CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761042Orig1s000

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 761042
Supporting document/s:	SDN 1 (0000): New BLA and Proprietary Name Request SDN 7 (0006): Proprietary Name Request SDN 8 (0007): Revised Draft PLLR Labeling
Applicant's letter date:	July 30, 2015 November 25, 2015 December 11, 2015
CDER stamp date:	July 30, 2015 November 25, 2015 December 11, 2015
Product:	GP2015 (proposed biosimilar to US-licensed Enbrel®)
Indication:	Same indications for which US-licensed Enbrel® (etanercept) is approved (Rheumatoid Arthritis, Polyarticular Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Plaque Psoriasis)
Applicant:	Sandoz, Inc.
Review Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Reviewer:	Andrea L. Benedict, Ph.D.
Acting Team Leader:	Carol M. Galvis, Ph.D.
Division Director:	Badrul Chowdhury, M.D., Ph.D.
Project Manager:	Leila Hann / Jessica Lee

Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

BLA 761042 was submitted by Sandoz, Inc. on July 30, 2015, under section 351(k) of the Public Health Services Act (PHS Act) to support registration of Erelzi (referred to during development as GP2015) as a biosimilar to US-licensed Enbrel® (etanercept). The BsUFA goal date was extended by 3 months for this BLA on April 29, 2016, due to submission of a major amendment for Quality information on April 28, 2016.

Etanercept products are dimeric soluble forms of the p75 TNF receptor that can bind TNF molecules. Etanercept products inhibit binding of TNF-α and TNF-β (lymphotoxin alpha [LT-α]) to cell surface TNF receptors, rendering TNF biologically inactive. US-licensed Enbrel® (US-Enbrel) is a subcutaneously administered product, originally developed by Immunex Corporation (BLA 103795, approval date November 2, 1998); indicated for the treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis. Sandoz intends to obtain approval for Erelzi as a biosimilar to etanercept for all currently approved US-Enbrel indications, with dosing regimens that are approved for US-Enbrel.[1]

The GP2015 nonclinical development program has been reviewed previously, and judged to be adequate for approval (Nonclinical Review, BLA 761042; April 29, 2016). No new nonclinical information has been submitted since the initial BLA review. This review includes only recommendations for 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 (only “Risk Summary” and “Data”), 8.2, 8.3, 10, 12.1, 12.2, and 13.1].

The original draft labeling for Erelzi was submitted on July 30, 2015. The proprietary name used for the GP2015 drug product in the draft labeling was (b) (4), which was denied by the Agency on October 26, 2015. Sandoz submitted the proposed proprietary name Erelzi on November 25, 2015, and was found conditionally acceptable on February 16, 2016. The sponsor submitted updated labeling to the BLA on December 11, 2015, to conform to the FDA requirements under the Pregnancy and Lactation Labeling Rule (PLLR).

1.2 Brief Discussion of Nonclinical Findings

The language in the nonclinical sections of the proposed Erelzi label (e.g. Established Pharmacological Classification under Indication and Usage in the Highlights of Prescribing Information section and Sections 8.1, 8.2, 10, 12.1, 12.2, and 13.1) is generally consistent with the labeling for US-licensed Enbrel®. However, certain references to "etanercept" have been revised to “etanercept products” as appropriate. The reason for this change is that the information applies to both the reference product (US-licensed Enbrel) and the proposed biosimilar product (GP2015).

[1] Sandoz has not sought approval for a dosage form that would allow weight-based dosing for juvenile idiopathic arthritis patients who weigh less than 63 kg. The labeling will reflect this limitation.

The initial 351(k) BLA for GP2015 (BLA 761042) was submitted on July 30, 2015, which is after the Pregnancy Lactation Labeling Rule (PLLR) went into effect on June 30, 2015. Sandoz submitted revised labeling in PLLR format on December 11, 2015, along with a review of available information regarding etanercept use in pregnant and lactating women. Recommendations have been made to the nonclinical sections of the sponsor's proposed labeling to comply with the FDA current practice for PLLR labeling of biosimilar products.

1.3 Recommendations

1.3.3 Labeling

The recommended text for the nonclinical sections of the Erelzi prescribing information is provided below.

INDICATIONS AND USAGE

ERELZI is a tumor necrosis factor (TNF) blocker indicated for the treatment of:

- Rheumatoid Arthritis (RA) (1.1)
- Polyarticular Juvenile Idiopathic Arthritis (JIA) in patients aged 2 years or older (1.2)
- Psoriatic Arthritis (PsA) (1.3)
- Ankylosing Spondylitis (AS) (1.4)
- Plaque Psoriasis (PsO) (1.5)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited published data on use of etanercept in pregnant women are insufficient to inform a drug-associated risk. Published studies with etanercept use during pregnancy have not reported a clear association with etanercept and major birth defect or miscarriage risk. Based on limited data, etanercept concentration in cord blood at the time of delivery showed that etanercept crossed the placenta in small amounts *[see Clinical Considerations]*. Developmental toxicity studies have been performed in rats and rabbits at doses ranging from 60- to 100-fold higher than the human dose and have revealed no evidence of harm to the fetus due to etanercept *[see Data]*. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

The estimated background risk of major birth defects and miscarriage for the indicated population(s) are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Developmental toxicity studies have been performed in rats and rabbits at doses ranging from 60- to 100-fold higher than the human dose and have revealed no evidence of harm to the fetus due to etanercept.

8.2 Lactation

Risk Summary

Limited data from published literature show that etanercept is present in low levels in human milk and minimally absorbed by a breastfed infant. There are no data on the effects on the breastfed infant, or the effects on milk production. The limited clinical data during lactation precludes a clear determination of the risk of etanercept products to an infant during lactation; therefore, developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ERELZI and any potential adverse effects on the breastfed child from ERELZI or from the underlying maternal condition.

10 OVERDOSAGE

Toxicology studies have been performed in monkeys at doses up to 30 times the human dose with no evidence of dose-limiting toxicities. No dose-limiting toxicities have been observed during clinical trials of etanercept. Single IV doses up to 60 mg/m^2 (approximately twice the recommended dose) have been administered to healthy volunteers in an endotoxemia study without evidence of dose-limiting toxicities.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. It plays an important role in the inflammatory processes of RA, polyarticular JIA, PsA, and AS and the resulting joint pathology. In addition, TNF plays a role in the inflammatory process of PsO. Elevated levels of TNF are found in involved tissues and fluids of patients with RA, JIA, PsA, AS, and PsO.

Two distinct receptors for TNF (TNFRs), a 55 kilodalton protein (p55) and a 75 kilodalton protein (p75), exist naturally as monomeric molecules on cell surfaces and in soluble forms. Biological activity of TNF is dependent upon binding to either cell surface TNFR.

Etanercept products are dimeric soluble forms of the p75 TNF receptor that can bind TNF molecules. Etanercept products inhibit binding of TNF-α and TNF-β (lymphotoxin alpha [LT-α]) to cell surface TNFRs, rendering TNF biologically inactive. In *in vitro* studies, large complexes of etanercept with TNF-α were not detected and cells expressing transmembrane TNF (that binds etanercept products) are not lysed in the presence or absence of complement.

12.2 Pharmacodynamics

Etanercept products can modulate biological responses that are induced or regulated by TNF, including expression of adhesion molecules responsible for leukocyte migration (eg, E-selectin, and to a lesser extent, intercellular adhesion molecule-1 [ICAM-1]), serum levels of cytokines (eg, IL-6), and serum levels of matrix metalloproteinase-3 (MMP-3 or stromelysin). Etanercept products have been shown to affect several animal models of inflammation, including murine collagen-induced arthritis.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of etanercept products or their effect on fertility. Mutagenesis studies were conducted with etanercept *in vitro* and *in vivo*, and no evidence of mutagenic activity was observed.

2 Drug Information

2.1 Drug

CAS Registry Number

185243-69-0

Proper Name

To be determined

Code Name

GP2015, glycoprotein 2015

Molecular Formula/Molecular Weight

$C_{4448}H_{6886}N_{1236}O_{1402}S_{72}$ (not including post-translational sugar moieties) / 934 amino acids / ~150 kDa (apparent molecular size determined by SDS-PAGE)

Structure or Biochemical Description

GP2015 is a genetically-engineered dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 kDa tumor necrosis factor receptor (TNFR) linked to the Fc portion of human immunoglobulin G1 (IgG1) that contains only the CH2, CH3, and hinge region. The GP2015 dimeric fusion protein contains 934 amino acids (homo-dimer: 467; Figure 1) produced by recombinant DNA technology in a Chinese Hamster Ovary (CHO) mammalian cell expression system.

Figure 1: Amino Acid Sequence of GP2015: Single Chain of Homo-dimer

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  1 LPAQVAFTPY APEPGSTCRL REYYDQTAQM CCSKCSPGQH AKVFCTKTSD
 51 TVCDSCEDST YTQLWNWVPE CLSCGSRCSS DQVETQACTR EQNRICTCRP
101 GWYCALSKQE GCRLCAPLRK CRPGFGVARP GTETSDVVCK PCAPGTFSNT
151 TSSTDICRPH QICNVVAIPG NASMDAVCTS TSPTRSMAPG AVHLPQPVST
201 RSQHTQPTPE PSTAPSTSFL LPMGPSPPAE GSTGDEPKSC DKTHTCPPCP
251 APELLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSHED PEVKFNWYVD
301 GVEVHNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA
351 PIEKTISKAK GQPREPQVYT LPPSREEMTK NQVSLTCLVK GFYPSDIAVE
401 WESNGQPENN YKTTPPVLDS DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE
451 ALHNHYTQKS LSLSPGK
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Amino acids: 467

Pharmacologic Class

Tumor necrosis factor blocker

2.2 Relevant INDs, NDAs, BLAs and DMFs

Application #	Description	Sponsor	Date
IND 114187	IND application in support of clinical testing of GP2015 in the U.S.	Sandoz, Inc.	7/14/2015 (IND submission date)
BLA 103795/ BLA (b) (4)	BLA application for reference product, Enbrel®	Immunex Corp.	11/2/1998 (approval date)

2.7 Regulatory Background

The GP2015 nonclinical development program has been reviewed previously, and judged to be adequate for approval (Nonclinical Review, BLA 761042; April 29, 2016). No new nonclinical information has been submitted since the initial BLA review.

Draft labeling was submitted with the original submission of BLA 761042 on July 30, 2015. An information request was sent on September 7, 2015, to advise the sponsor that the proposed prescribing information did not conform to the content and format requirements of the Pregnancy and Lactation Labeling Rule (PLLR) which was implemented on June 30, 2015. Another information request was sent to the sponsor on October 2, 2015 in response to an email for clarification from the sponsor (email to the RPM, Leila Hann, dated October 1, 2015), in which the FDA agreed that the (b) (4) under Section 8.1 Pregnancy may be omitted from the revised draft label and reiterated that the proposed labeling must comply with the PLLR content and format requirements as the application was submitted after the implementation date of PLLR. The sponsor provided proposed PLLR labeling changes to the RPM, Leila Hann, via email on October 8, 2016 and October 12, 2016, for preliminary comments from the FDA. On November 10, 2015, an information request was sent to the sponsor to submit a review and summary of the available published literature regarding etanercept use in pregnant and lactating women to support the changes in the Pregnancy, Lactation, (b) (4) subsections of labeling. The sponsor provided updated labeling and requested literature review on December 7, 2015, via email to the RPM, Leila Hann, and was subsequently submitted to the BLA on December 11, 2015. The FDA's recommended labeling revisions relevant to the nonclinical sections of the Erelzi label, as reflected in this review, were sent to the sponsor on July 29, 2016.

3 Studies Submitted

3.3 Previous Reviews Referenced

Pharmacology and Toxicology Review of BLA 761042 dated April 29, 2016.

11 Integrated Summary and Safety Evaluation

11.1 Labeling Evaluation

The language in the nonclinical sections of the proposed Erelzi label (e.g. Established Pharmacological Classification under Indication and Usage in the Highlights of Prescribing Information section and Sections 8.1, 8.2, 10, 12.1, 12.2, and 13.1) is generally consistent with the labeling for US-licensed Enbrel®. However, certain references to "etanercept" have been revised to "etanercept products" as appropriate. The reason for this change is that the information applies to both the reference product (US-licensed Enbrel) and the biosimilar product (GP2015).

The initial 351(k) BLA for GP2015 (BLA 761042) was submitted on July 30, 2015, which is after the Pregnancy Lactation Labeling Rule (PLLR) went into effect on June 30, 2015. The original draft labeling submitted to the BLA did not comply with PLLR content and format requirements. Sandoz subsequently submitted revised labeling in PLLR format on December 11, 2015 (see Section 2.7 Regulatory Background for further information). Recommendations have been made to the nonclinical sections of the sponsor's proposed labeling to comply with the FDA current practice for PLLR labeling of biosimilar products. Clinical Considerations and Human Data under Section 8.1 are outside the scope of the nonclinical review and will be addressed by the clinical team in collaboration with the Pediatric and Maternal Health Staff (PMHS).

11.2 Labeling Recommendations

The recommended text for the nonclinical sections of the Erelzi prescribing information is provided below. The Sponsor's text is from the revised draft Prescribing Information dated December 11, 2015 (SDN 8). Labeling recommendations were provided for Indications and Usage (under Highlights of Prescribing Information), Section 8.1 (only "Risk Summary" and "Data"), Section 8.2, Section 8.3, Section 10, Section 12.1, Section 12.2, and Section 13. The Maternal Health Team was consulted for Sections 8.1, 8.2, and 8.3 to achieve compliance with the Pregnancy and Lactation Labeling Rule (PLLR). Deletions in FDA revised text are represented by red ~~strikethrough~~ text and additions are indicated by blue underlined text.

Sponsor's Proposed Labeling:

INDICATIONS AND USAGE

(b) (4) is a tumor necrosis factor (TNF) blocker indicated for the treatment of:

- Rheumatoid Arthritis (RA) (1.1)
- Polyarticular Juvenile Idiopathic Arthritis (JIA) in patients aged 2 years or older (1.2)
- Psoriatic Arthritis (PsA) (1.3)
- Ankylosing Spondylitis (AS) (1.4)
- Plaque Psoriasis (PsO) (1.5)

FDA Proposed Revisions

INDICATIONS AND USAGE

(b) (4) ERELZI is a tumor necrosis factor (TNF) blocker indicated for the treatment of:

- Rheumatoid Arthritis (RA) (1.1)
- Polyarticular Juvenile Idiopathic Arthritis (JIA) in patients aged 2 years or older (1.2)
- Psoriatic Arthritis (PsA) (1.3)
- Ankylosing Spondylitis (AS) (1.4)
- Plaque Psoriasis (PsO) (1.5)

Reviewer Comments: The proprietary name was updated to Erelzi. Sandoz's proposed Established Pharmacologic Class (EPC) of "tumor necrosis factor (TNF) blocker" is consistent with the FDA EPC Text Phrase for etanercept.

Sponsor's Proposed Labeling: (Note: Clinical Considerations and Human Data under Section 8.1 are outside the scope of this nonclinical review and will not be addressed here).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

(b) (4)

Risk Summary

(b) (4) Based on limited data, etanercept concentration in cord blood at the time of delivery showed that etanercept crossed the placenta in small amounts.

Data

Animal Data

Developmental toxicity studies have been performed in rats and rabbits at doses ranging from 60- to 100-fold higher than the human dose and have revealed no evidence of harm to the fetus due to etanercept. (b) (4)

FDA Proposed Revisions

8.1 Pregnancy

(b) (4)

Risk Summary

(b) (4) Limited published data on use of etanercept in pregnant women are insufficient to inform a drug-associated risk. Published studies with etanercept use during pregnancy have not reported a clear association with etanercept and major birth defect or miscarriage risk. Based on limited data, etanercept concentration in cord blood at the time of delivery showed that etanercept crossed the placenta in small amounts *[see Clinical Considerations]*. Developmental toxicity studies have been performed in rats and rabbits at doses ranging from 60- to 100-fold higher than the human dose and have revealed no evidence of harm to the fetus due to etanercept *[see Data]*. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

The estimated background risk of major birth defects and miscarriage for the indicated population(s) are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Developmental toxicity studies have been performed in rats and rabbits at doses ranging from 60- to 100-fold higher than the human dose and have revealed no evidence of harm to the fetus due to etanercept. (b) (4)

Reviewer Comments: The proposed text for the Section 8.1 Pregnancy Risk Summary was discussed and harmonized with the recommendations from the Pediatric and Maternal Health Staff (PMHS) to comply with current PLLR requirements. As the current US-Enbrel label (revision 03/2015) has not been updated to the PLLR content and format at this time; no additional nonclinical information was added to Section 8.1 of the Erelzi prescribing information.

The Risk Summary was updated to include nonclinical information, which conforms to the current FDA practice for PLLR labeling. The nonclinical statement added to the Risk Summary, indicating that there were no adverse developmental effects when pregnant rats and rabbits were given etanercept, (b) (4)

Additionally, the statement (b) (4) is not needed and it is recommended that it should be removed from the label. The proprietary name was updated to Erelzi.

Sponsor's Proposed Labeling

8.2 Lactation

(b) (4)

Risk Summary

Limited data from published literature show that etanercept is present in low levels in human milk and minimally absorbed by a breastfed infant. (b) (4) development and health benefits of breastfeeding should be considered along with the mother's clinical need for (b) (4) and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.

FDA Proposed Revisions

8.2 Lactation

(b) (4)

Risk Summary

Limited data from published literature show that etanercept is present in low levels in human milk and minimally absorbed by a breastfed infant. There are no data on the effects on the breastfed infant, or the effects on milk production. The limited clinical data during lactation precludes a clear determination of the risk of etanercept products to an infant during lactation; therefore, developmental (b) (4) and health benefits of breastfeeding should be considered along with the mother's clinical need for (b) (4) ERELZI and any potential adverse effects on the breastfed child from ~~the drug~~ ERELZI or from the underlying maternal condition.

