NTKVDKKVEP KS**C**DKTHT**C**P P**C**PAPELLGG PSVFLFPPKP*
251	*KDTLMISRTP EVT**C**VVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN* [1]
301	*STYRVVSVLT VLHQDWLNGK EYK**C**KVSNKA LPAPIEKTIS KAKGQPREPQ*
351	*VYTLPPSRDE LTKNQVSLT**C** LVKGFYPSDI AVEWESNGQP ENNYKTTPPV*
401	*LDSDGSFFLY SKLTVDKSRW QQGNVFS**C**SV MHEALHNHYT QKSLSLSPGK*
	Light Chain
1	DILLTQSPAI LSVSPGERVS FS**C**RASQFVG SSIHWYQQRT NGSPRLLIKY
51	ASESMSGIPS RFSGSGSGTD FTLSINTVES EDIADYY**C**QQ SHSWPFTFGS
101	GTNLEVK*RTV AAPSVFIFPP SDEQLKSGTA SVV**C**LLNNFY PREAKVQWKV*
151	*DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYA**C**EVTHQG*
201	*LSSPVTKSFN RGE**C***

[1] Glycosylation site is Asn300 of the heavy chain.
Note: The amino acid sequences were defined according to both protein and gene structure. The letters shown denote the one-letter code for the 20 common amino acids. Variable regions for both heavy and light chains are indicated in normal

Figure 1. Amino acid sequence of CT-P13 (BLA 125544, CTD Module 2, Section 2.3.S)

Pharmacologic Class: Tumor necrosis factor (TNF) blocker.

2.2 Relevant INDs, NDAs, BLAs and DMFs

Application #	Description	Sponsor	Date
IND 118135	IND application in support of clinical testing of CT-P13 in the US	Celltrion, Inc.	10/17/13 (IND submission date)
BLA 103772	BLA application for innovator product, Remicade®	Centocor, Inc.	8/24/98 (approval date)

2.3 Drug Formulation

The CT-P13 drug product is provided as a lyophilized powder in 20 ml type I borosilicate glass vials (Table 1). The lyophilizate is reconstituted with 10 ml of sterile water for injection to yield a single dose formulation containing 10 mg/ml infliximab, pH 7.2. (b) (4)

Table 1. Drug product formulation for a single dose of CT-P13.

Ingredient	Quantity/Vial	Function	Grade
CT-P13	100 mg	Active ingredient	In-house
Sucrose	500 mg	(b) (4)	NF/Ph. Eur.
Sodium dihydrogen phosphate monohydrate	2.2 mg		USP
di-Sodium hydrogen phosphate dihydrate	6.1 mg		USP/Ph. Eur.
Polysorbate 80	0.5 mg		NF/Ph. Eur.

USP: United States Pharmacopoeia; NF: National Formulary; Ph. Eur.: European Pharmacopoeia

2.4 Comments on Novel Excipients

There are no novel excipients in the CT-P13 drug product formulation. (b) (4)

2.5 Comments on Impurities/Degradants of Concern

There are currently no impurities or degradants of concern.

2.6 Proposed Clinical Population and Dosing Regimen

The proposed clinical population and dosing regimen for CT-P13 are identical to those of the reference product.

The indications include:

- RA in combination with methotrexate (moderately to severely active disease)
- Ankylosing Spondylitis (active disease)
- Psoriatic arthritis

- Psoriasis (chronic severe)
- Crohn's disease and Ulcerative colitis in adult and pediatric patients (moderately to severely active disease and inadequate response to conventional therapy)[1]

The US-licensed Remicade dosage recommendation for RA is 3 mg/kg at 0, 2, and 6 weeks then every 8 weeks. The dose can be increased up to 10 mg/kg or treatment can be given as often as every 4 weeks. For Ankylosing Spondylitis, the treatment regimen is 5 mg/kg at 0, 2, and 6 weeks, then every 6 weeks. For all other indications the dosage is 5 mg/kg at 0, 2, and 6 weeks, then every 8 weeks with the provision that in adult Crohn's disease patients, the dose may be increased to 10 mg/kg if patients initially respond but later lose their response.

2.7 Regulatory Background

Notable nonclinical Pharmacology and Toxicology regulatory concerns were limited to the FDA response to a single question raised by Celltrion at a Biosimilar Biological Product Development (BPD) Type 3 meeting held on 7/10/13. Briefly, the Division stated that in vivo studies conducted in mice expressing human TNFα (e.g. Tg197 mice) would have been more informative for assessment of the safety and similarity of CT-P13 relative to US-licensed Remicade. However, additional animal studies beyond those that had already been conducted in SD rats were not recommended based upon the extensive human experience that was available.

CT-P13 has been tested vs. EU-approved infliximab in RA and AS patients in several studies outside of the United States. The pivotal clinical study to support marketing of CT-P13 in the US is study CT-P13 1.4, a single dose (5 mg/kg), 3-way bridging PK study with CT-P13, US-licensed Remicade, and EU-approved infliximab in healthy subjects.