Reviewer Comments: There is no animal data in the current US-Enbrel label (revision 03/2015) on the presence of etanercept in breast milk. No additional nonclinical studies regarding the presences of etanercept in breast milk were identified in the published literature report provided by the sponsor. The proposed text for the Section 8.2 Lactation Risk Summary was discussed and harmonized with the recommendations from the PMHS to comply with current PLLR requirements. Additionally, the statement (b) (4) is not needed and it is recommended that it should be removed from the label. The proprietary name was updated to Erelzi.

Sponsor's Proposed Labeling

(b) (4)

FDA Proposed Revisions

(b) (4)

Reviewer Comments: No nonclinical fertility studies have been conducted with etanercept. It is recommended that (b) (4) be removed from the label.

Sponsor's Proposed Labeling

10 OVERDOSAGE

Toxicology studies have been performed in monkeys at doses up to 30 times the human dose with no evidence of dose-limiting toxicities. No dose-limiting toxicities have been observed during clinical trials of etanercept. Single IV doses up to 60 mg/m^2 (approximately twice the recommended dose) have been administered to healthy volunteers in an endotoxemia study without evidence of dose-limiting toxicities.

Reviewer Comments: The sponsor did not propose any changes in Section 10 compared to the US-Enbrel reference product label. There are no FDA recommended changes to Section 10.

Sponsor's Proposed Labeling

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. It plays an important role in the inflammatory processes of RA, polyarticular JIA, PsA, and AS and the resulting joint pathology. In addition, TNF plays a role in the inflammatory process of PsO. Elevated levels of TNF are found in involved tissues and fluids of patients with RA, JIA, PsA, AS, and PsO.

Two distinct receptors for TNF (TNFRs), a 55 kilodalton protein (p55) and a 75 kilodalton protein (p75), exist naturally as monomeric molecules on cell surfaces and in soluble forms. Biological activity of TNF is dependent upon binding to either cell surface TNFR.

Etanercept is a dimeric soluble form of the p75 TNF receptor that can bind TNF molecules. Etanercept inhibits binding of TNF-α and TNF-β (lymphotoxin alpha [LT-α]) to cell surface TNFRs, rendering TNF biologically inactive. In *in vitro* studies, large complexes of etanercept with TNF-α were not detected and cells expressing transmembrane TNF (that binds etanercept) are not lysed in the presence or absence of complement.

12.2 Pharmacodynamics

Etanercept can modulate biological responses that are induced or regulated by TNF, including expression of adhesion molecules responsible for leukocyte migration (eg, E-selectin, and to a lesser extent, intercellular adhesion molecule-1 [ICAM-1]), serum levels of cytokines (eg, IL-6), and serum levels of matrix metalloproteinase-3 (MMP-3 or stromelysin). Etanercept has been shown to affect several animal models of inflammation, including murine collagen-induced arthritis.

FDA Proposed Revisions

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. It plays an important role in the inflammatory processes of RA, polyarticular JIA, PsA, and AS and the resulting joint pathology. In addition, TNF plays a role in the inflammatory process of PsO. Elevated levels of TNF are found in involved tissues and fluids of patients with RA, JIA, PsA, AS, and PsO.

Two distinct receptors for TNF (TNFRs), a 55 kilodalton protein (p55) and a 75 kilodalton protein (p75), exist naturally as monomeric molecules on cell surfaces and in soluble forms. Biological activity of TNF is dependent upon binding to either cell surface TNFR.

Etanercept products are~~is a~~ dimeric soluble forms of the p75 TNF receptor that can bind TNF molecules. Etanercept products inhibit~~s~~ binding of TNF-α and TNF-β (lymphotoxin alpha [LT-α]) to cell surface TNFRs, rendering TNF biologically inactive. In *in vitro* studies, large complexes of etanercept with TNF-α were not detected and cells expressing transmembrane TNF (that binds etanercept products) are not lysed in the presence or absence of complement.

12.2 Pharmacodynamics

Etanercept products can modulate biological responses that are induced or regulated by TNF, including expression of adhesion molecules responsible for leukocyte migration (eg, E-selectin, and to a lesser extent, intercellular adhesion molecule-1 [ICAM-1]), serum levels of cytokines (eg, IL-6), and serum levels of matrix metalloproteinase-3 (MMP-3 or stromelysin). Etanercept products have ~~has~~ been shown to affect several animal models of inflammation, including murine collagen-induced arthritis.

Reviewer Comments: References to etanercept in the context of mechanism of action and pharmacodynamics were revised to “etanercept products” when the information applies to both US-licensed Enbrel and Erelzi. As the in vitro data regarding drug-TNF-a complex formation was conducted with the US-licensed Enbrel reference product, the text was left as “etanercept”.

Sponsor's Proposed Labeling

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of etanercept or its effect on fertility. Mutagenesis studies were conducted *in vitro* and *in vivo*, and no evidence of mutagenic activity was observed.

FDA Proposed Revisions

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of etanercept products or ~~its~~their effect on fertility. Mutagenesis studies were conducted with etanercept *in vitro* and *in vivo*, and no evidence of mutagenic activity was observed.

Reviewer Comments: References to etanercept in the context of carcinogenesis and fertility were revised to "etanercept products" because the information applies to both US-licensed Enbrel and Erelzi. As mutagenesis studies were only conducted with the US-Enbrel reference product, it is defined in the statement that mutagenesis studies were conducted with "etanercept".

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/s/

ANDREA BENEDICT
08/12/2016

CAROL M GALVIS
08/12/2016
I concur

Pharmacology and Toxicology Secondary Review for BLA 761042

Date: July 29, 2016

To: **BLA 761042**
Erelzi (etanercept), referred to as GP2015 during development
Biosimilar to US-licensed Enbrel®
Sandoz, Inc.

From: Carol M. Galvis, PhD
Acting Pharmacology and Toxicology Team Leader
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Recommendation

I concur with the primary reviewer, Dr. Andrea Benedict, that the nonclinical development program is adequate and the application is recommended for approval from the nonclinical pharmacology and toxicology perspective (refer to Dr. Benedict's review dated April 29, 2016). There are no outstanding nonclinical issues.

Background

Sandoz, Inc. submitted BLA 761042 on July 30, 2015 to support registration of Erelzi (etanercept), under section 351(k) of the Public Health Service Act, as a biosimilar to US-licensed Enbrel®. Etanercept is a dimeric soluble form of the p75 TNF receptor that binds to TNF and inhibits TNF binding to cell surface receptors.

US-licensed Enbrel® was developed by Immunex Corporation under BLA 103795 and was originally approved on November of 1998. US-licensed Enbrel® is currently indicated for the treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis. Sandoz, Inc. seeks approval of Erelzi for the same indications at the same dosing regimens.

Summary of Pharmacology and Toxicology Data

Dr. Benedict's review dated April 29, 2016, included pharmacology studies in Tg197 mice comparing GP2015 vs. EU-approved Enbrel, pharmacokinetic studies in rabbits comparing GP2015 vs. EU-approved Enbrel, and a comparative 28-day repeat-dose toxicology study of GP2015 and EU-approved Enbrel in the cynomolgus monkey. As noted in Dr. Benedict's review, an adequate scientific bridge based on analytical similarity was demonstrated between GP2015, US-licensed Enbrel, and EU-approved Enbrel; therefore nonclinical studies comparing GP2015 and EU-approved Enbrel could be used to assess the safety of GP2015.

Collectively, there was no evidence in the aforementioned nonclinical studies to indicate potential safety concerns associated with GP2015 administration. The toxicokinetic profile of GP2015 was considered reasonably similar to that of EU-approved Enbrel in cynomolgus monkeys and rabbits. Further, the efficacy of GP2015 in Tg197 transgenic mice (i.e., reduced development of arthritis-related pathology) was similar to that of EU-approved Enbrel.

Labeling

Labeling is currently being discussed. A labeling review will be completed at a later date.

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/s/

CAROL M GALVIS
08/05/2016

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 761042
Supporting document/s:	SDN1 (0000): New BLA
Applicant's letter date:	July 30, 2015
CDER stamp date:	July 30, 2015
Product:	GP2015 (Etanercept; proposed biosimilar to Enbrel®)
Indication:	Rheumatoid Arthritis, Polyarticular Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Plaque Psoriasis
Applicant:	Sandoz, Inc.
Review Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Reviewer:	Andrea L. Benedict, Ph.D.
Supervisor/Team Leader:	Marcie L. Wood, Ph.D.
Division Director:	Badrul Chowdhury, M.D., Ph.D.
Project Manager:	Leila P. Hann

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1 Executive Summary

1.1 Introduction

BLA 761042 was submitted by Sandoz, Inc. on July 30, 2015, under section 351(k) of the Public Health Services Act (PHS Act) to support registration of GP2015 as a biosimilar to US-licensed Enbrel® (etanercept). Etanercept is a dimeric soluble form of the p75 TNF receptor that can bind TNF molecules. Etanercept inhibits binding of TNF-α and TNF-β (lymphotoxin alpha [LT-α]) to cell surface TNF receptors, rendering TNF biologically inactive. US-licensed Enbrel® (US-Enbrel) is a subcutaneously administered product, originally developed by Immunex Corporation (BLA 103795, Approval date November 2, 1998), indicated for the treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis. Sandoz intends to obtain approval for GP2015 for all currently approved US-Enbrel indications, with dosing regimens that are identical to US-Enbrel.

1.2 Brief Discussion of Nonclinical Findings

The pivotal nonclinical toxicology and toxicokinetic study submitted in support of a determination of biosimilarity of GP2015 to US-Enbrel was a 28-day comparative toxicity study in the cynomolgus monkey of GP2015 and EU-approved Enbrel® (EU-Enbrel). Sandoz established an adequate scientific bridge to justify the relevance of comparative data obtained using EU-Enbrel to support a demonstration of biosimilarity to US-licensed reference product.

Collectively, there was no evidence in the 28-day comparative repeat-dose toxicity study of GP2015 and EU-Enbrel conducted in cynomolgus monkeys to indicate potential safety concerns associated with GP2015 administration. The toxicokinetic profile of GP2015 was considered reasonably similar to that of EU-Enbrel in cynomolgus monkeys.

The nonclinical pharmacology, pharmacokinetic, and repeat-dose toxicity data submitted in support of the BLA demonstrate the similarity (i.e., comparable achieved exposures and safety) between GP2015 and EU-Enbrel from the nonclinical Pharmacology and Toxicology perspective.

1.3 Recommendations

1.3.1 Approvability

GP2015 is recommended for approval from the nonclinical Pharmacology and Toxicology perspective. Labeling will be addressed in a separate labeling review.

1.3.2 Additional Non Clinical Recommendations

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

2 Drug Information

2.1 Drug

CAS Registry Number:

185243-69-0

Proper Name:

To be determined

Code Name:

GP2015, glycoprotein 2015

Molecular Formula/Molecular Weight:

$C_{4448}H_{6886}N_{1236}O_{1402}S_{72}$ (not including post-translational sugar moieties) / 934 amino acids / ~150 kDa (apparent molecular size determined by SDS-PAGE)

Structure or Biochemical Description:

GP2015 is a genetically-engineered dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 kDa tumor necrosis factor receptor (TNFR) linked to the Fc portion of human immunoglobulin G1 (IgG1) that contains only the CH2, CH3, and hinge region. The GP2015 dimeric fusion protein contains 934 amino acids (homo-dimer: 467; Figure 1) produced by recombinant DNA technology in a Chinese Hamster Ovary (CHO) mammalian cell expression system.

Figure 1: Amino Acid Sequence of GP2015: Single Chain of Homo-dimer

```
  1 LPAQVAFTPY APEPGSTCRL REYYDQTAQM CCSKCSPGQH AKVFCTKTSD
 51 TVCDSCEDST YTQLWNWVPE CLSCGSRCSS DQVETQACTR EQNRICTCRP
101 GWYCALSKQE GCRLCAPLRK CRPGFGVARP GTETSDVVCK PCAPGTFSNT
151 TSSTDICRPH QICNVVAIPG NASMDAVCTS TSPTRSMAPG AVHLPQPVST
201 RSQHTQPTPE PSTAPSTSFL LPMGPSPPAE GSTGDEPKSC DKTHTCPPCP
251 APELLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSHED PEVKFNWYVD
301 GVEVHNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA
351 PIEKTISKAK GQPREPQVYT LPPSREEMTK NQVSLTCLVK GFYPSDIAVE
401 WESNGQPENN YKTTPPVLDS DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE
451 ALHNHYTQKS LSLSPGK
```

Amino acids: 467

Note: TNFR domain in black, Fc domain in red (*excerpted from the sponsor's submission*)

Pharmacologic Class:

Tumor necrosis factor blocker

2.2 Relevant INDs, BLAs and DMFs

Application #	Description	Sponsor	Date
IND 114187	IND application in support of clinical testing of GP2015 in the U.S.	Sandoz, Inc.	7/14/2015 (IND submission date)
BLA 103795/ BLA (b) (4)	BLA application for innovator product, Enbrel®	Immunex Corp.	11/2/1998 (approval date)

2.3 Drug Formulation

The GP2015 drug product will be provided as a 25 mg/0.5 mL and a 50 mg/1.0 mL solution for subcutaneous injection, supplied in pre-filled single-use syringes (clear glass barrel with fixed needle). The GP2015 drug product formulation will be comprised of GP2015 as drug substance, sodium citrate as buffer, sodium chloride as (b) (4), sucrose and L-lysine as (b) (4) and water for injection as (b) (4) (Table 1). The GP2015 drug product formulation is not identical to that of the reference product as it differs in the buffering agent (citrate vs. phosphate) and amino acid (b) (4) (lysine vs. arginine).

Table 1: Drug product formulation for a single dose of 50 mg or 25 mg GP2015

Ingredient	GP2015 50 mg/1.0 mL	GP2015 25 mg/0.5 mL	Function	Grade
GP2015	50 mg	25 mg	API	In-house
Citric acid anhydrous	0.786 mg	0.393 mg	Buffering agent	Ph. Eur., USP
Sodium citrate dihydrate	13.520 mg	6.760 mg	Buffering agent	Ph. Eur., USP/NF
Sucrose	10.000 mg	5.000 mg	(b) (4)	Ph. Eur., USP/NF
L-lysine-HCl	4.600 mg	2.300 mg		Ph. Eur., USP
Sodium chloride	1.500 mg	0.750 mg		Ph. Eur., USP/NF
Hydrochloric acid 25%	q.s.	q.s.	pH-modifier	Ph. Helv.
Sodium hydroxide	q.s.	q.s.	pH-modifier	Ph. Eur., USP/NF
Water for injection	ad 1.000 mL	ad 0.500 mL	(b) (4)	Ph. Eur., USP

Stated volumes, API, and excipient amounts do not account for the overfill
API; active pharmaceutical ingredient, q.s.; amount needed (quantum satis), USP; United States Pharmacopoeia, NF; National Formulary, Ph. Eur.; European Pharmacopoeia, Ph. Helv.; Pharmacopoeia Helvetica

2.4 Comments on Novel Excipients

The GP2015 formulation differs from the marketed Enbrel formulation (EU and US) by the buffering agent (citrate vs. phosphate) and amino acid (b) (4) (lysine vs. arginine).

L-lysine hydrochloride, an essential amino acid, is not found in other US-approved products for the subcutaneous route of administration; however it is found in US-approved products for the intravenous route of administration with a maximum daily dose of approximately 6.3 g (i.e., in a 60 kg human) for amino acid supplementation (KABIVEN®, label 09/2014). L-lysine is also widely available as a dietary supplement, with recommended doses up to 3 g/day or greater. It can be reasonably assumed that the systemic safety profile of L-lysine is known. Local toxicity of L-lysine can be clinically monitored.

There are no nonclinical safety concerns for L-lysine HCl at a maximum daily dose of 4.6 mg.

2.5 Comments on Impurities/Degradants of Concern

There are no impurities of degradants of concern.

2.6 Proposed Clinical Population and Dosing Regimen

The proposed clinical population and dosing regimen for GP2015 are identical to those of the reference product.

The indications include:

- Rheumatoid Arthritis
- Polyarticular Juvenile Idiopathic Arthritis in patients aged 2 years or older
- Psoriatic Arthritis
- Ankylosing Spondylitis
- Plaque Psoriasis

The US-licensed Enbrel® dosage for adult patients with Rheumatoid Arthritis or Psoriatic Arthritis is 50 mg once weekly with or without methotrexate. For Ankylosing Spondylitis, the treatment regimen is 50 mg once weekly. For adults with Plaque Psoriasis, the dosage is 50 mg twice weekly for 3 months, followed by 50 once weekly. For patients aged 2 years or older with Polyarticular Juvenile Idiopathic Arthritis, the treatment regimen is 0.8 mg/kg weekly, with a maximum dose of 50 mg per week.

2.7 Regulatory Background

Sandoz submitted IND 114187 on July 14, 2015, for the development of GP2015 as a proposed biosimilar to US-Enbrel, for the same patient populations and dosing regimen as the reference product. The opening IND comparative clinical study (Protocol GP15-301) was allowed to proceed on August 18, 2015. On July 30, 2015, Sandoz submitted the 351(k) BLA 761042 for the registration of GP2015 as a biosimilar to US-Enbrel.

The nonclinical pharmacology and toxicology information in support of BLA 761042 was fully reviewed under IND 114187 (see the Nonclinical 30-day Safety Review of Dr. Andrea L. Benedict; IND 114187, August 13, 2015, in Section 12 Appendix). A Nonclinical IR was sent to the sponsor on November 9, 2015, to request nonclinical information to address nonclinical issues that were noted during the 30-day safety review under IND 114187. The sponsor provided the requested nonclinical information on November 20, 2015, via email to Leila P. Hann, which was considered adequate to address the nonclinical deficiencies. The requested nonclinical information was formally submitted under IND 114187 on April 20, 2016. See the Nonclinical Memo Review of Dr. Andrea L. Benedict (April 25, 2016) for further information.

3 Studies Submitted

3.1 Studies Reviewed

There were no new nonclinical pharmacology and toxicology studies submitted in support of the registration of GP2015 under BLA 761042.

3.2 Studies Not Reviewed

The nonclinical pharmacology and toxicology studies provided in support of the registration of GP2015 under BLA 761042 were reviewed at the time of the IND submission under IND 114187. The reviewed nonclinical pharmacology and toxicology studies are listed in Table 2 below.

Table 2: Nonclinical studies submitted in support of BLA 761042 (reviewed under IND 114187)

Study Type	Study #	Title	Comparison
Primary Pharmacology	GP15-004	Assessment of the therapeutic profile of Enbrel® on the development of inflammatory polyarthritis in the human TNF transgenic model of arthritis (Tg197)	n/a
	GP15-007	Comparative study on the therapeutic efficacy of GP2015 and Enbrel® in preventing arthritic symptoms in the Tg197 transgenic mouse model of arthritis	GP2015 vs. EU-approved etanercept
Pharmacokinetics	GP15-001	Comparative pharmacokinetic study of two qualities of Enbrel® and five formulations of GP2015 following single subcutaneous administration to rabbits	GP2015 vs. EU-approved etanercept
	GP15-006	Comparative single s.c. dose pharmacokinetic study in rabbits on GP2015 (GMP DS) in 50 mM Citrate/Lysine formulation and GP2015 (GMP DS) in originator-like formulation vs. Enbrel®	GP2015 vs. EU-approved etanercept
General Toxicology	GP15-003	GP2015 and Enbrel®: Comparative Toxicity Study in the Cynomolgus Monkey with Subcutaneous Administration over 28 Days	GP2015 vs. EU-approved etanercept
	GP15-003-BA11012	Quantification of Etanercept in Cynomolgus monkey serum of preclinical study 8240755 (GP15-003) by ELISA (Note: Reviewed under GP15-003)	GP2015 vs. EU-approved etanercept
	GP15-003-BA11014	Detection of anti-Etanercept antibodies in Cynomolgus monkey serum of preclinical study 8240755 (GP15-003) by an ECL Bridging Immunogenicity Assay (Note: Reviewed under GP15-003)	GP2015 vs. EU-approved etanercept

3.3 Previous Reviews Referenced

Review	Author	Date	Notes
Nonclinical 30-day Safety Review of IND 114187	A.L. Benedict	August 13, 2015	See Section 12: Appendix
Nonclinical Memo Review of IND 114187	A.L. Benedict	April 25, 2015	Not included in this review
Nonclinical Pharmacology and Toxicology Review of BLA (b) (4) (BLA 103795)	M.D. Green	October 30, 1998	Not included in this review

4 Pharmacology

4.1 Primary Pharmacology

The primary pharmacology studies (GP15-004 and GP15-007) were reviewed under IND 114187. See the Nonclinical 30-day Safety Review of Dr. Andrea L. Benedict; IND 114187 (August 13, 2015) in Appendix, for full details.

4.2 Secondary Pharmacology

There were no secondary pharmacology studies submitted in support of BLA 761042.

4.3 Safety Pharmacology

There were no safety pharmacology studies submitted in support of BLA 761042.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

The comparative single-dose pharmacokinetic studies in rabbits (GP15-001 and GP15-006) were reviewed under IND 114187. See the Nonclinical 30-day Safety Review of Dr. Andrea L. Benedict; IND 114187 (August 13, 2015) in Appendix, for full details.

6 General Toxicology

6.1 Single-Dose Toxicity

There were no single-dose toxicity studies submitted in support of BLA 761042.

6.2 Repeat-Dose Toxicity

The comparative repeat-dose toxicity study in the cynomolgus monkey (GP15-003; including GP15-003-BA11012 and GP15-003-BA11014) was reviewed under IND 114187. See the Nonclinical 30-day Safety Review of Dr. Andrea L. Benedict; IND 114187 (August 13, 2015) in Appendix, for full details.

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 development toxicology studies submitted.

10 Special Toxicology Studies

There were no special toxicology studies submitted.

11 Integrated Summary and Safety Evaluation

BLA 761042 was submitted by Sandoz, Inc. on July 30, 2015, to support registration of GP2015 as a biosimilar to US-licensed Enbrel®. Sandoz provided primary pharmacology studies, single-dose pharmacokinetic studies, and a comparative 28-day repeat-dose toxicology study of GP2015 and EU-Enbrel in the cynomolgus monkey as nonclinical support for BLA 761042. These nonclinical studies were previously reviewed under IND 114187 (see the Nonclinical 30-day Safety Review of Dr. Andrea L. Benedict; IND 114187, August 13, 2015, in Appendix).

An adequate scientific bridge based on analytical similarity was demonstrated between GP2015, US-Enbrel, and EU-Enbrel; therefore nonclinical studies comparing GP2015 and EU-Enbrel could be used to assess the safety of GP2015.

Efficacy of GP2015 was demonstrated by Sandoz in Tg197 transgenic mice, which constitutively express human TNFα and develop a chronic, inflammatory polyarthritis. In this comparative efficacy study, no differences in efficacy (i.e., reduced development of arthritis-related pathology) were observed between GP2015 and EU-Enbrel, as compared to vehicle control mice, at a biweekly dose of 10 mg/kg for 2 or 4 weeks, when treatment was initiated at 6 weeks of age in Tg197 mice (Study GP15-007).

In a single-dose subcutaneous comparative PK study in male rabbits, PK profiles were shown to be similar between GP2015 and EU-Enbrel at a dose of 8 mg/kg (Study GP15-006).

For the pivotal nonclinical support of GP2015, Sandoz provided a comparative 28-day repeat-dose toxicology study of GP2015 and EU-Enbrel in the cynomolgus monkey (Study GP15-003). Sandoz selected the cynomolgus monkey to examine repeat-dose toxicity as it was determined to be the most relevant nonclinical species during the development of the reference product, due to the formation of neutralizing antibodies in rodent species (i.e., mouse, rat, and rabbit) with repeat-dose subcutaneous administration. A single dose level of 15 mg/kg of GP2015 or EU-Enbrel, given once every 3 days for 28-days (10 total treatments), was selected based on the highest dose examined in repeat-dose studies during the development of the reference product (i.e.,

US-Enbrel) in the cynomolgus monkey, which was found to be well tolerated and did not lead to dose-limiting toxicities. Additionally, repeated subcutaneous administration of lower doses of US-Enbrel (i.e., 1 or 5 mg/kg SC twice weekly) in cynomolgus monkeys resulted in decreased systemic exposure of etanercept with repeat dosing; whereas a dose level of 15 mg/kg US-Enbrel SC twice weekly suppressed the development of ADA and did not result in reduced systemic exposure with repeat dosing. The GP2015 formulation used in this study was identical to the final GP2015 drug product formulation. The vehicle control group received the GP2015 formulation without the API.

There were no treatment-related deaths with GP2015 or EU-Enbrel in the 28-day study. Treatment-related injection site reactions, consisting of moderate to severe erythema/rash, were noted in one GP2015-treated male and two EU-Enbrel-treated males on study Days 26-32, with correlating changes in red and white blood cell parameters and decreased platelets on Days 29-32. Additionally, increased body temperature and clinical chemistry changes on Day 26 were observed in the GP2015-treated male only. These findings may be the result of immunogenicity, which was supported by the observation of reduced systemic exposure in these animals on Day 28; however, immunogenicity could not be confirmed due lack of correlating ADA.

Microscopic findings were similar in GP2015- and Enbrel-treated animals. These included inflammatory lesions (hyperkeratosis, dermatitis, myositis, and cellulitis) of injection sites and minimal cortical eosinophilia/hypertrophy of the adrenal gland.

Systemic exposure (AUC_{0-72} and C_{max}) was similar in male and female monkeys receiving 15 mg/kg GP2015 or EU-Enbrel on Days 1 and 7. On Day 28, systemic exposure decreased in all drug-treated groups and systemic exposure was 2.2-fold higher in GP2015-treated males compared to females. The decreased systemic exposure in drug-treated animals and gender difference in the GP2015 groups on Day 28 were likely due to the development of ADAs. Etanercept-specific ADAs were confirmed in 2 GP2015 females, and 2 EU-Enbrel animals. However, as most GP2015- and EU-Enbrel-treated animals had decreased systemic exposure on Day 28, the incidence of ADA may have been underestimated due to lack of assay sensitivity in the presence of etanercept in the serum samples.

The overall safety, immunogenicity, and toxicokinectic profiles of GP2015 and EU-Enbrel in the cynomolgus monkey in the 28-day repeat-dose toxicity study were determined to be similar and do not indicate potential safety concerns associated with GP2015 administration.

The nonclinical pharmacology, pharmacokinetic, and repeat-dose toxicity data submitted in support of the BLA demonstrate the similarity (i.e., comparable nonclinical efficacy, achieved exposures, and safety profiles) between GP2015 and EU-Enbrel 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.

12 Appendix/Attachments

Appendix 1: Nonclinical 30-day Safety Review of Dr. Andrea L. Benedict; IND 114187, August 13, 2015

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

PHARMACOLOGY/TOXICOLOGY IND REVIEW AND EVALUATION

Application number:	114187
Supporting document/s:	SDN 11
Sponsor's letter date:	7/13/2015
CDER stamp date:	7/14/2015
Product:	GP2015 (Etanercept Biosimilar)
Indication:	Same indications for which US-licensed Enbrel (etanercept) is approved (Rheumatoid Arthritis, Polyarticular Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Plaque Psoriasis)
Sponsor:	Sandoz, Inc.
Review Division:	Division of Pulmonary, Rheumatology, and Allergy Products
Reviewer:	Andrea L. Benedict, Ph.D.
Supervisor/Team Leader:	Marcie L. Wood, Ph.D.
Division Director:	Badrul Chowdhury, M.D., Ph.D.
Project Manager:	Leila Hann

Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

IND 114187 was submitted for the development of GP2015, a proposed etanercept biosimilar product. The proposed opening IND study (Protocol GP15-301) is a Phase 3, 48-week, randomized, double-blind, parallel-group, 2-treatment period study in patients with moderate to severe RA using GP2015 and EU-authorized Enbrel® (EU-Enbrel) at subcutaneous doses of 50 mg/week. Previous clinical experience with GP2015 includes two Phase 1 PK similarity studies in healthy volunteers using GP2015 and EU-Enbrel (Protocol GP15-101) or GP2015 and US-licensed Enbrel® (US-Enbrel) (Protocol GP15-102) at subcutaneous doses of 50 mg, as well as an ongoing Phase 3, 52-week, safety and efficacy study (Protocol GP15-302) in patients with moderate to severe plaque psoriasis using GP2015 and EU-Enbrel.

1.2 Brief Discussion of Nonclinical Findings

In vitro pharmacological similarity assays between GP2015, US-Enbrel, and EU-Enbrel, including TNFα neutralization, TNFα binding, C1q binding, FcγRIa, FcγRIIa, FcγRIIIa, and FcRn binding, as well as apoptosis, ADCC, and CDC bioassays were provided as part of the product quality assessment and were evaluated by the product quality review team. Data indicate that GP2015 has similar pharmacological activity as etanercept (Enbrel).

A comparative efficacy study was conducted in a Tg197 human TNFα-expressing transgenic mouse model of polyarthritis (Study GP15-007). No differences in efficacy (i.e., reduced development of arthritis-related pathology) were observed between EU-Enbrel and GP2015 treatment, at a biweekly dose of 10 mg/kg for 2 or 4 weeks, when treatment was initiated at 6 weeks of age.

A GLP single-dose (SC) comparative PK study was conducted in rabbits (Study GP15-006). In this study, a single 8 mg/kg subcutaneous administration of two GP2015 formulations (i.e., an originator-like formulation or a formulation containing 50 mM Citrate/25 mM Lysine as the buffer/amino acid components) and EU-Enbrel produced no clinical signs or signs of local intolerance in male rabbits. In general, no major differences in PK parameters were noted between the two GP2015 formulations and EU-Enbrel.

A repeat-dose toxicology study comparing GP2015 and EU-Enbrel was conducted in cynomolgus monkeys. Monkeys (n = 3/sex/group) received 0 (GP2015 placebo control), 15 mg/kg GP2015, or 15 mg/kg EU-Enbrel by subcutaneous injection (SC) once every 3 days for 28-days.

Findings observed in GP2015 and EU-Enbrel treatment groups were generally similar, however one GP2015-treated male and two EU-Enbrel-treated males developed injection site reactions after the ninth injection (~Days 26-32). Symptoms were more severe in the GP2015-treated male, including a slight fever on Days 26-27, a more extensive rash involving the injection sites, right hind limb, and the right inguinal and abdomen region that also displayed ecchymosis, and more substantial changes in

hematology (RBC and WBC parameters) and clinical chemistry parameters. However due to the small number of animals utilized in this study, the significance of the increased symptom severity in this GP2015-treated animal is unclear.

Changes in hematology parameters occurred mainly in GP2015- and EU-Enbrel-treated males on Days 29-32, and included increased WBCs and absolute and relative reticulocytes, lymphocytes, monocytes and LUCs, and decreased absolute and relative neutrophils. Platelets were decreased on Days 22 [GP2015 males] and 29 and increased on Days 31-32. Platelet crit was also increased on Days 31-32. The changes in group means for the GP2015- and EU-Enbrel-treated males were largely driven by the changes observed in the individual animals with injection site reactions.

Microscopic findings in GP2015- and EU-Enbrel-treated animals included inflammatory lesions (hyperkeratosis, dermatitis, myositis, and cellulitis) in injection sites, as well as minimal cortical eosinophilia/hypertrophy of the adrenal gland, versus controls. The incidence of injection site myositis and cellulitis was increased in GP2015 animals compared to EU-Enbrel animals.

Systemic exposure to GP2015 and EU-Enbrel was similar on Days 1 and 7, and decreased in both treatment groups on Day 28, likely due to ADA formation in both GP2015 and EU-Enbrel treatment groups. GP2015 and EU-Enbrel groups developed ADA to a similar extent (2/6 animals per treatment group). However, the presence of etanercept in serum may have impaired the detection of anti-etanercept antibodies in the assay system, leading to false negative ADA results for other GP2015- and EU-Enbrel-treated animals, as evidenced by decreased systemic exposure in most drug-treated animals on Day 28.

1.3 Recommendations

1.3.1 Clinical Study (ies) Safe to Proceed: Yes

The proposed clinical study (Protocol GP15-301) is reasonably safe to proceed from the nonclinical perspective.

1.3.3 Additional Recommendation(s) (Non-hold comments/advice to sponsor) *if any.*

The following nonclinical non-hold comments should be conveyed to the sponsor:

1) The original study protocol and the ECG data for the 28-day toxicology study in the cynomolgus monkey (GP15-003) were absent from the final study report document. Provide the full, signed study protocol and line listings of animal ECG data to the IND for review.
2) The drug product and GP2015 placebo/vehicle formulations were not clearly described in the study reports for the following in vivo nonclinical studies: GP15-007, GP15-006, GP15-003. Provide a full description of the vehicle and drug product formulations used in these nonclinical studies.

2 Drug Information

2.1 Drug

CAS Registry Number: 185243-69-0

Generic Name: Etanercept biosimilar

Code Name: GP2015

Molecular Formula/Molecular Weight: $C_{4448}H_{6886}N_{1236}O_{1402}S_{72}$ / ~150 kDa (Apparent molecular size determined by SDS-PAGE)

Structure or Biochemical Description:

GP2015 is a genetically-engineered dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 kDa tumor necrosis factor receptor (TNFR) linked to the Fc portion of human immunoglobulin G1 (IgG1) that contains only the C_H2, C_H3, and hinge region. The GP2015 dimeric fusion protein contains 934 amino acids (homo-dimer: 467; Figure 1) produced by recombinant DNA technology in a Chinese Hamster Ovary (CHO) mammalian cell expression system.

Figure 1: Amino Acid Sequence of GP2015: Single Chain of Homo-dimer

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  1 LPAQVAFTPY APEPGSTCRL REYYDQTAQM CCSKCSPGQH AKVFCTKTSD
 51 TVCDSCEDST YTQLWNWVPE CLSCGSRCSS DQVETQACTR EQNRICTCRP
101 GWYCALSKQE GCRLCAPLRK CRPGFGVARP GTETSDVVCK PCAPGTFSNT
151 TSSTDICRPH QICNVVAIPG NASMDAVCTS TSPTRSMAPG AVHLPQPVST
201 RSQHTQPTPE PSTAPSTSFL LPMGPSPPAE GSTGDEPKSC DKTHTCPPCP
251 APELLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSHED PEVKFNWYVD
301 GVEVHNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA
351 PIEKTISKAK GQPREPQVYT LPPSREEMTK NQVSLTCLVK GFYPSDIAVE
401 WESNGQPENN YKTTPPVLDS DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE
451 ALHNHYTQKS LSLSPGK
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Amino acids: 467

Note: TNFR domain in black, Fc domain in red (*excerpted from the sponsor's submission*)

Pharmacologic Class: Anti-TNF-α fusion protein

2.2 Relevant INDs, NDAs, BLAs and DMFs

BLA 103795/BLA [redacted] (b) (4) (Enbrel; etanercept)

2.3 Drug Formulation

GP2015 drug product is formulated for subcutaneous (SC) injection at a concentration of 50 mg/mL. GP2015 drug product contains sodium citrate, citric acid, sodium chloride, sucrose, and L-lysine-HCl in water for injection, pH 6.3. Sodium hydroxide and hydrochloric acid will be used for pH adjustment as needed. The composition of the

GP2015 drug product is provided in the table below (Table 1; excerpted from the sponsor's submission). The drug product will be supplied in a pre-filled syringe intended for single application, containing 1 mL of drug product corresponding to 50 mg of etanercept.