3 Studies Submitted

3.1 Studies Reviewed

Study #	Type	Title	Comparison
GRD-RD-10-061	Pharmacology	Comparative TNFα binding affinity from different species of CT-P13 and Remicade®	CT-P13 vs. EU-approved infliximab
8214160	Human tissue cross-reactivity	CT-P13: Study to Assess the Potential Cross Reactivity of CT-13 (infliximab) with a Selected Panel of Human Tissues and comparability to Remicade (infliximab)	CT-P13 vs. EU-approved infliximab
N09067	PK	CT-P13 and Remicade®: Single Intravenous Dose Pharmacokinetics Comparison Study in Rats	CT-P13 vs. EU-approved infliximab

Study #	Type	Title	Comparison
8214158	Toxicity/TK	2-week Repeat-Dose Intravenous Toxicity and Toxicokinetic Study with CT-P13 and Remicade® in Rats	CT-P13 vs. EU-approved infliximab

3.2 Studies Not Reviewed

Study #	Type	Title	Reason not reviewed
G09197	Toxicity	CT-P13 and Remicade®: 2-week Intravenous Dose Toxicity Comparison Study in Rats	Toxicokinetic data was not collected
8214167	Toxicity/TK, dose finding	2- week Intravenous Injection Dose Finding Study with Remicade® in Rats	EU infliximab only was tested (no CT-P13 comparator)

3.3 Previous Reviews Referenced (not included in this review)

Review	Author	Date
Nonclinical 30 day safety review of IND 118135	M. Whittaker	11/12/13
Pharmacology Review of BLA 98-0012 (Remicade)	L. Black	7/30/98

4 Pharmacology

4.1 Primary Pharmacology

- Study title: Comparative TNFα binding affinity from different species of CT-P13 and Remicade®
- Study #: GR-RD-10-061

The reference product is known to bind only to human and chimpanzee TNFα. The current non-GLP study was carried out to confirm that neither CT-P13 (Batch No. 09B9401, 09B9502, 10B9301) nor EU-approved infliximab (Batch No. 9RMA60902, 9RMA60102, 9RMA60401) is capable of binding to TNFα derived from species commonly used in toxicology studies including rhesus monkey, pig, dog, rat, and mouse.

Experiments were conducted using standard BIAcore 3000 (GE Healthcare) methods. CT-P13 or EU-approved infliximab was immobilized to the sensor chip. Recombinant TNFα from each species was obtained from commercial sources. Binding assays measured the binding of TNFα from each species (10 µg/ml) to immobilized CT-P13 or EU-approved infliximab. Anti-rhesus, pig, dog, rat, or mouse TNFα antibodies served as positive controls.

Neither CT-P13 nor EU-approved infliximab demonstrated specific binding to TNFα from any of the species tested in this study.

4.2 Secondary Pharmacology

There were no secondary pharmacology studies submitted.

4.3 Safety Pharmacology

There were no safety pharmacology studies submitted.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

- Study Title: CT-P13 and Remicade®: Single Intravenous Dose Pharmacokinetics Comparison Study in Rats
- Study #: N09067

Methods
Study N09067 was a single dose, IV (tail vein) pharmacokinetic study in adult (~10 weeks) male Sprague-Dawley rats. Celltrion acknowledged that these data may not be predictive of human PK profiles given that neither CT-P13 nor Remicade® binds to rat TNFα.

This was a non-GLP study which was carried out using "generally recognized good laboratory practices" according to the study report. A single dose of CT-P13 (lot BP0306) or EU-approved infliximab (lot 9RMA60902) was administered at 10 mg/kg or 50 mg/kg. There were 5 rats per dose group. Blood samples were taken from the tail vein prior to dosing and out to 2 weeks after dose administration (0.25, 2, 8, 24, 48, 72, 120, 168, 216, 264, and 336 h post dose).

Results
There were no unscheduled deaths, abnormal clinical observations, or differences in body weight between treatment groups.

Serum CT-P13 and EU-approved infliximab were detected using ELISA. The lower limit of quantitation was reported to be 10 ng/ml. The serum concentration vs. time profiles for both 10 mg/kg and 50 mg/kg CT-P13 and EU-approved infliximab appear comparable, as seen in Figure 2.

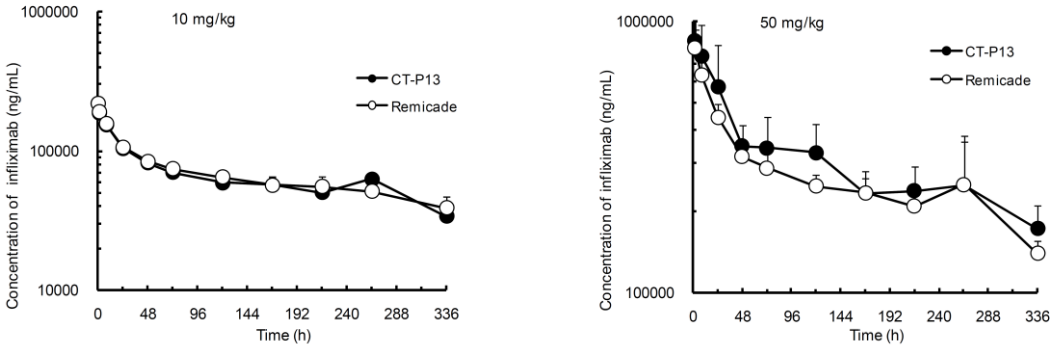

Figure 2. Mean serum concentrations of CT-P13 and EU-approved infliximab in rats after a single 10 mg/kg (left panel) or 50 mg/kg (right panel) injection.