Table 1: GP2015 drug product formulation (50 mg/mL)

Component	Amount	Function
Etanercept	50 mg	API
Citric acid anhydrous	0.786 mg	Buffering agent
Sodium citrate dihydrate	13.520 mg	Buffering agent
Sucrose	10.000 mg	(b) (4)
L-lysine-HCl	4.600 mg	
Sodium chloride	1.500 mg	
Hydrochloric acid 25%	q.s.	
Sodium hydroxide	q.s.	
Water for injection	ad 1.000 mL	

Stated volumes, API, and excipient amounts do not account for the overfill

API - active pharmaceutical ingredient

q.s. - amount needed (quantum satis)

2.4 Comments on Novel Excipients

The GP2015 formulation differs from the marketed Enbrel formulation (EU and US) by the buffering agent (citrate vs. phosphate) and amino acid (b) (4) (lysine vs. arginine).

L-lysine hydrochloride, an essential amino acid, is not found in other US-approved products for the subcutaneous route of administration; however it is found in US-approved products for the intravenous route of administration with a maximum daily dose of approximately 6.3 g (i.e., in a 60 kg human) for amino acid supplementation (KABIVEN®, label 09/2014). L-lysine is also widely available as a dietary supplement, with recommended doses up to 3 g/day or greater. It can be reasonably assumed that the systemic safety profile of L-lysine is known. Local toxicity of L-lysine can be clinically monitored.

At this time there are no nonclinical safety concerns for L-lysine HCl at a maximum daily dose of 4.6 mg.

2.5 Comments on Impurities/Degradants of Concern

None.

2.6 Proposed Clinical Protocol

The sponsor has proposed a Phase 3, randomized, double-blind, parallel-group, two treatment period study (Protocol GP15-301) in patients with moderate to severe RA to assess the similarity in efficacy, safety, and immunogenicity between GP2015 and EU-Enbrel.

(b) (4)

2.7 Previous Clinical Experience

The completed and ongoing studies conducted with GP2015 are presented below in Table 2. Two healthy volunteer PK studies were completed to compare the PK characteristics and the safety profile of GP2015 with EU-Enbrel (GP15-101) and US-Enbrel (GP15-102). Two additional PK studies in healthy male volunteers have been conducted to examine PK parameters after SC administration of GP2015 from a pre-filled syringe versus an autoinjector (GP15-103), as well as in a single-dose cross-over study of GP2015 and EU-Enbrel (GP15-104; ongoing). A Phase 3 confirmatory safety and efficacy study (GP15-302) of GP2015 and EU-Enbrel in patients with moderate to severe chronic plaque-type psoriasis is currently ongoing at 71 study sites world-wide.

Table 2: Summary of completed and ongoing clinical studies of GP2015

Study	Treatments	Dose and Duration	Population	N	Status
GP15-101 (PK Study)	• GP2015 • EU-Enbrel	50 mg SC, single dose	Healthy Volunteers	54	Completed
GP15-102 (PK Study)	• GP2015 • US-Enbrel	50 mg SC, single dose	Healthy Volunteers	57	Completed

Study	Treatments	Dose and Duration	Population	N	Status
GP15-103 (PK Study: Device Comparison)	• GP2015-Pre-filled syringe • GP2015-Autoinjector	50 mg SC, single dose	Healthy Male Volunteers	51	Completed
GP15-104 (PK Study: Single-dose crossover)	• GP2015 • EU-Enbrel	50 mg SC, single dose (35 day washout between doses)	Healthy Male Volunteers	54	Ongoing
GP15-302 (Confirmatory Safety and Efficacy Study)	• GP2015 • EU-Enbrel	50 mg SC, 2x/week up to 12 weeks, then 1x/week up to 52 weeks	Patients with moderate to severe chronic plaque-type psoriasis	531	Ongoing

2.8 Regulatory Background

A Type B Pre-IND meeting was held with the sponsor on July 9, 2012. The sponsor's nonclinical question to the FDA was in general regards to the adequacy of their nonclinical program to support the initiation of clinical trials in the US under an IND, as well as for support of a 351(k) BLA. In the FDA's nonclinical comments, the sponsor was advised that pending review upon an IND submission, the comparative nonclinical studies presented in the pre-IND package appeared to be generally acceptable to support clinical development of GP2015, and that adequacy of nonclinical studies to support approval of a 351(k) BLA will be made after review of quality, nonclinical, and clinical data. It was also noted that the in vivo nonclinical studies utilized EU-Enbrel as the comparator product and that an adequate bridge to US-Enbrel would be required to use the nonclinical safety data, which would likely include a 3-way bridging clinical PK/PD study, as well as a direct physico-chemical comparison of all 3 products (US-licensed Enbrel, EU-approved etanercept, and GP2015). See the Meeting Minutes document dated July 26, 2012, for further details.

A Type 2 BPD meeting was held with the sponsor on December 19, 2012. Guidance on aspects of clinical study design and study end points was provided. The sponsor indicated that (b) (4) and inquired if EU-Enbrel would be acceptable. The FDA stated that this would be acceptable if adequate justification, scientific rationale, and data to bridge to US-Enbrel were provided to the IND. See the Meeting Minutes document dated January 16, 2013, for further details. IND 114187 was submitted on July 15, 2015.

3 Studies Submitted

3.1 Studies Reviewed

Primary Pharmacology

GP15-004 Assessment of the therapeutic profile of ENBREL® on the development of inflammatory polyarthritis in the human TNF transgenic model of arthritis (Tg197)

GP15-007	Comparative study on the therapeutic efficacy of GP2015 and Enbrel® in preventing arthritic symptoms in the Tg197 transgenic mouse model of arthritis
Pharmacokinetics	
GP15-001	Comparative pharmacokinetic study of two qualities of Enbrel® and five formulations of GP2015 following single subcutaneous administration to rabbits
GP15-006	Comparative single s.c. dose pharmacokinetic study in rabbits on GP2015 (GMP DS) in 50 mM Citrate/Lysine formulation and GP2015 (GMP DS) in originator-like formulation vs. Enbrel®
General Toxicology	
GP15-003	GP2015 and Enbrel®: Comparative Toxicity Study in the Cynomolgus Monkey with Subcutaneous Administration over 28 Days
GP15-003-BA11012	Quantification of Etanercept in Cynomolgus monkey serum of preclinical study 8240755 (GP15-003) by ELISA (Note: Reviewed under GP15-003)
GP15-003-BA11014	Detection of anti-Etanercept antibodies in Cynomolgus monkey serum of preclinical study 8240755 (GP15-003) by an ECL Bridging Immunogenicity Assay (Note: Reviewed under GP15-003)

3.2 Studies Not Reviewed

None.

3.3 Previous Reviews Referenced

None.

4 Pharmacology

4.1 Primary Pharmacology

Comparative pharmacodynamic (PD) effects and efficacy of GP2015 versus EU-Enbrel were assessed in the human TNFα-expressing Tg197 transgenic mouse model of rheumatoid arthritis. The pilot study to establish the optimal EU-Enbrel dose in the Tg197 mouse model (GP15-004) and the comparative single and multiple dose study with GP2015 and EU-Enbrel (GP15-007) are summarized below.

GP15-004: Assessment of the therapeutic profile of ENBREL® on the development of inflammatory polyarthritis in the human TNF transgenic model of arthritis (Tg197)

Objective: Study GP15-004 was a single and multiple dose pilot study in the Tg197 mouse to establish the optimal EU-Enbrel dosing level that would likely reveal any potential differences in efficacy between GP2015 and EU-Enbrel.

Methods: In this study, Tg197 mice were separated into 15 groups of 8 age-matched mice (n = 3 males and 5 females/group). Treatments were initiated upon the

establishment of arthritis at 7 weeks of age. Groups 1-5 received a single bolus IP (0, 3, 10, or 30 mg/kg) or SC (10 mg/kg) injection of EU-Enbrel and were sacrificed 72 hours post-dose. Groups 6-10 received biweekly EU-Enbrel treatment (0, 3, 10, or 30 mg/kg; IP) from 7 weeks of age up to 10 weeks of age, and groups 11 to 15 received biweekly EU-Enbrel treatment (0, 3, 10, or 30 mg/kg; IP) from 7 weeks of age up to 12 weeks of age. All animals were sacrificed approximately 72 hours after the last dose. One additional group of Tg197 mice (n = 4) was used as a control for disease status (sacrificed just prior to the first dose administration at 7 weeks of age).

Body weight and in-life arthritic scores (e.g., 0 = no arthritis to 3.0 = heavy arthritis) were recorded weekly from 3 weeks of age until the end of the experiment. Histopathological examination was conducted on the ankle joints and a histopathological score of 0 to 4 was assigned based on severity of disease progression (e.g., 0 = no detectable pathology to 4 = extensive cartilage destruction and bone erosion). Statistical analysis was conducted by a Kruskal-Wallis multiple comparison test with Dunn's post analysis and Mann-Whitney (2-tail, 95% CI) analysis.

Results: The mean body weights, arthritic scores, and histological ankle joint scores for each group at the end of each treatment period (i.e., 72 hr post-single bolus dose at 7 weeks of age, biweekly treatments from 7-10 weeks of age, and biweekly treatments from 7-12 weeks of age) are represented in the table below (Table 3). At 7 weeks of age, the untreated Tg197 mice presented with in-life findings of mild arthritis and advanced arthritis-related histopathological findings in the ankle joints. Similar arthritis and histopathological scores were observed in the saline control-treated mice at 72 hrs post-dose.

With a single bolus administration of 3 to 30 mg/kg EU-Enbrel at 7 weeks of age, there was a slight increase in body weights, a small, but statistically significant (14-18%) improvement in histopathological score, but no improvement in arthritic score at any dose level. The SC route of administration produced similar results to the IP route at the 10 mg/kg dosing level.

With biweekly EU-Enbrel treatment from 7 weeks to either 10 or 12 weeks of age, there was a dose-dependent increase in body weight and a statistically significant improvement in both arthritic and histological scores, with the exception of the 3 mg/kg dosing level which lacked statistical significance at both endpoints for histological score. At 30 mg/kg EU-Enbrel for both the Week 10 and 12 endpoints, an approximate 50-60% improvement in arthritic and histological score was observed compared to vehicle controls. The arthritic and histological scores at Week 10 and 12 were similar between the SC and IP routes of administration at the 10 mg/kg dosing level.

Table 3: Summary data from a pilot study to assess optimal dose and route of administration of EU-Enbrel in Tg197 mice (Study GP15-004)

Endpoint	Dose Frequency	Group	Treatment	BW (g)	Change in BW (% ctrl)	Arthritic Score (AS)	Change in AS (% ctrl)	Histological Score (HS)	Change in HS (% ctrl)
7 weeks	n/a	7 wk#	None	14.53	n/a	1.13	n/a	3.38	n/a
7 weeks; 72 hr post-	Single bolus	G1	0 mg/kg, IP	14.93	–	1.02	–	3.38	–
		G2	3 mg/kg, IP	14.94	0%	0.95	7%	2.90**	14%

Endpoint	Dose Frequency	Group	Treatment	BW (g)	Change in BW (% ctrl)	Arthritic Score (AS)	Change in AS (% ctrl)	Histological Score (HS)	Change in HS (% ctrl)
treatment		G3	10 mg/kg, IP	15.66	5%	1.05	-3%	2.88**	15%
		G4	10 mg/kg, SC	15.98	7%	1.00	2%	2.84*	16%
		G5	30 mg/kg, IP	15.76	6%	1.02	0%	2.78**	18%
Week 10	Biweekly; Week 7-10	G6	0 mg/kg, IP	15.60	–	1.38	–	3.65	–
		G7	3 mg/kg, IP	16.86	8%	1.02*	26%	3.50	4%
		G8	10 mg/kg, IP	18.00	15%	0.86***	38%	2.90**	21%
		G9	10 mg/kg, SC	19.54	25%	0.88***	36%	2.66***	27%
		G10	30 mg/kg, IP	18.81	21%	0.68***	51%	1.68***	54%
Week 12	Biweekly; Week 7-12	G11	0 mg/kg, IP	15.38	–	1.55	–	3.69	–
		G12	3 mg/kg, IP	17.15	12%	1.11**	28%	3.50	5%
		G13	10 mg/kg, IP	18.11	18%	0.91***	41%	2.71*	27%
		G14	10 mg/kg, SC	19.73	28%	0.98***	37%	3.13**	15%
		G15	30 mg/kg, IP	21.20	38%	0.63***	59%	1.88**	49%

#Untreated Tg197 control mice (n = 2/sex) used for assessing baseline disease status
*P<0.05, **P<0.01, ***P<0.0001
Note: Change in AS and HS represents the improvement in scores relative to vehicle controls at the respective time point.

Conclusions: In the Tg197 mouse model of rheumatoid arthritis, EU-Enbrel treatment at doses of 3-30 mg/kg lead to dose-dependent improvements in disease severity when treatment was initiated at 7 weeks of age. Single bolus IP (3, 10, and 30 mg/kg) or SC (10 mg/kg) administration resulted in slight improvements in histological scores of the ankle joints (~14-18%), but did not affect in-life arthritic score at 72 hours after dosing. Biweekly IP (3, 10, and 30 mg/kg) and SC (10 mg/kg) dosing from 7 to 10 or 12 weeks of age resulted in dose-dependent and statistically significant improvements in arthritic scores for all EU-Enbrel-treated groups and significant improvements in historical scores for groups treated with ≥10 mg/kg EU-Enbrel. The 30 mg/kg dosing level produced the greatest changes in disease severity in this model system.

GP15-007: Comparative study on the therapeutic efficacy of GP2015 and Enbrel® in preventing arthritic symptoms in the Tg197 transgenic mouse model of arthritis

Objective: To compare the therapeutic effect of GP2015 and EU-Enbrel on the development of pathology in the Tg197 transgenic mouse model of polyarthritis at a dose sensitive to detect variance in efficacy between the test article and the comparator.

Methods: In a pilot study of EU-Enbrel (Study GP15-004; described above), the sponsor determined that the optimum dose was 10 mg/kg, given by either the IP or SC route of administration. In this study (Study GP2015-007), Tg197 mice were separated into 6 groups of 20 age-matched mice (n = 10/sex/group; Groups 1-6) and 2 groups of 10 age-matched mice (n = 5/sex/group; Groups 7-8). Treatments were initiated upon the establishment of arthritis at 6 weeks of age. Groups 1 and 2 received 10 mg/kg EU-Enbrel or GP2015, respectively, as a single IP bolus injection and were sacrificed 72 hours post-dose. Groups 3 and 4 received biweekly IP administration of 10 mg/kg EU-Enbrel or GP2015, respectively, from 6 weeks to 8 weeks of age. In Groups 5-8,

animals received biweekly IP administration from 6 weeks to 10 weeks of age with the following: 10 mg/kg EU-Enbrel (Group 5), 10 mg/kg GP2015 (Group 6), 0 mg/kg (vehicle control; Group 7), and 30 mg/kg EU-Enbrel (Group 8). All animals were sacrificed approximately 3 days after the last dose. One additional group of Tg197 mice (n =4; 2/sex/group) was used as a control for disease status (sacrificed just prior to the first dose administration at 6 weeks of age).

Body weight and in-life arthritic scores (e.g., 0 = no arthritis to 3.0 = heavy arthritis) were recorded weekly from 5 weeks of age until the end of the experiment. Histopathological examination was conducted on the ankle joints and a histopathological score of 0 to 4 was assigned based on severity of disease progression (e.g., 0 = no detectable pathology to 4 = extensive cartilage destruction and bone erosion). Statistical analysis was conducted by a Mann-Whitney (2-tail, 95% CI) analysis.

Results: The mean body weights, arthritic scores, and histological ankle joint scores for each group at the end of each treatment period (i.e., 72 hr post-single bolus dose at 6 weeks of age, biweekly treatments from 6-8 weeks of age, and biweekly treatments from 6-10 weeks of age) are represented in the table below (Table 4). At 6 weeks of age, the untreated Tg197 mice presented with in-life findings of mild arthritis and advanced arthritis-related histopathological findings in the ankle joints.

A statistically significant difference was observed between the single bolus 10 mg/kg EU-Enbrel (Group 1) and single bolus 10 mg/kg GP2015 (Group 2) treatments for the histopathological score at 6 weeks of age. The 10 mg/kg GP2015 group had a 21% greater improvement in histopathological score as compared to the 10 mg/kg EU-Enbrel group at this time point (Group 1 vs Group 2; P=0.0015). There was no difference in body weights or arthritic scores between the single bolus 10 mg/kg EU-Enbrel and GP2015 groups. No other differences were observed between the 10 mg/kg EU-Enbrel and 10 mg/kg GP2015 groups at either Weeks 8 or 10 for any parameter.

The 30 mg/kg EU-Enbrel-treated group (Group 8) had similar improvements in body weight (31%), arthritic score (57%), and histopathological score (57%), compared to vehicle controls (Group 7), as was observed at the same dose in the EU-Enbrel pilot study (Study GP15-004; described above) using comparable EU-Enbrel treatment frequency and duration. There were statistically significant and dose-dependent improvements in arthritic and histopathological scores between the 10 mg/kg EU-Enbrel-treated group (Group 5) and the 30 mg/kg EU-Enbrel-treated group (Group 8), as was also observed at these doses in the pilot study with EU-Enbrel.