Mean pharmacokinetic parameters are listed in Table 2. Pharmacokinetic analysis was performed on individual serum concentration data using WinNonlin® (version 5.2.1). AUC_t represents area under serum concentration-time curve from the start of dosing to the time of last sampling (t = 336h). C_{max} and AUC_t values are comparable between CT-P13 and EU-approved

infliximab after a single dose. The systemic exposure of both products increased approximately proportionally with dose.

Table 2. Mean pharmacokinetic parameters for CT-P13 and EU-approved infliximab after a single dose in male rats.

	CT-P13		EU-approved infliximab		CT-P13: EU-approved infliximab ratio	
	C_{max} (µg/ml)	AUC_t (µg*h/ml)	C_{max} (µg/ml)	AUC_t (µg*h/ml)	C_{max}	AUC_t
10 mg/kg	216.9 ± 19.6	21,953 ± 4,653	220.0 ± 23.1	22,404 ± 2,158	98.5%	98.0%
50 mg/kg	1,191 ± 254	103,575 ± 24,840	1,051 ± 104	90,362 ± 14,358	113%	115%

6 General Toxicology

6.1 Single-Dose Toxicity

There were no single-dose toxicity studies submitted in support of BLA 125544.

6.2 Repeat-Dose Toxicity

Study title: 2 Week Repeat-Dose Intravenous Toxicity and Toxicokinetic Study with CT-P13 and Remicade® in Rats

Study no.:	8214158
Study report location:	BLA 125544 Supporting Document 1 Module 4.2.3.2
Conducting laboratory and location:	(b) (4)
Date of study initiation:	December 23, 2009
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	CT-P13 Lot 09B9401 99.88% EU-approved infliximab Lot # 8RMA605 99.9%

Key Study Findings

- The rat is not a pharmacologically relevant species to evaluate the *in vivo* similarity of CT-P13 and EU-approved infliximab, as neither molecule cross reacts with rat TNFα
- There were no observed treatment related mortalities
- Potential histopathology findings were limited to:
  - Liver: Kupffer Cell hyperplasia (minimal)
  - Thymus: individual lymphocyte necrosis (minimal)
  - **The findings were observed to a similar extent in CT-P13 and EU-approved infliximab treated animals**
- The only notable differences between CT-P13 and EU-approved infliximab were in PK parameters.
  - CT-P13 C_{max} values ranged from 64.6 – 93.2% of EU-approved infliximab
  - CT-P13 AUC_{0-168} values ranged from 68.0 – 90.1% of EU-approved infliximab
- There was no evidence in SD rats to indicate potential clinical safety concerns associated with CT-P13 administration. The safety of CT-P13 and EU-approved

infliximab was judged to be similar from the nonclinical Pharmacology and Toxicology perspective.

Methods

Doses:	CT-P13: 0, 10, 40 mg/kg EU-approved infliximab: 0, 10, 40 mg/kg
Frequency of dosing:	Once per week
Route of administration:	Intravenous
Dose volume:	10 ml/kg
Formulation/Vehicle:	0.9% Sodium chloride for injection ((b) (4) .)
Species/Strain:	Rat / Hsd: Sprague Dawley ▪ Animals were housed individually
Number/Sex/Group:	See Table 3
Age:	10 – 11 weeks
Weight:	Male: 289 – 324 g Female: 187 – 228 g
Satellite groups:	Toxicokinetic animals were included in each treatment group (See Table 3)
Unique study design:	Not applicable
Deviation from study protocol:	There were no deviations considered to affect the outcome or interpretation of the data

Table 3. Outline of 2 week rat study 8214158.

Group	Subgroup	No. of Animals Male	No. of Animals Female	Dose Level (mg/kg/dose)	Dose Concentration[c] (mg/mL)
1 (Control)[a]	1 (Toxicity)	10	10	0	0
	2 (TK/IGN)[b]	3	3	0	0
2 (Low CT-P13)	1 (Toxicity)	10	10	10	1
	2 (TK/IGN)[b]	9	9	10	1
3 (High CT-P13)	1 (Toxicity)	10	10	40	4
	2 (TK/IGN)[b]	9	9	40	4
4 (Low Remicade®)	1 (Toxicity)	10	10	10	1
	2 (TK/IGN)[b]	9	9	10	1
5 (High Remicade®)	1 (Toxicity)	10	10	40	4
	2 (TK/IGN)[b]	9	9	40	4

a Group 1 received diluent/control article, 0.9% Sodium Chloride for Injection, USP, only.
b Toxicokinetic/Immunogenicity [(TK/IGN) also called Subgroup 2] animals were included solely for the purpose of blood sample collections.
c The dose volume was 10 mL/kg.

Observations and Results

Mortality

Animals were checked twice daily (a.m. and p.m.) for mortality, abnormalities, and signs of pain or distress.

There was no evidence for treatment related mortality in any treatment group.

Clinical Signs

Cageside observations were conducted once daily during the dosing phase, except on days when detailed observations were conducted. Detailed observations were conducted once during the predose phase, before dosing on Day 1, and weekly thereafter, and on the day of scheduled sacrifice. In addition, detailed observations were recorded for each animal approximately 1 hour postdose (based on the last animal dosed/sex/group).

There was no evidence for treatment related effects on clinical signs in any treatment group.

Body Weights

Body weights were recorded once during the predose phase, before dosing on Days 1 and 8, and on Day 14 of the dosing phase.