Table 4: Summary data from a comparative efficacy study of EU-Enbrel and GP2015 in the Tg197 mouse model of rheumatoid arthritis (Study GP15-007)

Endpoint	Dose Frequency	Group	Treatment	BW (g)	Change in BW (% ctrl)	Arthritic Score (AS)	Change in AS (% ctrl)	Histological Score (HS)	Change in HS (% ctrl)
6 weeks	n/a	6 wk[#]	None	14.1	n/a	1.19	n/a	2.81	n/a
6 weeks; 72 hr post-dose	Single bolus	G1	E: 10 mg/kg	15.48	n/a	0.98	n/a	2.45	n/a
		G2	GP: 10 mg/kg	15.57	n/a	1.01	n/a	1.93[†]	n/a
Week 8	Biweekly; Week 6-8	G3	E: 10 mg/kg	17.24	n/a	0.86	n/a	2.53	n/a
		G4	GP: 10 mg/kg	17.38	n/a	0.84	n/a	2.50	n/a

Endpoint	Dose Frequency	Group	Treatment	BW (g)	Change in BW (% ctrl)	Arthritic Score (AS)	Change in AS (% ctrl)	Histological Score (HS)	Change in HS (% ctrl)
Week 10	Biweekly; Week 6-10	G5	E: 10 mg/kg	18.23*	[17%]	1.04**	[27%]	3.13	[13%]
		G6	GP: 10 mg/kg	18.90*	[21%]	0.90***	[37%]	2.89	[19%]
		G7	Ctrl: 0 mg/kg	15.60	–	1.43	–	3.58	–
		G8	E: 30 mg/kg	20.41**	[31%]	0.61***	[57%]	1.53	[57%]

(E) EU-Enbrel, (GP) GP2015, (Ctrl) Vehicle Control, (n/a) Not Applicable
[#]Untreated Tg197 control mice (n = 2/sex) used for assessing baseline disease status
[†]P=0.0015, relative to mean 10 mg/kg EU-Enbrel values (Group 2) at Week 6
*P<0.05, **P<0.01, ***P<0.0001, relative to mean vehicle control values at Week 10
Note: Change in AS and HS represents the improvement in scores relative to vehicle controls at Week 10.

Conclusions: In the Tg197 mouse model of rheumatoid arthritis, no differences in efficacy were observed between EU-Enbrel and GP2015 treatment, at a biweekly dose of 10 mg/kg for 2 or 4 weeks (i.e., 8 or 10 week of age), when treatment was initiated at 6 weeks of age. After a single bolus IP administration of 10 mg/kg EU-Enbrel or GP2015, a statistically significant difference was noted between these groups for histopathological ankle score, with the 10 mg/kg GP2015 treatment resulting in a 21% improvement over the score of the EU-Enbrel-treated animals. The significance of this slightly enhanced histological score after a single administration of GP2015 is not clear at this time and was not observed with biweekly treatment for 2-4 weeks.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Two GLP pharmacokinetic (PK) and local tolerance studies were conducted in rabbits with single subcutaneous doses of GP2015 in varying formulations compared to EU-Enbrel. These studies are summarized below (Studies GP15-001 and GP15-006).

GP15-001: Comparative pharmacokinetic study of two qualities of Enbrel® and five formulations of GP2015 following single subcutaneous administration to rabbits

Objective: To compare the PK and local tolerance of five formulations of a GP2015 compared to two qualities of EU-Enbrel following a single subcutaneous administration to rabbits.

Methods: In the GLP pilot study (GP15-001), male Himalayan rabbits (n = 10/group) received a single SC administration of 8 mg/kg GP2015 or EU-Enbrel into the back region of the animal. The sponsor noted that since the beginning of 2009, a change in product quality of US-Enbrel and EU-Enbrel has been observed (discussed in IND Item 8: Nonclinical Summary 3.3.1, referencing IND Item 7, 4.2.1.S.3, Appendix 1, Chapter 2.2). Therefore, batches of two qualities of EU-Enbrel (referred to as 'pre-shift' and 'post-shift' material) were tested in this pilot PK study. The different GP2015 formulations tested contained the identical components to the originator-like formulation, with the exception of the indicated buffer salts (citrate or (b) (4)) and amino acids (lysine or (b) (4)) that were exchanged from the phosphate/arginine used in the marketed Enbrel. Groups, GP2015 formulations, EU-Enbrel qualities, and batch

numbers are presented in Table 5 below. Body weights were recorded at group randomization, on treatment administration day, and at the termination of the experiment. Body temperature was recorded from 2 animals/group at pre-dose and 6, 24, 30, and 48 hours post-dose. Blood samples were collected pre-dose, at 2, 6, 12, 18, 24, 32, 48 hours post-dose, and on Days 4, 6, and 8, and were used for the determination of serum concentrations of etanercept by ELISA.

Table 5: Experimental groups and formulations from a pilot single SC dose comparative PK and local tolerance study of GP2015 and EU-Enbrel in male rabbits (Study GP15-001)

Group	Test Article	Quality/Formulation	Dose Volume	Batch No.
1	EU-Enbrel	"new quality" / 'post-shift', originator formulation	0.16 mL/kg	E51371
2	EU-Enbrel	"old quality" / 'pre-shift', originator formulation	0.32 mL/kg (Note: Test item was reconstituted)	33569
3	GP2015	Originator-like formulation	0.16 mL/kg	1030ML220_5
4	GP2015	50 mM citrate/25 mM lysine	0.16 mL/kg	1030ML220_1
5	GP2015	(b) (4) mM citrate/lysine	0.16 mL/kg	1030ML220_2
6	GP2015	mM citrate (b) (4)	0.16 mL/kg	1030ML220_3
7	GP2015	mM (b) (4) /lysine	0.16 mL/kg	1030ML220_4

Results: There were no deaths, changes in clinical signs, or local injection site reactions after administration of any of the GP2015 formulations or either EU-Enbrel qualities. There were no treatment-related changes in body weight or body temperature at any time point examined.

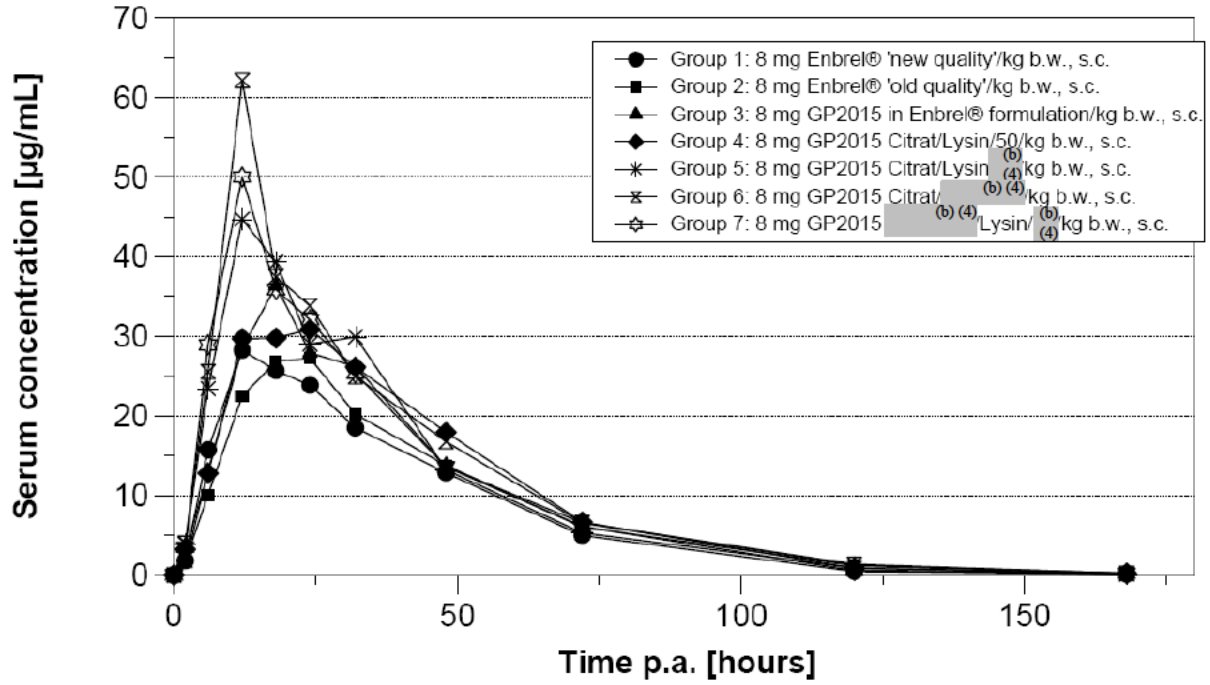
PK parameters are presented in tabular (Table 6) and graphical (Figure 2; excerpted from the sponsor's submission) formats below. The C_{max} and AUC values for the groups treated with GP2015 in (b) (4) mM citrate/lysine (Group 5), (b) (4) mM citrate/ (b) (4) (Group 6), or in (b) (4) mM (b) (4) /lysine (Group 7) was slightly higher than the C_{max} and AUC values for the groups treated with EU-Enbrel 'post-shift' (Group 1) or GP2015 in originator-like formulation (Group 3). The t_{max} values for these same GP2015 formulation groups (i.e., 5,6, and 7) were lower than the t_{max} values for the groups treated with 'post-shift' Enbrel (Group 1) and GP2015 in originator-like formulation (Group 3) or in 50 mM citrate/25 mM lysine (Group 4).

Table 6: Mean PK parameters from a pilot single-dose PK comparison study of GP2015 and EU-Enbrel in male rabbits (Study GP15-001)

Group	C_{max}		t_{max}		$t_{1/2}$		$AUC_{0\text{-}168\ h}$	
	(µg/mL)	R	(h)	R	(h)	R	(µg*h/mL)	R
1) EU-Enbrel new quality/post-shift	32.43 ± 13.51	– –	19.80 ± 5.51	– –	17.69 ± 2.09	– –	1255.72 ± 394.30	– –
2) EU-Enbrel old quality/pre-shift	29.97 ± 13.46	0.92#2 –	20.40 ± 4.20	1.03#2 –	19.86 ± 3.84	1.12#2 –	1337.82 ± 434.24	1.07#2 –
3) GP2015 in originator formulation	38.82 ± 23.97	1.20#2 –	19.40 ± 5.97	0.98#2 –	19.03 ± 2.69	1.08#2 –	1538.91 ± 568.72	1.23#2 –
4) GP2015 Citrat/Lysin/50	38.73 ± 13.73	1.19#2 1.00#3	21.20 ± 11.6	1.07#2 1.09#3	16.86 ± 2.86	0.95#2 0.89#3	1603.17 ± 504.85	1.28#2 1.04#3
5) GP2015 Citrat/Lysin/(b) (4)	46.86 ± 10.49	1.44#2 1.21#3	16.40 ± 6.24	0.83#2 0.85#3	16.14 ± 2.45	0.91#2 0.85#3	1693.35 ± 305.88	1.35#2 1.10#3
6) GP2015 Citrat/(b) (4)	65.42 ± 50.96	2.02#2 1.69#3	12.00 ± 2.83	0.61#2 0.62#3	18.48 ± 2.22	1.04#2 0.97#3	1912.41 ± 680.80	1.52#2 1.24#3
7) GP2015 (b) (4)/Lysin(b) (4)	50.38 ± 11.42	1.55#2 1.30#3	12.60 ± 1.90	0.64#2 0.65#3	17.32 ± 1.54	0.98#2 0.91#3	1719.09 ± 318.00	1.37#2 1.11#3

(): ±SD; R: Ratio of means; #2: Comparison to Group 1, #3: Comparison to Group 3

Figure 2: Mean serum levels of etanercept in male rabbits treated with GP2015 or EU-Enbrel in a pilot single-dose PK comparison study (Study GP15-001)



Conclusion: After a single 8 mg/kg subcutaneous administration of five GP2015 formulations or 2 qualities of EU-Enbrel, there were no clinical signs or signs of local intolerance in male rabbits. No major differences in PK parameters were observed between 'pre-shift' (old quality) and 'post-shift' (new quality) EU-Enbrel. Of the five tested GP2015 formulations, the PK parameters of GP2015 in the originator-like

formulation and GP2015 in 50 mM citrate/25 mM lysine were the most similar to both EU-Enbrel-treated groups.

GP15-006: Comparative single s.c. dose pharmacokinetic study in rabbits on GP2015 (GMP DS) in 50 mM Citrate/Lysine formulation and GP2015 (GMP DS) in originator-like formulation vs. Enbrel®

Objective: To compare the PK and local tolerance of two formulations of a GP2015 compared to EU-Enbrel following a single subcutaneous administration to rabbits.

Methods: In this GLP study (GP15-006), male Himalayan rabbits (n = 20/group) received one single SC administration of 8 mg/kg GP2015 or EU-Enbrel into the back region of the animal. Groups and batch numbers are presented in Table 7 below. In group 2, the GP2015 formulation contained the identical components to the originator-like formulation, with the exception of the indicated buffer salt (citrate) and amino acid (lysine) that was exchanged from the phosphate/arginine used in the marketed Enbrel. Clinical signs (e.g., behavioral changes, reaction to treatment, or illness) were observed individually before and after dosing and cage-side observations were performed regularly until the termination of the experiment, with special attention paid to the injection site. Body weights were recorded at group randomization, on treatment administration day, and at experiment termination. Blood samples were collected pre-dose, at 2, 6, 12, 18, 24 hours post-dose, and on Days 3, 4, 5, 6, and 8 post-dose, and were used for the determination of serum concentrations of etanercept by ELISA.

Table 7: Experimental groups from a single SC dose comparative PK and local tolerance study of GP2015 and EU-Enbrel in rabbits (Study GP15-006)

Group	Test Article (50 mg/mL)	Quality/Formulation	Dose Volume	Batch No.
1	EU-Enbrel	"new quality" / 'post-shift', originator formulation	0.16 mL/kg	E51371
2	GP2015	50 mM Citrate Lysine	0.16 mL/kg	1049ML234_1
3	GP2015	Originator-like formulation	0.16 mL/kg	1049ML234_2

Study Deviation: It was noted that the analytical report for EU-Enbrel presenting the actual protein content was not available at the time of issuance of the final report, however this was added in an amendment and a dose correction for the PK parameters C_{max}, $AUC_{0\text{-}168h}$ and $AUC_{0\text{-}inf}$ was conducted. This deviation did not alter the overall outcome of the study results as the difference between nominal and actual protein content was minimal. Dose corrected PK parameters are given below (Table 8).

Results: There were no deaths, changes in clinical signs, body weight, or local injection site reactions after administration of either GP2015 formulation or EU-Enbrel.

Mean PK parameters are presented in Table 8 and Figure 3 (excerpted from the sponsor's submission) below. There were no statistical differences in C_{max}, half-life, and AUC values between the two GP2015 formulations and EU-Enbrel. The t_{max} value for the animals given GP2015 in originator-like formulation (Group 3) was increased by 20% ($P \leq 0.05$) compared to the EU-Enbrel group (Group 1). A small, but non-statistically significant increase (~12%) in t_{max} values was also noted between the animals given GP2015 in 50 mM citrate/25 mM lysine formulation (Group 2) and EU-

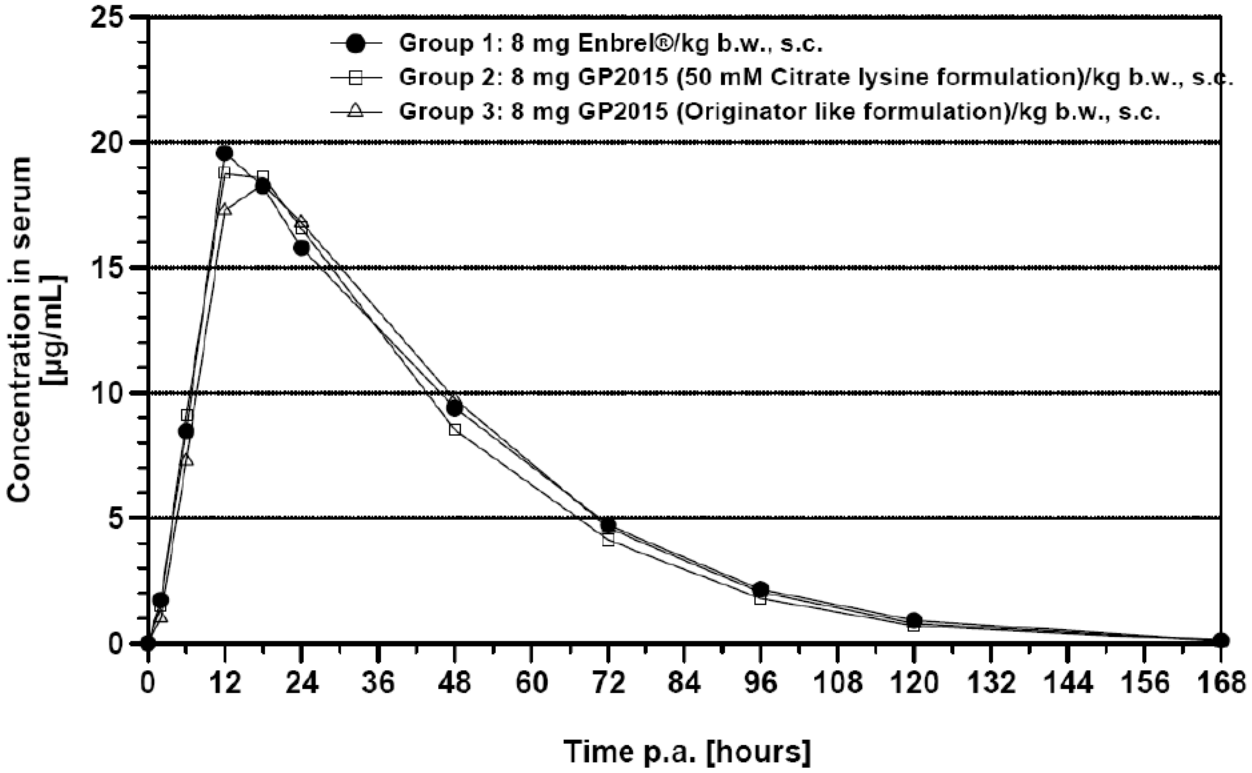
Enbrel (Group 1). The PK ratios were similar for both the GP2015 in 50 mM citrate/25 mM lysine formulation and GP2015 in originator-like formulation, in comparison to the EU-Enbrel group.

Table 8: Mean PK parameters from a single-dose PK comparison study of GP2015 and EU-Enbrel in rabbits (Study GP15-006)

Group	C_{max}		t_{max}		$t_{1/2}$		$AUC_{0\text{-}168\ h}$	
	µg/mL)	R	(h)	R	(h)	R	(µg*h/mL)	R
1) Enbrel new quality/post-shift	20.62 ± 10.22	–	14.70 ± 3.06	–	19.56 ± 2.11	–	937.31 ± 319.46	–
2) GP2015 50 mM Citrate Lysine	20.22 ± 6.70	0.98	16.50 ± 4.30	1.12	18.80 ± 1.47	0.96	896.98 ± 217.67	0.96
3) GP2015 originator formulation	19.18 ± 4.94	0.93	17.70 ± 4.12	1.20	18.73 ± 1.92	0.96	929.56 ± 207.66	0.99

(): ±SD; R: Ratio of means; Comparison to group 1

Figure 3: Mean serum concentrations of etanercept in male rabbits after a single SC dose of GP2015 or EU-Enbrel (Study GP15-006)



Conclusion: After a single 8 mg/kg subcutaneous administration of two GP2015 formulations and EU-Enbrel, there were no clinical signs or signs of local intolerance in male rabbits. The animals treated with GP2015 in the originator-like formulation had a slightly longer time to maximum serum concentration (t_{max}) than the EU-Enbrel-treated animals. In general, no major differences in PK parameters were noted between the two GP2015 formulation and EU-Enbrel.

6 General Toxicology

6.2 Repeat-Dose Toxicity

Study title: GP2015 and Enbrel®: Comparative Toxicity Study in the Cynomolgus Monkey with Subcutaneous Administration over 28 Days

Study no.:	GP15-003, GP15-003-BA11012 (TK Report), GP15-003-BA11012 (Immunogenicity Report)
Study report location:	Electronic Submission
Conducting laboratory and location:	(b) (4)
Date of study initiation:	March 23, 2011
GLP compliance:	Yes, United Kingdom GLP (signed May 5, 2015)
QA statement:	Yes (signed May 5, 2015)
Drug, lot #, and % purity:	GP2015 (Batch: DS lot; 1049ML234_1, DP lot; B056401 (Nonclinical Summary; Same as used in Clinical Protocols GP15-101 and GP15-102); Purity: 97.9% / 49.85 mg/mL) EU-Enbrel® (Batch: E88057; Purity: 94.6% / 51.61 mg/mL) Note: Dose formulations were supplied ready to use in sealed glass vials to (b) (4). The study report states that formulation analysis was not required to confirm the initial concentrations.

Key Study Findings

- Cynomolgus monkeys received 0 mg/kg (vehicle: GP2015 Placebo), 15 mg/kg GP2015, or 15 mg/kg Etanercept (EU-Enbrel) once every 3 days for 28 days.
- No treatment-related effects on mortality, body weight, food consumption, ophthalmic exams, ECG, urinalysis, or macroscopic findings were observed.
- Injection site reactions (i.e., erythema/rash; moderate to severe) were observed after the 9th injection in one GP2015-treated male (Animal No. 5M) and two EU-Enbrel-treated males (Animals No. 7M and 8M). Reactions resolved before the termination of the study on Day32, except for a slight erythema in Animal No. 8M.
- Hematology findings in GP2015- and EU-Enbrel-treated males occurred largely on Days 29-32, and included increased WBCs and absolute and relative reticulocytes, lymphocytes, monocytes and LUCs, and decreased absolute and relative neutrophils. Platelets were decreased on Days 22 [GP2015 males only] and 29 and increased on Days 31-32. Platelet crit was also increased on Days 31-32. The changes in group means for the GP2015- and EU-Enbrel-treated males were largely influenced by the changes observed in the individual animals with injection site reactions (i.e., Animal Nos. 5M, 7M and 8M). Hematology

changes in females on Day 22 included increased reticulocytes, monocytes, and LUC in the GP2015-treated group and increased absolute LUC in the EU-Enbrel-treated group.

- The GP2015 male with fever and injection site reactions (5M) had changes (as compared to its pre-treatment values) in the following clinical chemistry parameters, that correlated with the onset of the symptoms on Day 26: increased AST (+190%), ALT (+113%), ALP (+40.5%), and total bilirubin (+430%) and decreased GGT (-45.5%), sodium (-5%), potassium (-16%), chloride (-5%), calcium (-10.4%), albumin (-31%), AG ratio (-46%), and glucose (-57.5%).
- IgM levels were elevated in all GP2015 males (+126%), notably Animal No.4 (+375%), and in two EU-Enbrel-treated males (7M; +59% and 9M; +77.5%), as compared to controls. IgG levels were elevated in EU-Enbrel-treated male 8M (+49.8% vs control group mean).
- Microscopic findings in GP2015- and EU-Enbrel-treated animals included inflammatory lesions (hyperkeratosis, dermatitis, myositis, and cellulitis) in injection sites, as well as minimal cortical eosinophilia/hypertrophy of the adrenal gland, as compared to controls. The incidence of injection site myositis and cellulitis was increased in GP2015 animals compared to EU-Enbrel animals.
- On Days 1 and 7, systemic exposure to GP2015 was similar in animals (males and females) receiving 15 mg/kg GP2015 or EU-Enbrel. On Day 28, systemic exposure decreased in all drug-treated groups and systemic exposure was 2.2-fold higher in GP2015-treated males compared to females. The decrease in systemic exposure and gender difference in the GP2015 groups on Day 28 are likely due to the presence of ADAs, though this was not confirmed with ADA data.
- Etanercept-specific ADAs were confirmed in two GP2015 females (13F and 14F), and 2 EU-Enbrel animals (8M and 16F). Levels of etanercept in serum may have interfered with the detection of anti-etanercept antibodies leading to false negative ADA results for other GP2015- and EU-Enbrel-treated animals.

Methods

Doses:	0 (vehicle matching GP2015), 15 mg/kg GP2015, 15 mg/kg EU-Enbrel® (Etanercept)
Frequency of dosing:	Once every 3 days for 28 days on Days 1, 4, 7, 10, 13, 16, 19, 22, 25, and 28
Route of administration:	Subcutaneous injection; Four injection sites (IJ) in the dorsal thoracic region were used (left anterior [IJ1], right anterior [IJ2], left posterior [IJ3], right posterior [IJ4]). Each injection site was used in turn.
Dose volume:	0.3 mL/kg; Loaded syringes were weighed prior to dosing and on completion of dosing of each animal. The study report states that administered volumes of each test article were within the range 99% to 108% of the expected volumes based on the assumption that 1 ml of formulation weighs 1 g.
Formulation/Vehicle:	GP2015 placebo buffer: citrate/lysine/50 formulation (50 mM citrate/25 mM lysine), sponsor states in the Nonclinical Summary (IND Item 8: Section 4.4) that the formulation contained the following excipients: citric acid (b) (4), L-lysine HCl, sodium chloride, (b) (4), and water for injection, which is the intended clinical formulation. Study report did not contain a detailed description of the formulation. This will be requested in a non-hold comment.
Species/Strain:	*Macaca fascicularis* / Cynomolgus monkey
Number/Sex/Group:	3/sex/group
Age:	143-218 weeks at treatment initiation
Weight:	Males: 4.62-6.71 kg and Females: 3.8-5.12 kg at treatment initiation
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	Deviations from the protocol did not adversely affect study outcome or data interpretation

Observations and Results

Mortality

Animals were examined for mortality and moribundity twice daily, in the morning and evening.

All animals survived until the scheduled necropsies at the termination of the dosing phase.

Clinical Signs

On non-dosing days, detailed observations of clinical signs were recorded daily. On dosing days 1, 4, 7, 10, 13, and 16, clinical signs were observed twice, at 6 and 24 hr post-dose. Due to the lack of signs seen previously, the 6 hour observations on Days 19, 22 and 25 were performed approximately 4 hours post-dose. On Day 28, when rashes first occurred in EU-Enbrel-treated animals, observations were recorded at 6 hours after dosing. Injections sites were observed once daily and scored via a modified Draize scale. Detailed physical examinations were also performed once daily throughout the study.

Injection site reactions were noted in male animals of both treatment groups, as presented in Table 9. These reactions were also documented as a clinical observation of rash (on days noted in Table 9). One GP2015-treated male (5M) displayed moderate to severe erythema of injection site 1 on Days 26-29 and slight erythema of injection site 1 on Days 30-31. Additionally, on Day 27, erythematous blotches were seen in the inguinal and abdomen region (right side) and these blotches displayed ecchymosis (extravasation of blood into the subcutaneous tissue). The rash at injection site 1 spread to involve a large area between dosing sites 1 and 3. On Day 29, the erythema correlated with the clinical sign of abdominal rash. Clinical observation of rash was also noted on Days 28-30 on the right hind limb of this animal. The erythema and rashes resolved in this animal on Day 32.

Two EU-Enbrel-treated males (7M and 8M) displayed slight to severe erythema of several injection sites starting on Day 28. Animal No. 7M experienced symptoms on Days 28-29, and Animal No. 8M experienced symptoms on Days 28-32.

No other treatment-related changes in clinical signs were observed following administration of GP2015 or EU-Enbrel.

Table 9: Summary of injection site reactions and clinical signs in monkeys administered subcutaneous GP2015 or Enbrel

Animal	Day 26	Day 27	Day 28	Day 29	Day 30	Day 31	Day 32 (necropsy)
5M Male GP2015	**IJ1: Rash** Moderate/ severe erythema	**IJ1: Rash** Moderate/ severe erythema	**IJ1: Rash*** Moderate/ severe erythema	**IJ1: Rash*** Well defined erythema	**IJ1: Rash*** Slight erythema	**IJ1: Rash** Slight erythema	
7M Male Enbrel			**IJ1: Rash** Moderate/ severe erythema **IJ4: Rash** Slight Erythema	**IJ1: Rash** Slight erythema **IJ4: Rash** No Erythema			

8M Male Enbrel			**IJ1: Rash** Well defined erythema **IJ2: Rash** Well defined erythema **IJ3: Rash** Slight erythema **IJ4** Slight Erythema	**IJ1: Rash** Slight erythema **IJ2: Rash** Well defined erythema **IJ3: Rash** Slight erythema	**IJ2: Rash** Slight erythema **IJ4** Slight erythema	**IJ2: Rash** Well defined erythema	**IJ1: Rash** Slight erythema **IJ2: Rash** No erythema

(IJ) Injection Site Number, * On Days 28-30, 5M also had erythematous blotches in the inguinal and abdomen region (right side), which displayed ecchymosis, and rashes on the right hind limb.

Body Weights

Body weights were recorded on Day -9, each day of dosing, and at necropsy.

No treatment-related changes in body weight were observed following administration of GP2015 or Enbrel.

Feed Consumption

Food consumption for each animal was measured qualitatively by daily visual monitoring.

The study report did not contain data or summary information for the qualitative food consumption monitoring. However, since there were no treatment-related changes in body weight or body weight gain for either GP2015- or EU-Enbrel-treated groups, it is unlikely food consumption was greatly affected by treatment.

Ophthalmoscopy

Ophthalmic exams were performed on all animals pre-treatment and in Week 4. A mydriatic agent was instilled into the eyes before examinations.

No treatment-related ophthalmic changes were noted following administration of GP2015 or EU-Enbrel.

ECG

ECG, heart rate, and blood pressure recordings were performed on all animals pre-treatment and 23 to 25 hours post-dosing on Days 5 and 26. ECG tracing were recorded using fixed limb leads I, II, and III, and the augmented leads aVR, aVL, and aVF. Heart rate (in BPM) was quantitatively measured from lead II. Qualitative assessment for rhythm and wave abnormalities was performed and reported. Systolic, diastolic, and mean arterial blood pressure were measured by indirect high definition oscillometry (HDO) blood pressure monitor.

The study report states that qualitative assessment of the ECG tracings did not indicate any abnormalities and no data were presented in the report. This data will be requested

in a non-hold comment for review. There were no treatment-related changes in heart rate or blood pressure with administration of GP2015 or EU-Enbrel.

Body temperatures were recorded pre-treatment and between 23 and 25 hours post-dosing on Days 5 and 26 on all animals. Additional body temperatures were taken from Animal No. 5 (GP2015-treated male) on Days 27 and 28, due to being warm to the touch when handled, and on Day 29 until necropsy for all male animals, due to rash development in some male animals.

The body temperature of one GP2015-treated male (5M) was found to be slightly elevated above the normal range (37-40°C) on Day 26 (40.1°C) and Day 27 (40.1, 40.2, 40.4°C). This correlated with the injection site reactions and rashes observed in this animal.

Hematology

Blood samples (~0.5 mL each for hematology and coagulation parameters) were collected, after an overnight fast, from the femoral vein or artery from all animals pre-treatment (Week -1) and on Day 22. Additional blood samples were collected from Animal No. 5M on Day 28, due to elevated temperature, and all male animals on Day 29, 31, and 32, due to the appearance of rashes. An adequate battery of hematology parameters was examined.

Changes in group mean hematology parameters compared to controls are presented in Table 10. Hematology changes in individual animals with injection site reactions compared to the control group means or compared to the last individual analysis for that parameter before the onset of the change are presented in Table 11.

For many parameters, the mean pre-dose values (i.e., Week -1) varied largely from the mean control values. However, taking the pre-dosing changes from controls and small sample size (i.e., n = 3/sex/group) into account, several parameters still indicated potential treatment-related changes in both the GP2015 and EU-Enbrel groups, especially for males on Days 29-32.

For GP2015- and EU-Enbrel-treated males, several changes in hematology parameters were observed on Days 29-32, and also on Day 28 for the GP2015-treated male with the slight fever and injection site reactions (5M). These included increased WBCs and absolute and relative reticulocytes, lymphocytes, monocytes and LUCs, and decreased absolute and relative neutrophils. Platelets were decreased on Days 22 [GP2015 males] and 29 and increased on Days 31-32. Platelet crit was also increased on Days 31-32. However, the changes in group means for the GP2015- and Enbrel-treated males were largely influenced by the changes observed in the individual animals with injection site reactions (i.e., Animal Nos. 5M, 7M and 8M), as shown in Table 11. The GP2015-treated male with the slight fever and injection sites reactions (5M) also had decreased hemoglobin and RBCs on Day 28 as compared to its individual values on Day 22 and relative to the vehicle control group means on Day 29-32 (~ -27%). This animal also had increased prothrombin time and activated partial thromboplastin time on Day 28. One of the EU-Enbrel-treated males with injection site reactions (8M) also had increased prothrombin time on Day 28.

On Day 22, LUCs were increased in females of both GP2015- and EU-Enbrel-treated groups. On Day 22, GP2015 females also had increased absolute and relative reticulocytes and monocytes, and EU-Enbrel females had increased absolute neutrophils.

Table 10: % Change in mean hematology parameters in GP2015 or Enbrel-treated cynomolgus monkeys compared to controls

Hematology Parameter	Timepoint[#]	Males		Females	
		GP2015 15 mg/kg	Enbrel 15 mg/kg	GP2015 15 mg/kg	Enbrel 15 mg/kg
Reticulocytes (Abs)	Week -1	-36%	-11%	+28%	+17%
	Day 22	-38%	-13%	+52%	-26%
	Day 29	-12%	-22%	–	–
	Day 31	+11%	+12%	–	–
	Day 32	+52%	+38%	–	–
Reticulocytes (%)	Week -1	-40%	-20%	+20%	0%
	Day 22	-36%	-14%	+50%	-31%
	Day 29	0%	-15%	–	–
	Day 31	+25%	+33%	–	–
	Day 32	+73%	+40%	–	–
Platelets	Week -1	+4%	+20%	17%	5%
	Day 22	-19%	0%	17%	22%
	Day 29	-23%	-25%	–	–
	Day 31	+27%	+24%	–	–
	Day 32	+33%	+46%	–	–
Platelet Crit (%)	Week -1	+13%	+16%	0%	3%
	Day 22	-18%	0%	0%	18%
	Day 29	-9%	-19%	–	–
	Day 31	+31%	+26%	–	–
	Day 32	+40%	+46%	–	–
WBC (Abs)	Week -1	+59%	+23%	4%	9%
	Day 22	-6%	3%	1%	29%
	Day 29	+37%	-1%	–	–
	Day 31	+34%	+32%	–	–
	Day 32	+33%	+43%	–	–
Neutrophils (Abs)	Week -1	+66%	-8%	41%	63%
	Day 22	-14%	+8%	18%	80%
	Day 29	-31%	-33%	–	–
	Day 31	+4%	+6%	–	–
	Day 32	+3%	+35%	–	–
Lymphocytes (Abs)	Week -1	+44%	+53%	-21%	-23%
	Day 22	+3%	-5%	-25%	-17%
	Day 29	+98%	+15%	–	–
	Day 31	+65%	+50%	–	–
	Day 32	+84%	+53%	–	–
Monocytes (Abs)	Week -1	+75%	+75%	+50%	0%
	Day 22	+25%	+50%	+100%	+25%
	Day 29	+50%	+150%	–	–