CT-P13 did not affect body weight gain in male or female rats, while HD EU-approved infliximab treated female rats had statistically significantly decreased mean body weight gain (Control: 23 ± 7.1 g; HD: 14 ± 4.7 g) over the course of the 2 week study. The large standard error in these two mean values lessens the impact of this observation.

Feed Consumption

Food consumption was measured for main study animals on Days 1 to 8 and 8 to 14 of the dosing phase.

There were no observed effects on mean food consumption in any treatment group.

Ophthalmoscopy

Ophthalmic examinations were performed using an indirect ophthalmoscope once during the predose phase and during the final week of the dosing phase by a veterinarian.

No visible lesions were observed in the eyes of any animal in the study.

Clinical pathology

Blood samples were collected for protocol-specified hematology, coagulation, and clinical chemistry tests from fasted animals via a jugular vein on day 15.

Hematology

Blood samples from each main study animal were analyzed for measurement of a complete battery of hematology (Table 4) and coagulation parameters (Prothrombin time & APTT).

Table 4. Hematology parameters examined in study 8214158.

red blood cell (erythrocyte) count	platelet count
hemoglobin	white blood cell (leukocyte) count
hematocrit	differential blood cell count
mean corpuscular volume	blood smear
mean corpuscular hemoglobin	reticulocyte count
mean corpuscular hemoglobin concentration	

There were no marked treatment related effects of CT-P13 or EU-approved infliximab observed on any parameter.

Clinical Chemistry

Blood samples from each main study animal were analyzed for measurement of a complete battery of clinical chemistry parameters (Table 5).

Table 5. Clinical chemistry parameters examined in study 8214158.

glucose	alkaline phosphatase
urea nitrogen	gamma glutamyltransferase
creatinine	aspartate aminotransferase
total protein	calcium
albumin	inorganic phosphorus
globulin	sodium
albumin/globulin ratio	potassium
cholesterol	chloride
total bilirubin	triglycerides
alanine aminotransferase	

There were no marked treatment related effects of CT-P13 or EU-approved infliximab observed on any parameter.

Urinalysis

Urine samples were collected from fasted animals on day 15. Urinalysis parameters measured are seen below:

Table 6. Urinalysis parameters examined in study 8214158.

Urinalysis	
appearance (clarity and color)	pH
bilirubin	protein
blood	specific gravity
glucose	urobilinogen
ketones	volume
microscopic examination of sediment	

There were no marked treatment related effects of CT-P13 or EU-approved infliximab observed on any urinalysis parameter.

Anatomic Pathology

All toxicity animals were fasted overnight, sacrificed, and necropsied on Day 15. Necropsy included an examination of the external features of each carcass, external body orifices, abdominal, thoracic, and cranial cavities, organs and tissues. A complete battery of tissues was removed from each animal and preserved in 10% neutral buffered formalin (Table 7).

Table 7. List of tissues examined in Study 8214158.

adrenal (2)	mammary gland (females)
aorta	muscle, biceps femoris
brain	optic nerve (2)[a]
cecum	ovary (2)
cervix	pancreas
colon	pituitary gland
duodenum	prostate
epididymis (2)	rectum
esophagus	salivary gland [mandibular (2)]
eye (2)[a]	sciatic nerve
femur with bone marrow (articular surface of the distal end)	seminal vesicle
	skin/subcutis
Harderian gland[a]	spinal cord (cervical, thoracic, and lumbar)
heart	spleen
ileum	sternum with bone marrow
injection site(s)	stomach
jejunum	testis (2)[a]
kidney (2)	thymus
lesions	thyroid (2 lobes) with parathyroid
liver	tongue
lung with large bronchi	trachea
lymph node (mandibular)	urinary bladder
lymph node (mesenteric)	uterus
	vagina

a Preserved in modified Davidson's fixative.

Gross Pathology
There were no observed CT-P13 or EU-approved infliximab related macroscopic findings.
Organ Weights
The following organs were weighed in each animal:

adrenal (2)	pituitary gland
brain	prostate
epididymis (2)	salivary gland [mandibular (2)]
heart	seminal vesicle
kidney (2)	spleen
liver	testis (2)
lung	thymus
ovary (2)	thyroid (2 lobes) with parathyroid
	uterus

There was no evidence for CT-P13 or EU-approved infliximab related effects on the weight of any of these organs.

Histopathology

Adequate Battery

The tissue list in Table 7 is considered adequate. All tissues were examined microscopically in control and HD groups only. Only liver and thymus were examined in control, LD, and HD groups.

Peer Review

Yes

Histological Findings

Analysis of histopathology data mainly focused on identifying lesions that occurred with greater incidence or severity in CT-P13 treated relative to EU-approved infliximab treated rats (Table 8). Given that neither CT-P13 nor EU-approved infliximab binds to rat TNFα, the effects observed in this study are off-target effects unrelated to the pharmacological activity of drug treatment.

Injection site findings included edema, hemorrhage, and inflammation in males and females. There was no clear evidence of exacerbation of these findings by either treatment.

Fibrosis (minimal) was observed at the apex of the **heart** in 1/10 HD CT-P13 treated male rats (#B76741). Foci of necrosis, focal inflammation and fibrosis are observed as

background findings in the heart in young rats[2]. Extramedullary hematopoiesis was observed in the heart of a second HD CT-P13 male (#B76752). It is notable that myocardial degeneration was observed in 1/10 control male rats (#B76709) in addition to 1/10 HD CT-P13 treated rats (#B76735). Furthermore, lymphocyte/macrophage infiltration was frequently observed (3/10 – 4/10) in controls as well as HD male CT-P13 and EU-approved infliximab treated rats. No such findings were observed in females. Taken together, the evidence suggests that the observed single incidence heart lesion observations in HD male rats in this study are background findings.