Hematology Parameter	Timepoint[#]	Males		Females	
		GP2015 15 mg/kg	Enbrel 15 mg/kg	GP2015 15 mg/kg	Enbrel 15 mg/kg
	Day 31	+50%	+100%	–	–
	Day 32	+25%	+75%	–	–
LUCs (Abs)	Week -1	+200%	+100%	0%	0%
	Day 22	0%	+100%	+200%	+100%
	Day 29	+700%	+200%	–	–
	Day 31	+100%	+100%	–	–
	Day 32	+100%	+200%	–	–
Neutrophils (%)	Week -1	-2%	-22%	33%	44%
	Day 22	-2%	0%	13%	39%
	Day 29	-49%	-53%	–	–
	Day 31	-23%	-29%	–	–
	Day 32	-22%	-12%	–	–
Lymphocytes (%)	Week -1	-2%	18%	-22%	-24%
	Day 22	-3%	-5%	-25%	-34%
	Day 29	+40%	+36%	–	–
	Day 31	+24%	+22%	–	–
	Day 32	+37%	+14%	–	–
Monocytes (%)	Week -1	0%	+25%	+25%	-25%
	Day 22	+25%	+50%	+100%	0%
	Day 29	+25%	+200%	–	–
	Day 31	-20%	+60%	–	–
	Day 32	-25%	25%	–	–
LUCs (Abs)	Week -1	+100%	0%	0%	0%
	Day 22	0%	+100%	+200%	0%
	Day 29	+500%	+400%	–	–
	Day 31	+100%	+100%	–	–
	Day 32	0%	+100%	–	–

[#]Blood samples collected from all animals on Week -1 (pre-treatment) and Day 22; Blood samples were only collected from males on Days 29-32

Table 11: % Change in individual hematology parameters for GP2015- and Enbrel-treated males with injection site reactions compared to control means or compared to last individual analysis before the event

Hematology/ Coagulation Parameter	Animal No./Sex and Treatment	% Change compared to mean control values	% Change compared to last analysis (individual animal) prior to start of event
Hemoglobin		Day 28	Day 28 vs Day 22
	5M (GP2015)	n/a	-26%
RBC (Abs)		Day 28	Day 28 vs Day 22
	5M (GP2015)	n/a	-23%
Reticulocytes (Abs)		Day 32	Day 32 vs Day 31
	5M (GP2015)	+185%	+136%

Hematology/ Coagulation Parameter	Animal No./Sex and Treatment	% Change compared to mean control values	% Change compared to last analysis (individual animal) prior to start of event
	7M (Enbrel)	+89%	+72%
	8M (Enbrel)	+19%	+35%
Reticulocytes (%)		Day 32	Day 32 vs Day 31
	5M (GP2015)	+260%	+125%
	7M (Enbrel)	+100%	+67%
	8M (Enbrel)	+33%	+33%
Platelets		Day 29	Day 29 vs Wk -1
	5M (GP2015)	-42%	-40%
	7M (Enbrel)	-31%	-34%
	8M (Enbrel)	-50%	-50%
Neutrophils		Day 29	Day 29 vs Day 22
	5M (GP2015)	-77%	-85%
	7M (Enbrel)	-94%	-88%
	8M (Enbrel)	-81%	-85%
Lymphocytes		Day 29	Day 29 vs Day 22
	5M (GP2015)	+138%	+265%
Basophils		Day 29	Day 29 vs Day 22
	5M (GP2015)	NC (mean = 0)	+300%
Monocytes		Day 29	Day 29 vs Day 22
	8M (Enbrel)	+350%	+125%
LUCs		Day 29	Day 29 vs Day 22
	5M (GP2015)	+2000%	+950%
	8M (Enbrel)	+600%	+250%
Prothrombin time		Day 28	Day 28 vs Day 22
	5M (GP2015)	n/a	+13%
		Day 29	Day 29 vs Day 22
	8M (Enbrel)	+28%	+22%
Activated partial thromboplastin time		Day 28	Day 28 vs Day 22
	5M (GP2015)	n/a	+78%

(n/a) Not applicable, no blood samples collected from male control animals on Day 28 for comparison
(NC) Not calculated due to control value being zero

Clinical Chemistry

Blood samples (~0.6 mL) were collected, after an overnight fast, from the femoral vein or artery from all animals pre-treatment and on Day 22. Additional blood samples were collected from Animal No. 5M on Day 28, due to elevated temperature, and all male animals on Day 29, 31, and 32, due to the appearance of rashes, and from animals 3M (Control; Days 26 and 29), 5M (GP2015; Day 26) and 9M (EU-Enbrel; Days 26, 27 and 29), due to hemolysed samples or insufficient sample volume for analysis. Serum samples (0.2 mL) obtained from males on the day of necropsy were analyzed for the level of immunoglobulins, IgG, IgM, and IgE. An adequate battery of clinical chemistry parameters was examined.

On Day 26, elevations in aspartate aminotransferase (+190%), alanine aminotransferase (+113%), alkaline phosphatase (+40.5%), and total bilirubin (+430%) were seen in the GP2015 male with fever and injection site reactions (5M) as compared to its pre-treatment values. In addition, this animal showed decreases in gamma glutayltransferase (-45.5%), sodium (-5%), potassium (-16%), chloride (-5%), calcium (-10.4%), albumin (-31%), AG ratio (-46%), and glucose (-57.5%) as compared to its pre-treatment values. Elevated total bilirubin was also observed in one EU-Enbrel-treated male (9M) on Day 29 (+135%) and another GP2015-treated male (6M) on Day 22 (+140%), in addition to 5M, as compared to pre-treatment values.

All IgE levels, including controls, were below the level of detection. In comparison to the vehicle controls, IgM levels were elevated in all GP2015 males (+126%), notably Animal No.4 (+375%), and in two EU-Enbrel-treated males (7M; +59% and 9M; +77.5%). In comparison to the range of individual control values, IgG levels were elevated in EU-Enbrel-treated male 8M (+49.8% vs control group mean).

Urinalysis

Urine samples were collected via quick catch from all animals pre-treatment and in Week 4. During urine collection, food was not offered and water was removed. An adequate battery of urinalysis parameters was examined.

No treatment-related changes in urinalysis parameters were noted with either GP2015 or EU-Enbrel.

Gross Pathology

Necropsies were performed 3 days after the last dose administration. All animals were given a ketamine sedative followed by an intravenous overdose of sodium pentobarbitone. Once death had been confirmed, the animal was exsanguinated. A full macroscopic examination was performed under the general supervision of the study pathologist and all lesions were recorded.

No treatment-related changes in macroscopic findings were noted with either GP2015 or EU-Enbrel.

Organ Weights

The following organs were weighed: adrenals, brain, heart, kidneys, liver, lungs, ovaries, pituitary, prostate, spleen, testes with epididymides, thyroids with parathyroids, uterus including cervix. Bilateral organs were weighed together. Organ weights relative to terminal body weight were also calculated.

Mean organ weight changes, as compared to controls, are presented in Table 12 below. Increased adrenal gland and spleen weights were observed in certain animals in the GP2015- and EU-Enbrel-treated groups compared to vehicle controls, which resulted in higher group means for these organs. Adrenal gland weight was increased by 109% in 1/3 EU-Enbrel-treated males (9M) and by approximately 31.5% in 2/3 EU-Enbrel-treated females (16F and 17F). Spleen weight was increased in 1/3 GP2015-treated males (5M: +99%), 2/3 EU-Enbrel-treated males (7M: +58%; 8M: +145%), and 1/3 EU-Enbrel-treated females (16F: +47%). Variability in organ weight was noted for other organs in both treatment groups (i.e., kidneys, thyroid/parathyroid, and pituitary); however, the

absolute individual animal values fell within the variation range of the vehicle control-treated animals and there were no correlating histopathological findings in these organs; therefore these changes do not appear to be treatment-related. Ovary weight was increased by 40% in EU-Enbrel-treated females, but not in GP2015-treated females. There were no correlating macroscopic or microscopic finding in the ovaries of this group and all females in this study were documented as mature, so the significance of this finding is unclear.

Table 12: % Change in mean organ weights in GP2015 or Enbrel-treated cynomolgus monkeys compared to controls

	Males			Females		
Organ	**Control** 0 mg/kg	**GP2015** 15 mg/kg	**Enbrel** 15 mg/kg	**Control** 0 mg/kg	**GP2015** 15 mg/kg	**Enbrel** 15 mg/kg
Adrenals (g)	0.712±0.11	0.751±0.03	0.971±0.03	0.712±0.06	0.751±0.06	0.795±0.25
% ctrl	–	5%	36%	–	nc	12%
% BW	–	14%	42%	–	nc	6%
Spleen (g)	7.99±1.7	11.4±3.9	13.8±5.3	8.29±2.7	10.1±0.1	9.78±3.2
% ctrl	–	43%	73%	–	22%	18%
% BW	–	57%	86%	–	12%	16%
Kidneys (g)	17.8±4.3	20.9±4.3	20.5±0.5	14.6±0.7	17.9±2.3	16.9±2.0
% ctrl	–	17%	15%	–	23%	16%
% BW	–	27%	23%	–	11%	12%
Pituitary (g)	0.090±0.03	0.080±0.01	0.074±0.01	0.082±0.02	0.060±0.02	0.063±0.02
% ctrl	–	-12%	-18%	–	-26%	-23%
% BW	–	nc	-13%	–	-35%	-30%
Thyroid/ Parathyroid (g)	0.707±0.05	0.719±0.13	0.442±0.08	0.349±0.21	0.526±0.25	0.481±0.10
% ctrl	–	nc	-38%	–	51%	38%
% BW	–	nc	-35%	–	46%	40%
Ovaries (g)	n/a	n/a	n/a	0.451±0.03	0.431±0.20	0.631±0.07
% ctrl				–	nc	40%
% BW				–	nc	34%

(nc) No appreciable change from control, (n/a) Not applicable

Histopathology

Adequate Battery: The following tissues were fixed in 10 % neutral buffer formalin (with the exception of eyes/optic nerve and testes, which were fixed in Davidson's fluid and Bouin's fixative, respectively): Adrenals, aorta, brain, cecum, colon, dosing sites, duodenum, eyes with optic nerves, femur (with femur and articular surface), gall bladder, gross lesions, heart, ileum (including Peyer's patch), jejunum, kidneys, larynx, liver, lungs, lymph nodes (mandibular and mesenteric), mammary area, muscle, esophagus, ovaries, oviducts, pancreas, pituitary, prostate, rectum, salivary glands (submandibular, parotid, and sublingual), sciatic nerve, seminal vesicles, skin/subcutis, spinal cord (cervical), spleen, sternum (with bone marrow), stomach, testes with epididymides, thymus, thyroid with parathyroids, tongue, trachea, ureters, urinary bladder, uterus and cervix, and vagina.

Tissues listed above were appropriately processed, stained with hematoxylin and eosin, and examined microscopically.

Peer Review: A peer review was not conducted.

Histological Findings

A summary of the microscopic findings are presented in Table 13.

At the injection sites (i.e., IJ1-4), perivascular mononuclear cell infiltration was noted in the three males with injection site reactions, (i.e., GP2015-treated male 5M and EU-Enbrel-treated males 7M and 8M), as well as another GP2015-treated male (4M), all GP2015-treated females and two EU-Enbrel-treated females (16F and 18F). The sponsor suggests that this change generally correlated with those animals demonstrating decreased exposure and production of ADAs and as such was considered to be related to immunogenicity. However, this cannot be definitively determined due to the lack of sensitivity of the ADA assay for clearly determining ADA positive animals. Additionally, there was an overall increase in inflammatory lesions in the skin at the injection sites of treated animals compared with control animals, including hyperkeratosis, dermatitis, myositis, and cellulitis, which the sponsor considered to be non-specific inflammatory responses to administration of GP2015 and EU-Enbrel. The incidence of myositis and cellulitis was slightly increased in animals treated with GP2015 as compared to EU-Enbrel. As the injection site findings are generally minimal in severity and clinically monitorable, they are not considered adverse or dose-limiting.

Minimal cortical eosinophilia/hypertrophy of the adrenal gland was observed in 1/3 GP2015-treated males and females, 3/3 EU-Enbrel-treated males, and 1/3 EU-Enbrel-treated females. This finding was characterized by increased eosinophilic cytoplasm in cortical adrenocytes without an overall increase in adrenal gland size. This finding was not observed in any control-treated animal. The sponsor suggests that this finding is consistent with minor stress rather than direct adrenal gland toxicity. While cortical hypertrophy of the adrenal gland can be associated with stress responses[1], the ability to differentiate direct toxicity from indirect stress-related effects can be difficult, given the

[1] Everds et al. (2012) Interpreting the stress responses during routine toxicity studies: A review of the biology, impact, and assessment. *Toxicologic Pathology*. (00): 1-55.

normal variability in immune parameters due to differences in health, age, and experimental conditions. Therefore, the treatment-dependent relationship of this finding is unclear. However, due to the minimal severity of the adrenal gland findings, they are not considered dose-limiting.

Minimal pigment in the spleen and pigmented macrophages in the liver were observed in 1/3 GP2015-treated males (5M) and 1/3 EU-Enbrel-treated males (7M). Spleen pigment was characterized by minor accumulations of brown pigment within the red pulp of the spleen and the pigmented macrophages in the liver were characterized by single or few macrophages containing brown pigment within the sinusoids of the liver parenchyma. The sponsor indicated that these findings may correlate with RBC hemolysis in these animals. Due to the findings of reduced RBCs and hemoglobin and increased total bilirubin in this animal, it appears reasonable that the pigment in the spleen and liver macrophages resulted from RBC hemolysis and subsequent phagocytic activity in the spleen and liver. Increased hemopoiesis of the bone marrow of the femur and sternum were also observed in 1/3 GP2015-treated males (5M), correlating with the changes in red and white blood cell parameters in this animal. Minimal mineralization of the ovaries was observed in 2/3 GP2015-treated females and 1/3 EU-Enbrel-treated females. Overall, there are no concerning microscopic differences between GP2015- and Enbrel-treatment.

Table 13: Summary of histopathology findings in cynomolgus monkeys receiving GP2015 or Enbrel (once every 3 days) for 4 weeks

	Males			Females		
Tissue/Histopathology Finding	**Control** 0 mg/kg	**GP2015** 15 mg/kg	**Enbrel** 15 mg/kg	**Control** 0 mg/kg	**GP2015** 15 mg/kg	**Enbrel** 15 mg/kg
Injection Site 1 (IJ1): Left Anterior	*3*	*3*	*3*	*3*	*3*	*3*
Perivascular Mononuclear Cell Infiltration	**0**	**2***	**2**	**0**	**2**	**0**
Minimal (Grade 1)	0	2	1	0	2	0
Slight (Grade 2)	0	0	1	0	0	0
Cellulitis	**0**	**0**	**2**	**0**	**3**	**3**
Minimal (Grade 1)	0	0	2	0	2	3
Slight (Grade 2)	0	0	0	0	1	0
Myositis	**1**	**1**	**1**	**1**	**2**	**0**
Minimal (Grade 1)	1	1	1	1	1	0
Moderate (Grade 3)	0	0	0	0	1	0
Hyperkeratosis	**0**	**0**	**1**	**0**	**0**	**0**
Minimal (Grade 1)	0	0	1	0	0	0
Injection Site 2 (IJ2): Right Anterior	*3*	*3*	*3*	*3*	*3*	*3*
Perivascular Mononuclear Cell Infiltration	**0**	**2***	**2**	**0**	**3**	**2**
Minimal (Grade 1)	0	1	1	0	3	2
Slight (Grade 2)	0	1*	1	0	0	0

Tissue/Histopathology Finding	Males			Females		
	Control 0 mg/kg	GP2015 15 mg/kg	Enbrel 15 mg/kg	Control 0 mg/kg	GP2015 15 mg/kg	Enbrel 15 mg/kg
Cellulitis	**0**	**1**	**2**	**0**	**3**	**1**
Minimal (Grade 1)	0	1	1	0	1	1
Slight (Grade 2)	0	0	1	0	2	0
Myositis	**0**	**2***	**1**	**0**	**3**	**0**
Minimal (Grade 1)	0	2	1	0	3	0
Injection Site 3 (IJ3): Left Posterior	*3*	*3*	*3*	*3*	*3*	*3*
Perivascular Mononuclear Cell Infiltration	**0**	**1***	**2**	**0**	**0**	**0**
Minimal (Grade 1)	0	1	2	0	0	0
Cellulitis	**0**	**0**	**2**	**0**	**2**	**2**
Minimal (Grade 1)	0	0	2	0	2	2
Myositis	**0**	**1**	**0**	**1**	**2**	**0**
Minimal (Grade 1)	0	1	0	1	2	0
Hyperkeratosis	**0**	**0**	**1**	**0**	**0**	**1**
Minimal (Grade 1)	0	0	1	0	0	1
Dermatitis	**1**	**2***	**2**	**1**	**1**	**0**
Minimal (Grade 1)	1	2	2	1	1	0
Injection Site 4 (IJ4): Right Posterior	*3*	*3*	*3*	*3*	*3*	*3*
Perivascular Mononuclear Cell Infiltration	**0**	**1***	**2**	**0**	**2**	**0**
Minimal (Grade 1)	0	1	2	0	2	0
Cellulitis	**0**	**1**	**1**	**0**	**2**	**2**
Minimal (Grade 1)	0	1	1	0	2	2
Myositis	**0**	**1***	**1**	**0**	**2**	**0**
Minimal (Grade 1)	0	1	1	0	2	0
Dermatitis	**0**	**2***	**3**	**0**	**1**	**1**
Minimal (Grade 1)	0	1*	3	0	1	1
Slight (Grade 2)	0	1	0	0	0	0
Adrenal Gland	*3*	*3*	*3*	*3*	*3*	*3*
Cortical Eosinophilia/ Hypertrophy	**0**	**1***	**3**	**0**	**1**	**1**
Minimal (Grade 1)	0	1	3	0	1	1
Femur + Marrow	*3*	*3*	*3*	*3*	*3*	*3*
Increased Hemopoiesis	**0**	**1***	**0**	**0**	**0**	**0**
Minimal (Grade 1)	0	1	0	0	0	0
Sternum + Marrow	*3*	*3*	*3*	*3*	*3*	*3*
Increased Hemopoiesis	**0**	**1***	**0**	**0**	**0**	**0**

Tissue/Histopathology Finding	Males			Females		
	Control 0 mg/kg	GP2015 15 mg/kg	Enbrel 15 mg/kg	Control 0 mg/kg	GP2015 15 mg/kg	Enbrel 15 mg/kg
Minimal (Grade 1)	0	1	0	0	0	0
Liver	*3*	*3*	*3*	*3*	*3*	*3*
Pigmented Macrophages	**0**	**1***	**1**	**0**	**0**	**0**
Minimal (Grade 1)	0	1	1	0	0	0
Spleen	*3*	*3*	*3*	*3*	*3*	*3*
Pigment	**0**	**1***	**1**	**0**	**0**	**0**
Minimal (Grade 1)	0	1	1	0	0	0
Ovaries	*N/A*	*N/A*	*N/A*	*3*	*3*	*3*
Mineralization	–	–	–	**0**	**2**	**1**
Minimal (Grade 1)				0	2	1

*Microscopic findings from Animal No. 5 (GP2015 Male)

Toxicokinetics

Blood samples for toxicokinetics (1.4 mL) were collected from the femoral vein or artery from all animals on the following days and time points:

- Days 1 and 7 at pre-dose and at 2, 6, 12, 18, 24, 32, 48, and 72 hours post-dose
- Days 13, 16, 19, 22, and 25 at pre-dose
- Day 28 at pre-dose and at 2, 6, 12, 18, 24, 32, 48, 72, and 96 hours post-dose

Relative bioavailability (F_{rel}) was calculated to characterize the comparative systemic exposure of GP2015 relative to EU-Enbrel.