In the **liver**, incidence of Kupffer cell hypertrophy increased with dose in both CT-P13 and EU-approved infliximab treated male and females. This effect appears to be clearly treatment related. The incidence and severity of these findings was comparable between CT-P13 and EU-approved infliximab treated animals. Nearly all animals, including controls, had evidence of minimal lymphocyte/macrophage infiltration in the liver. Small aggregates of lymphoid cells in the liver are commonly seen as background findings in rats. 1/10 LD CT-P13 treated males (#B76722) had focal coagulative necrosis of the liver. This finding appears to be anomalous given the low incidence and the fact that it was not observed in HD animals which had 3 – 4 fold higher systemic CT-P13 exposure. Systemic exposure values for this animal were not available as the study design utilized satellite animals for toxicokinetic measurements.

Pancreas was a target organ in 1/10 HD CT-P13 females (#B76831). This animal had evidence of chronic focal inflammation (slight) as well as atrophy (slight). Lymphocyte/macrophage infiltration was observed in the pancreas of 2/10 HD CT-P13 males vs. 1/10 concurrent control males. This was also observed in 1/10 HD EU-approved infliximab treated females. Lymphocyte infiltration in the pancreas is reported as a common background finding in young rats[3].

A developmental anomaly was observed in the **spinal cord** of 1/10 HD CT-P13 females. The pathologist's comment states the presence of "an epithelial cell rest within the ventral nerve root". This finding is not considered to be treatment related given that adult rats (10 – 11 weeks) were used in this study.

Focal lymphocyte/macrophage infiltration was observed in the **biceps** femoris in 1/10 HD CT-P13 males (#B76744) and 1/10 HD CT-P13 females (#B76829). Animals were housed individually, so these findings are not related to injuries resulting from group housing of rats. There was no evidence of inflammation of the biceps in these animals. Furthermore there were no correlating clinical signs. These findings are not considered to be adverse.

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[2] Greaves, P. (2007) Histopathology of preclinical toxicology studies, 3d Edition. Elsevier.

[3] McInnes, EF. (2011) Background lesions in laboratory animals: a color atlas. Elsevier, Edinburgh.

Incidence of **thymic necrosis** was increased to a similar degree in CT-P13 and EU-approved infliximab treated males and females. While this effect appears to be treatment related, the extent of the impact was comparable between CT-P13 and EU-approved infliximab.

Single findings of minimal vacuolation in the **pituitary** and lymphocyte/macrophage infiltration in the **urinary bladder** in HD CT-P13 males do not provide clear evidence of treatment related adverse findings.

Table 8. Microscopic findings in rats treated with CT-P13 or EU-approved infliximab in study 8214158. NE = Not examined.

	Males					Females				
	Control	CT-P13		EU-infliximab		Control	CT-P13		EU-infliximab	
Dose (mg/kg)	0	10	40	10	40	0	10	40	10	40
n=	10	10	10	10	10	10	10	10	10	10
Heart										
Fibrosis										
Focal, minimal (apex)	0	NE	1	NE	0	0	NE	0	NE	0
Hematopoiesis, extramedullary										
Focal, minimal	0	NE	1	NE	0	0	NE	0	NE	0
Liver										
Hyperplasia, Kupffer cell										
minimal	0	2	7	4	7	0	2	6	3	7
Necrosis, coagulative										
Focal, minimal	0	1	0	0	0	0	0	0	0	0
Muscle, Biceps Femoris										
Infiltrate, lymphocytes/macrophages										
Focal, minimal	0	NE	1	NE	0	0	NE	1	NE	0
Pancreas										
Infiltrate, lymphocytes/macrophages										
Focal, minimal	1	NE	2	NE	0	0	NE	0	NE	1
Inflammation, chronic										
Focal, slight	0	NE	0	NE	0	0	NE	1	NE	0

	Males					Females				
	Control	CT-P13		EU-infliximab		Control	CT-P13		EU-infliximab	
Dose (mg/kg)	0	10	40	10	40	0	10	40	10	40
n=	10	10	10	10	10	10	10	10	10	10
Atrophy										
Focal, slight	0	NE	0	NE	0	0	NE	1	NE	0
Pituitary										
Vacuolation, chromophobe										
Increased, minimal	0	NE	1	NE	0	0	NE	0	NE	0
Thymus										
Cyst										
present	0	0	1	0	0	0	0	0	0	0
Necrosis, individual lymphocytes										
Increased, minimal	0	1	1	1	2	0	2	2	2	1
Urinary bladder										
Infiltrate, lymphocytes/macrophages	0	NE	1	NE	0	0	0	0	0	0

Toxicokinetics

Blood samples were taken for toxicokinetic analysis from satellite animals on days 1 and 8 at 0.25, 2, 8, 24, 72, and 168 hours post dose. Up to 3 animals/sex/group were bled at each time point.

Serum concentrations of CT-P13 and EU-approved infliximab were quantified by ELISA, using plates coated with recombinant human TNFα. For CT-P13 quantitation, the standard curve was prepared using a reference lot of CT-P13 (Lot BP0306). For EU-approved infliximab quantitation, the standard curve was prepared using a reference lot of EU-approved infliximab (Lot 8RMKA84201).

The serum concentration vs. time plots after dose 1 and dose 2 are seen in Figure 3.

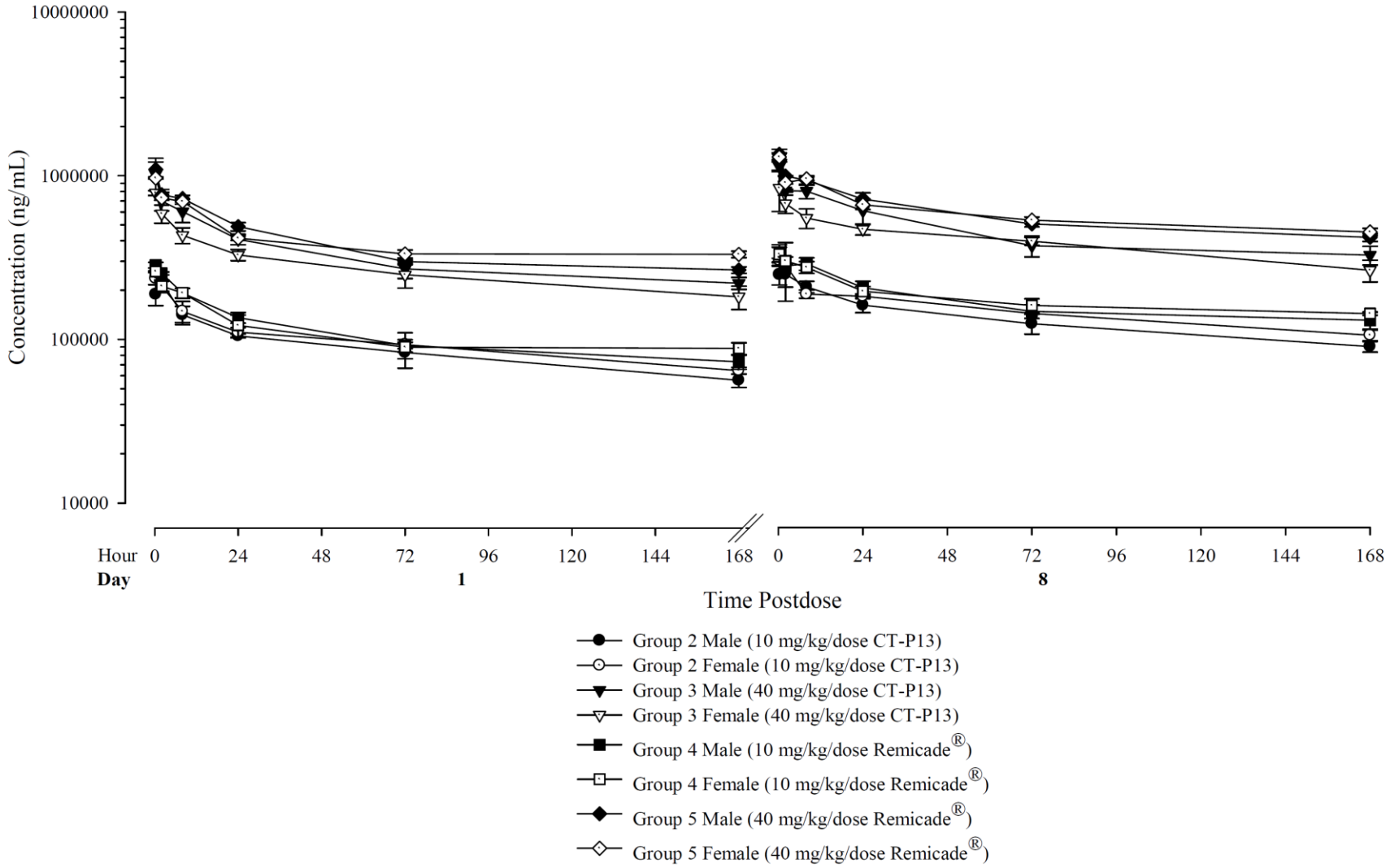

Figure 3. Serum concentration vs. time profiles for CT-P13 and EU-approved infliximab in male (closed symbols) and female (open symbols) rats after dose 1 (left side) and dose 2 (right side) in study 8214158.

Mean toxicokinetic parameters after Dose 1 and Dose 2 are seen in Table 9. C_{max} and AUC_{0-168} increased approximately proportionally with dose for both CT-P13 and EU-approved infliximab. There were no clear differences in TK parameters between males and females. CT-P13 values for C_{max} and systemic exposure (AUC_{0-168}) were consistently lower than EU-approved infliximab in males and females on day 1 and day 8. CT-P13 C_{max} values ranged from 64.6 – 93.2% of EU-approved infliximab. CT-P13 AUC_{0-168} values ranged from 68.0 – 90.1% of EU- approved infliximab.

Table 9. Toxicokinetic parameters in male and female rats after dose 1 and dose 2 in study 8214158.