Mean TK parameters are presented in Table 14 below. On Days 1 and 7, systemic exposure of GP2015 and EU-Enbrel was similar between males and females. There was evidence of systemic accumulation after repeat dosing for both GP2015- and EU-Enbrel-treated groups on Day 7. Decreased systemic exposure (AUC and C_{max}) was observed on Day 28 in 2 GP2015 males (4M, 5M), 2 EU-Enbrel males (7M, 8M) and all GP2015 and EU-Enbrel females. On Day 28, it was also noted that systemic exposure was 2.2-fold higher in GP2015-treated males compared to females. The reduction in exposure was likely related to the development of ADA in these animals; however due to technical and sensitivity limitations of the assay, etanercept-specific ADAs could only be confirmed in two GP2015 females (13F and 14F), and 2 EU-Enbrel animals (8M and 16F). There was a general correlation between drug exposure and detection of ADA (e.g. 8M had the lowest AUC on Day 28). In both GP2015- and EU-Enbrel-treated animals, the half-life was decreased on Day 28 versus Days 1 and 7 in all treated animals, and to a greater extent, in animals with confirmed ADA.

The comparative systemic exposures between the GP2015- and EU-Enbrel-treated groups are shown in Table 15. Generally, the exposure to GP2015 was similar to that of EU-Enbrel on Days 1 and 7; with relative bioavailability (F_{rel}) estimates for $AUC_{0\text{-}72h}$ and C_{max} of GP2015-treaeted animals ranging from 81-101% in males and 88-136% in females as compared to EU-Enbrel-treated animals. On Day 28, F_{rel} estimates for $AUC_{0\text{-}72h}$ and C_{max} ranged from 109-127% in males and 66-78% in females. However,

due to the potential ADA immune responses and high variability between animals observed on Day 28, as well as the low number of animals (n = 3/sex/group) for each comparison, exposure data and the assessment of relative bioavailability should be interpreted cautiously.

Table 14: Mean TK parameters for cynomolgus monkeys receiving GP2015 or Enbrel

Treatment (15 mg/kg)	AUC_{0-72h} (µg*h/mL)						C_{max} (µg/mL)					
	Day 1		Day 7		Day 28		Day 1		Day 7		Day 28	
	M	F	M	F	M	F	M	F	M	F	M	F
GP2015	4020 (164)	4390 (1050)	5570 (690)	5610 (223)	2180 (1950)	987 (653)	78.4 (9.89)	83.9 (22.3)	98.9 (8.16)	95.9 (13.5)	49.3 (39.7)	27.1 (14.6)
Enbrel	4050 (463)	3230 (275)	6300 (810)	6200 (810)	2000 (3100)	1500 (1240)	77.9 (13.6)	62.2 (5.76)	122 (33.6)	109 (6.36)	38.7 (55.8)	34.9 (22.0)
Treatment (15 mg/kg)	**$t_{1/2}$ (h)**						**t_{max} (h)**					
	Day 1		Day 7		Day 28		Day 1		Day 7		Day 28	
	M	F	M	F	M	F	M	F	M	F	M	F
GP2015	45.9 (NC)	59.4 (16.3)	55.8 (NC)	66.1 (NC)	13.8 (2.76)	7.93 (2.65)	24.7 (7.02)	22.0 (3.46)	18.0 (10.4)	22.7 (10.1)	22.0 (3.46)	24.0 (0.0)
Enbrel	61.1 (NC)	50.4 (NC)	62.0 (29.3)	83.2 (27)	12.6 (8.22)	13.2 (6.82)	24.0 (0.0)	29.3 (4.62)	16.0 (9.17)	24.0 (0.0)	20.0 (6.93)	26.7 (4.62)

(NC) Not calculable due to n = 1 or 2/group for that parameter

Table 15: Comparative systemic exposure of cynomolgus monkeys receiving GP2015 or Enbrel (relative bioavailability [F_{rel}] of GP2015 relative to Enbrel)

Study Day	F_{rel} AUC_{0-72h} (%)		F_{rel} C_{max} (%)	
	M	F	M	F
Day 1	99.3	136	101	135
Day 7	88.4	90.5	81.1	88.0
Day 28	109	65.8	127	77.7

Immunogenicity (Study BA11014-R): Blood samples (~0.9 mL) were collected from the femoral vein or artery for immunogenicity assessments for all animals at one pre-treatment time point and on Days 7, 13, and 32 (prior to necropsy). An ECL bridging immunogenicity assay (developed by HEXAL AG) was used to detect anti-etanercept antibodies in the monkey serum. If results were above the cut off value (i.e., 98.8 counts) then a confirmatory assay was conducted to determine the specificity of the anti-etanercept antibodies for GP2015 or EU-Enbrel. The serum sample was considered to contain specific anti-etanercept antibodies if a reduction of the mean count value of at least 50% was observed after addition of excess of etanercept (GP2015 or EU-Enbrel).

Animals with detectable ADAs are presented in Table 16. Etanercept-specific ADAs were confirmed in two GP2015 females (13F and 14F) and 2 EU-Enbrel animals (8M and 16F). The other animals with results above the threshold cut-off value tested negative or unspecific for etanercept in the confirmatory assay. However, the sponsor notes that although the ADA assay has an acceptable drug tolerance, it cannot be

excluded that the presence of etanercept in serum impaired the detection of anti-etanercept antibodies. Therefore, the determined concentration of anti-etanercept antibodies may be low or non-detectable due to drug interference. The possibility of serum drug interference seems reasonable based on the decrease seen in systemic exposure on Day 28 in GP2015-treated (M: 4, 5 / F: 15) and EU-Enbrel-treated (M: 7 / F: 17, 18) animals that did not have a confirmed positive response in the ADA assay.

Table 16: Detectable anti-Etanercept antibodies in monkeys from a 4-week toxicology study of GP2015 or Enbrel

Treatment	Sex	Animal No.	Day	Mean Count	Outcome of Confirmatory Assay
Control	Male	1	-7	104	Negative
GP2015	Male	4	32	100	Negative
		5	32	99	Negative
	Female	**13**	**32**	**1591**	**Positive: Etanercept Specific**
		14	**32**	**506**	**Positive: Etanercept Specific**
		15	32	108	Negative: Unspecific
Enbrel	Male	7	32	115	Negative: Unspecific
		8	**32**	**1635**	**Positive: Etanercept Specific**
		9	32	101	Negative
	Female	**16**	**32**	**450**	**Positive: Etanercept Specific**
		17	-7	104	Negative

Dosing Solution Analysis

Dosing formulations for the GP2015 drug product, EU-Enbrel, and the GP2015 placebo were supplied to (b) (4) by the sponsor in ready to use vials. The study report states that formulation analysis was not required to confirm the initial concentrations, as pre-study formulation analysis was conducted by the sponsor. On Days 1 and 28 following completion of dosing, approximately 1 mL aliquots from the residues remaining from each formulation were removed from the crimped glass vials and stored in polypropylene cryo vials at a nominal -80°C and dispatched to the Sponsor. No analysis was performed by (b) (4).

The sponsor provided certificates of test article analysis for the GP2015 drug product, EU-Enbrel, and the GP2015 placebo for the pre-study analytical analysis (Certificate signed March 24, 2011) and for the retest of only the GP2015 drug product on December 3, 2012. The dosing solution analysis appears to be acceptable for this study.

11 Integrated Summary and Safety Evaluation

IND 114187 was submitted for the development of GP2015, a proposed etanercept biosimilar product. The proposed opening IND study (Protocol GP15-301) is a Phase 3, 48-week, randomized, double-blind, parallel-group, 2-treatment period study in patients with moderate to severe RA using GP2015 and EU-Enbrel at subcutaneous doses of 50 mg/week. Previous clinical experience with GP2015 includes two Phase 1 PK similarity studies in healthy volunteers using GP2015 and either EU-Enbrel or US-Enbrel as comparator products at subcutaneous doses of 50 mg, as well as an ongoing Phase 3,

52-week, safety and efficacy study in patients with plaque psoriasis using GP2015 and EU-Enbrel.

A Type B Pre-IND meeting was held with the sponsor on July 9, 2012. At this meeting the sponsor was advised that since the *in vivo* nonclinical studies utilized EU-Enbrel as the comparator product, an adequate bridge to US-Enbrel would be required to use the nonclinical safety data, which would likely include a bridging 3-way clinical PK/PD study, as well as a direct physico-chemical comparison of all 3 products (US-licensed Enbrel, EU-approved Enbrel, and GP2015). In an email dated August 3, 2015, the quality reviewer confirmed that adequate 3-way analytical similarity was established between GP2015, US-Enbrel, and EU-Enbrel, which is important as the comparative PD, PK, and toxicology studies in support of this IND were conducted with GP2015 and EU-Enbrel, not US-Enbrel.

In support of the safety of the proposed clinical protocol, this review evaluated the results of a comparative efficacy study in Tg197 human TNFα-expressing transgenic mice (Study GP15-007), a GLP single-dose (SC) comparative PK study in rabbits (Study GP15-006), and a GLP comparative 28-day SC toxicology study in the cynomolgus monkey (Study GP15-003).

In the comparative efficacy study in a Tg197 human TNFα-expressing transgenic mouse model of polyarthritis (Study GP15-007), no differences in efficacy (i.e., reduced development of arthritis-related pathology) were observed between EU-Enbrel and GP2015, at a biweekly dose of 10 mg/kg for 2 or 4 weeks, when treatment was initiated at 6 weeks of age.

In the GLP single-dose (SC) comparative PK study in rabbits (Study GP15-006), a single 8 mg/kg subcutaneous administration of two GP2015 formulations (i.e., an originator-like formulation or a formulation containing 50 mM Citrate/25 mM Lysine as the buffer/amino acid components) and EU-Enbrel, produced no clinical signs or signs of local intolerance in male rabbits. The animals treated with GP2015 in the originator-like formulation had a slightly longer t_{max} than the EU-Enbrel-treated animals. In general, no major differences in PK parameters were noted between the two GP2015 formulation and EU-Enbrel.

In the GLP comparative 28-day SC toxicology study in the cynomolgus monkey (Study GP15-003), Cynomolgus monkeys received 0 mg/kg (vehicle: GP2015 Placebo), 15 mg/kg GP2015, or 15 mg/kg EU-Enbrel once every 3 days for 28 days. No treatment-related effects on mortality, body weight, food consumption, ophthalmic exams, ECG, urinalysis, or macroscopic findings were observed.

Injection site reactions (i.e., erythema/rash; moderate to severe) were observed after the 9th injection in one GP2015-treated male (Animal No. 5M) and two EU-Enbrel-treated males (Animals No. 7M and 8M), and these resolved before the termination of the study on Day32, except for a slight erythema in Animal No. 8M. These animals also had correlating red and white blood cell parameter changes. Increased body temperature (Days 26-27) and clinical chemistry changes (Day 26) were also observed in GP2015 animal 5M. These changes were generally most marked in the GP2015-treated animal (5M) that displayed the most pronounced skin reaction and included decreases (up to -26%) in hemoglobin and red blood cells and a concomitant increase

of reticulocytes (up to 2.6-fold). Additionally, a marked decrease (-31 to -50%) in platelets was seen in the GP2015-treated male 5M and the EU-Enbrel-treated males 7M and 8M. This was followed by a rebound increase, and slightly prolonged clotting times were also seen in animals 5M and 8M. The sponsor indicates that the spectrum of the findings observed in these drug-treated animals (e.g., injection site rash/erythema, abdominal/inner thigh ecchymosis, regenerative anemia as a consequence of red blood cell hemolysis and thrombocytopenia) may be the clinical consequence of immunogenicity, which was supported by the observed reduced systemic exposure of these animals on Day 28. This may be a reasonable explanation; but cannot be confirmed due lack of correlating ADA data. In addition, apparent treatment-related findings observed in GP2015-treated animal 5M were more severe than in the two Enbrel-treated males. However due to the small number of animals utilized in this study per treatment group, it cannot be concluded that increased symptom severity in the GP2015-treated animal represents a true difference between GP2015 and EU-Enbrel. Based on the prior human experience with GP2015 and clinical monitorability, there are no nonclinical concerns at this time.

Hematology findings in GP2015- and EU-Enbrel-treated males occurred mostly on Days 29-32, and included increased WBCs and absolute and relative reticulocytes, lymphocytes, monocytes and LUCs, and decreased absolute and relative neutrophils. Platelets were decreased on Days 22 [GP2015 males] and 29 and increased on Days 31-32. Platelet crit was also increased on Days 31-32. The changes in group means for the GP2015- and EU-Enbrel-treated males were largely driven by the changes observed in the individual animals with injection site reactions, as described above. Hematology changes in females on Day 22 included increased reticulocytes, monocytes, and LUC in the GP2015-treated group and increased absolute LUC in the EU-Enbrel-treated group.

For clinical chemistry parameters, the GP2015 male with fever and injection site reactions (5M) had changes that correlated with the onset of the symptoms on Day 26, including increased AST (+190%), ALT (+113%), ALP (+40.5%), and total bilirubin (+430%) and decreased GGT (-45.5%), sodium (-5%), potassium (-16%), chloride (-5%), calcium (-10.4%), albumin (-31%), AG ratio (-46%), and glucose (-57.5%).

IgM levels were elevated in all GP2015 males (+126%), notably Animal No.4 (+375%), and in two EU-Enbrel-treated males (7M; +59% and 9M; +77.5%), as compared to controls. IgG levels were elevated in EU-Enbrel-treated male 8M (+49.8% vs control group mean).

Microscopic findings in GP2015- and Enbrel-treated animals included inflammatory lesions (hyperkeratosis, dermatitis, myositis, and cellulitis) in injection sites, as well as minimal cortical eosinophilia/hypertrophy of the adrenal gland, as compared to controls. The incidence of injection site myositis and cellulitis was increased in GP2015 animals compared to EU-Enbrel animals.

On Days 1 and 7, systemic exposure to GP2015 was similar in animals (males and females) receiving 15 mg/kg GP2015 or EU-Enbrel. On Day 28, systemic exposure decreased in all drug-treated groups and systemic exposure was 2.2-fold higher in GP2015-treated males compared to females. The decrease in systemic exposure and

gender difference in the GP2015 groups on Day 28 are likely due to the development of ADAs, but was not confirmed by ADA data.

Etanercept-specific ADAs were confirmed in two GP2015 females (13F and 14F), and 2 EU-Enbrel animals (8M and 16F). However, the presence of etanercept in serum may have interfered with the detection of anti-etanercept antibodies in the assay system, leading to false negative ADA results for other GP2015- and EU-Enbrel-treated animals, as evidenced by decreased systemic exposure in most drug-treated animals on Day 28.

Nonclinical Conclusion and Recommendation

Analytical similarity was demonstrated between GP2015 and etanercept (US- and EU-Enbrel), so nonclinical studies comparing GP2015 and EU-Enbrel could be used to assess the safety of GP2015. Based on similar PK and toxicity profiles of GP2015 and EU-Enbrel, there are no nonclinical safety concerns for the proposed clinical study in RA patients, in which subjects will receive the approved dose of EU-Enbrel (50 mg/week). There is also previous clinical experience with GP2015.

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ANDREA BENEDICT
04/29/2016

MARCIE L WOOD
04/29/2016

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR BLA 761042

BLA Number: 761042 **Applicant:** Sandoz, Inc. **Stamp Date:** 7/30/2015

Drug Name: GP2015 **BLA Type:** 351(k)

On **initial** overview of the NDA/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 pharmacology and toxicology studies compared GP2015 vs. EU-approved etanercept. An assessment of biosimilarity between GP2015 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).	X		The formulation to be marketed is the same formulation used in the pivotal in vivo pharmacology and toxicology studies.
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		

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR BLA 761042

	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. Changes in labeling, including PLLR formatting, will be addressed in a labeling review.
10	Have any impurity, degradant, extractable/leachable, etc. issues been addressed? (New toxicity studies may not be needed.)			To be determined in consultation with the Product Quality reviewer.
11	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable.
12	If the applicant is entirely or in part supporting the safety of their product by relying on nonclinical information for which they do not have the right to the underlying data (i.e., a 505(b)(2) application referring to a previous finding of the agency and/or literature), have they provided a scientific bridge or rationale to support that reliance? If so, what type of bridge or rationale was provided (e.g., nonclinical, clinical PK, other)?			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 BLA 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.

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/s/

ANDREA BENEDICT
09/15/2015

MARCIE L WOOD
09/15/2015