			CT-P13		EU-infliximab		CT-P13: EU-infliximab ratio	
			C_{max} (µg/ml)	AUC_{0-168} (µg*h/ml)	C_{max} (µg/ml)	AUC_{0-168} (µg*h/ml)	C_{max}	AUC_{0-168}
Day 1	10 mg/kg	Male	226	14,684	284	17,859	79.6%	82.2%
		Female	236	16,045	260	17,800	90.8%	90.1%
	40 mg/kg	Male	1,016	53,582	1,090	62,056	93.2%	86.3%
		Female	784	45,029	968	64,675	81.0%	69.6%
Day 8	10 mg/kg	Male	249	22,050	329	28,214	75.7%	78.2%
		Female	303	24,860	331	29,379	91.5%	84.6%
	40 mg/kg	Male	1,137	75,492	1,353	95,452	84.0%	79.1%
		Female	841	65,999	1,301	97,119	64.6%	68.0%

Anti-drug antibodies (ADA) against CT-P13 or EU-approved infliximab were measured by ELISA. For detection of anti-CT-P13 antibodies, plates were coated with CT-P13 (Lot BP0306). Diluted serum samples were added to the plates along with biotinylated CT-P13. (In this way, anti-CT-P13 antibodies in the sample could theoretically simultaneously bind to the CT-P13 on the plate as well as the biotinylated CT-P13 that is co-incubated). Streptavidin-HRP is then added to detect the anti-CT-P13 antibodies bound to biotinylated CT-P13. TMB was used as the detection substrate.

The ELISA for anti-EU-approved infliximab antibody detection was designed in a similar way, with EU-approved infliximab (Lot 8RMKA84201) substituted for CT-P13. Goat anti-human kappa light chain was used as the positive control antibody in both assays.

There was no conclusive evidence for anti-CT-P13 or anti-EU-approved infliximab antibody formation in treated animals. The validity of the assay system is questionable given that positive anti-CT-P13 signals were obtained in pre-dosing serum samples of 4 rats in a screening assay.

These samples were not detected as positive in confirmatory assays. There were no serum samples that tested positive for anti-EU-approved infliximab antibodies at any point.

Dosing Solution Analysis

Duplicate samples were taken from the middle of all dose preparations on Days 1 and 8 to be analyzed for concentration verification. Mean test article concentrations for CT-P13 were 98.8 – 100% of nominal values and 93.2 – 94.4% for EU-approved infliximab.

7 Genetic Toxicology

Genetic toxicology studies are not applicable to biologic products.

8 Carcinogenicity

There were no carcinogenicity studies submitted.

9 Reproductive and Developmental Toxicology

There were no reproductive and developmental toxicology studies submitted.

10 Special Toxicology Studies

- Study title: CT-P13: Study to Assess the Potential Cross Reactivity of CT-13 (infliximab) with a Selected Panel of Human Tissues and comparability to Remicade (infliximab)
- Study #: 8214160

This GLP-compliant study was conducted to satisfy Japanese regulatory requirements.

Methods
Human tissue samples were derived from a panel of 3 donors. Specific tissues examined are listed in Table 10.

Table 10. List of human tissues examined for binding of CT-P13 and EU-approved infliximab in Study 8214160.

adrenal	endothelium	ileum	ovary	prostate	thyroid
urinary bladder	eye	colon	pancreas	skin	tonsil
blood cells	fallopian tube	heart	parathyroid	spinal cord	ureter
bone marrow	Esophagus	kidney	parotid	spleen	uterus-cervix
Breast	gastric antrum	liver	peripheral nerve	striated muscle	uterus-endometrium
brain – cerebrum	gastric body	lung	pituitary	testis	
brain- cortex	duodenum	lymph node	placenta	thymus	

The positive control tissue used was human TNFα protein coated polystyrene beads injected into murine skin. Negative control tissue was prepared in a similar way, but with un-coated beads.

CT-P13 (Lot BP0306), EU-approved infliximab (lot 8RMA605), and IgG1 kappa (negative control antibody) were labeled with biotin using the commercial Immunoprobe Biotinylation Kit (Sigma Aldrich). The final protein concentration of both biotinylated CT-P13 and EU-approved infliximab was 2.25 mg/ml. The final protein concentration of biotinylated IgG1 kappa was 1.05 mg/ml.

Frozen tissue sections were sectioned at 5 µm and stained according to standard immunohistochemical staining methods. Staining was performed with concentrations of 5, 2.5 and 1.25 µg/ml biotinylated CT-P13, EU-approved infliximab, and IgG1 kappa. Biotin-labeled antibodies were added to sections and incubated for 18 hours. Specific staining was detected using the VECTASTAIN Elite ABC Reagent plus DAB.

Results
Variable minimal – mild specific staining was observed with both CT-P13 and EU-approved infliximab within the vascular smooth muscle of a single large blood vessel in the **thyroid** of donor 2. There was additional variable minimal-mild specific staining observed with both CT-P13 and EU-approved infliximab within the vascular smooth muscle of occasional blood vessels in the **tonsil** of donor 1.

The sponsor states that the specificity of this staining is questionable given that positive staining of blood vessels was not observed in any other tissues.

11 Integrated Summary and Safety Evaluation

Nonclinical studies conducted by Centocor Biotech, Inc. in support of initial approval of the innovator product (U.S. licensed Remicade®) established that infliximab cross-reacts with TNFα from human and chimpanzee only. There was no activity with TNFα derived from dog, baboon, rhesus or cynomolgus monkey, pig-tail macaque, marmoset, cotton-top tamarin, pig, rabbit, rat, or mouse. Celltrion conducted a similar study in support of CT-P13, in which neither CT-P13 nor EU-approved infliximab exhibited specific binding to TNFα derived from mouse, rat, dog, pig, or rhesus monkey (Study GR-RD-10-061).

Infliximab efficacy was demonstrated by Centocor in Tg197 transgenic mice, which constitutively express human TNFα and develop a chronic, inflammatory polyarthritis. Centocor carried out toxicity studies of infliximab in rats for up to seven days duration to evaluate potential non-specific/non target-mediated effects of infliximab. Studies conducted in chimpanzees showed that infliximab was well tolerated at doses up to 30 mg/kg/day for at least 3 consecutive days and at doses up to 15 mg/kg/day for at least 5 consecutive days. The studies conducted in chimpanzees were considered to be the only relevant studies to assess the safety of infliximab administration to humans.

Celltrion chose to conduct nonclinical studies with CT-P13 in the SD rat, despite it not being a pharmacologically relevant species. Celltrion argued that the rat is capable of providing insight into off-target toxicity as well as clearance mechanisms related to neonatal Fc receptor (FcRn) binding (rat FcRn binds rat and human IgG with similar affinity). At a BPD Type 3 meeting held on 7/10/13, the Division stated that in vivo studies conducted in mice expressing human TNFα (e.g. Tg197 mice) would have been more informative for assessment of the safety and similarity of CT-P13 relative to US-licensed Remicade. However, additional animal studies beyond those that had already been conducted in SD rats were not recommended based upon the extensive human experience that was available.

A single dose (IV) TK study in male SD rats showed comparable TK profiles between CT-P13 and EU-approved infliximab at doses of 10 mg/kg and 50 mg/kg (Study N09067).

The pivotal nonclinical study in support of CT-P13 was a 2 week GLP toxicity/TK study (1 dose per week) in SD rats in which animals received IV CT-P13 or EU-approved infliximab at 10 or 40 mg/kg (Study 8214158). Histopathology findings in the liver (minimal Kupffer cell hyperplasia) and thymus (minimal lymphocyte necrosis) were observed to a similar extent in CT-P13 and EU-approved infliximab treated animals. There was no evidence for immunogenicity. CT-P13 values for C_{max} and systemic exposure (AUC_{0-168}) were consistently lower than EU-approved infliximab (~65 – 90%) in males and females on day 1 and day 8. The safety of CT-P13 and EU-approved infliximab was judged to be similar from the nonclinical Pharmacology and Toxicology perspective.

Centocor, the sponsor of the innovator product, published a paper describing developmental toxicity studies that were carried out in mice (Crl:CD-1® (ICR)) using a surrogate antibody

(cV1q) derived from a rat anti-mouse TNFα monoclonal antibody[4]. cV1q doses at up to 40 mg/kg had no effect on fertility or reproduction parameters in mice.

As described in the Draft Guidance: *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (February, 2012)*, if the overall CMC similarity assessment between CT-P13 and US-licensed Remicade is judged to be adequate, additional nonclinical evaluations examining safety pharmacology, reproductive toxicology, immunotoxicity, and carcinogenic potential of CT-P13 are not warranted.

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 considered to be comparable to EU-approved infliximab in rats.

The pharmacology and animal data submitted to the BLA demonstrate the similarity (i.e., comparable achieved exposures and similar safety) between CT-P13 and EU-approved infliximab from the nonclinical Pharmacology and Toxicology perspective.

The BLA is recommended for approval from the nonclinical perspective. No additional animal studies are required. There are no outstanding issues from the nonclinical Pharmacology and Toxicology perspective.

[4] Treacy G. (2000) Using an analogous monoclonal antibody to evaluate the reproductive and chronic toxicity potential for a humanized anti-TNFα monoclonal antibody. *Human & Experimental Toxicology*. 19: 226-228.

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/s/

MATTHEW T WHITTAKER
05/04/2015

TIMOTHY W ROBISON
05/04/2015
I concur

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR BLA

BLA Number: 125,544 **Applicant:** Celltrion **Stamp Date:** 9/5/14

Drug Name: CT-P13 **BLA Type:** 351(k)

On **initial** overview of the BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		The pivotal in vivo toxicology studies compared CT-P13 vs. EU-approved infliximab. These studies include a single dose IV study (Study N09067) and 2 week IV study (1x/week dosing [Study 8214158]) in rats. An assessment of biosimilarity between CT-P13 and the reference product based on these studies as well as in the in vitro biochemical characterization assays will preclude the necessity for conduct of safety pharmacology, carcinogenicity, mutagenicity, and teratogenicity studies.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			Not applicable. The drug product formulation of CT-P13 is (b) (4) of the reference product.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	X		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	X		Study 8214158 was conducted in accordance with GLP regulations.

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR BLA

	Content Parameter	Yes	No	Comment
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		Sections 8.1, 8.3, 12.1, 12.3, and 13.1 are consistent with the labeling for the reference product.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		To be determined in consultation with the Product Quality reviewer.
11	Has the applicant addressed any abuse potential issues in the submission?			Not applicable. Based on its mechanism of action, CT-P13 is not expected to have abuse liability.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? *Yes*

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

The NDA is fileable from the nonclinical perspective.

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

There are no potential review issues from the nonclinical perspective at this time.

Matthew Whittaker 9/22/14

Reviewing Pharmacologist Date

Timothy Robison 9/22/14

Team Leader/Supervisor Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

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/s/

MATTHEW T WHITTAKER
09/22/2014

TIMOTHY W ROBISON
09/22/2014
I concur