CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761042Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	*Electronic Stamp Date*
From	Nikolay P. Nikolov, M.D.
Subject	Cross-Discipline Team Leader Review
BLA #	351(k) BLA 761042
Applicant	Sandoz, Inc.
Date of Submission	July 30, 2015, Major Amendment April 28, 2016
BsUFA Goal Date	May 30, 2016, Extended to August 30, 2016
Proprietary Name (Proposed) / Nonproprietary names	Erelzi, Erelzi Sensoready Pen / GP2015[1], etanercept-szzs
Dosage Forms / Strength	• 50 mg/mL solution in a single-dose prefilled syringe (PFS) • 25 mg/0.5 mL solution in a single-dose PFS • 50 mg/mL solution in a single-use prefilled pen injector
Route of Administration	Subcutaneous
Proposed Indication(s)	• Rheumatoid arthritis • Juvenile Idiopathic Arthritis • Ankylosing spondylitis • Psoriatic arthritis • Plaque psoriasis
Recommended:	*Approval*

1. Introduction

This document is a cross discipline team leader (CDTL) review of the biologics license application (BLA) 761042 submitted by Sandoz under section 351(k) of the Public Health Service Act (PHS Act) for GP2015, a proposed biosimilar to US-licensed Enbrel (etanercept). Sandoz is seeking licensure of GP2015 for the following indications for which US-licensed Enbrel is licensed:[2]

1) Rheumatoid Arthritis (RA):
    - Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in patients

[1] In this document, I generally refer to Sandoz's proposed product by the Sandoz descriptor "GP2015" which was the name used to refer to this product during development. Subsequently, the nonproprietary name for this proposed product was determined to be "etanercept-szzs."
[2] FDA-approved Enbrel labeling

with moderately to severely active rheumatoid arthritis (in combination with methotrexate, MTX, or used alone);

2) Polyarticular Juvenile Idiopathic Arthritis (JIA):
   - Reducing signs and symptoms of moderately to severely active polyarticular JIA in patients ages 2 and older;

3) Psoriatic Arthritis (PsA):
   - Reducing signs and symptoms, inhibiting the progression of structural damage of active arthritis, and improving physical function in patients with psoriatic arthritis (in combination with MTX in patients who do not respond adequately to MTX alone);

4) Ankylosing Spondylitis(AS):
   - Reducing signs and symptoms in patients with active ankylosing spondylitis;

5) Plaque Psoriasis (PsO):
   - Treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

The application consists of:

- Extensive analytical data intended to support (i) a demonstration that GP2015 and US-licensed Enbrel are highly similar, (ii) a demonstration that GP2015 can be manufactured in a well-controlled and consistent manner, leading to a product that is sufficient to meet appropriate quality standards and (iii) the analytical element of the scientific bridge to justify the relevance of comparative data generated using the European Union (EU)-approved Enbrel to support a demonstration of the biosimilarity of GP2015 to US-licensed Enbrel.

- Three single-dose pharmacokinetic (PK) studies (101 and 102, 104, and cross-study comparison Report 105) providing a comparison of GP2015, US-licensed Enbrel, and EU-approved Enbrel intended to (i) support PK similarity of GP2015 and US-licensed Enbrel and (ii) provide the PK element of the scientific bridge to justify the relevance of the comparative data generated using EU-approved Enbrel to support a demonstration of the biosimilarity of GP2015 to US-licensed Enbrel.

- A comparative clinical study (Study 302) between GP2015 and EU-approved Enbrel to support a demonstration of no clinically meaningful differences between GP2015 and US-licensed Enbrel. This is a 52-week, randomized, double-blind, multicenter study conducted outside the U.S. in 531 patients with moderate to severe, chronic plaque-type psoriasis (PsO), who were randomized 1:1 to GP2015 or EU-approved Enbrel at a dose of 50 mg twice weekly for 12 weeks (treatment period 1, TP1). Patients who completed the Week 12 visit and achieved at least a Psoriasis Area Severity Index

(PASI) 50 response at that visit were re-randomized to either continue on their initial treatment or to undergo pre-defined transitions between the two products from Week 12 to Week 30 (treatment period 2, TP2). This application includes an assessment of safety and immunogenicity in patients who completed TP2.

- A scientific justification for extrapolation of data to support a demonstration of biosimilarity in each of the non-studied indications for which Sandoz is seeking licensure, specifically rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS).

Sandoz submitted comparative analytical data on the GP2015 lots used in clinical studies intended to support a demonstration of biosimilarity ("clinical product lots") and on the proposed commercial product. Based on our review of the data provided, Sandoz's comparative analytical data for GP2015 demonstrates that it is highly similar to US-licensed Enbrel notwithstanding minor differences in clinically inactive components.

Sandoz used a non-US-licensed comparator (EU-approved Enbrel) in some studies intended to support a demonstration of biosimilarity to US-licensed Enbrel. Accordingly, Sandoz provided scientific justification for the relevance of that data by establishing an adequate scientific bridge between EU-approved Enbrel, US-licensed Enbrel, and GP2015. Review of an extensive battery of test results provided by Sandoz confirmed adequacy of the scientific bridge and hence the relevance of comparative clinical and non-clinical data with EU-approved Enbrel to support a demonstration of biosimilarity to US-licensed Enbrel.

The results of the clinical development program indicate that Sandoz's data support the demonstration of "no clinically meaningful differences" between GP2015 and the US-licensed Enbrel in terms of safety, purity, and potency in the indications studied. Specifically, the results from the comparative clinical efficacy, safety, and PK studies adequately support the determination that there are no clinically meaningful differences between GP2015 and US-licensed Enbrel. Further, the single transition from EU-approved Enbrel to GP2015 during treatment period 2 in Study 302 did not result in a different safety or immunogenicity profile. This would support the safety of the clinical scenario where non-treatment naïve patients undergo a single transition to GP2015.

In considering the totality of the evidence, the data submitted by Sandoz show that GP2015 is highly similar to US-licensed Enbrel, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between GP2015 and US-licensed Enbrel in terms of the safety, purity, and potency of the product to support the demonstration that GP2015 is biosimilar to the US-licensed Enbrel in the studied indication of PsO.

The Applicant has also provided an extensive data package to address the scientific considerations for extrapolation of data to support biosimilarity to other conditions of use and

potential licensure of GP2015 for each of the indications for which US-licensed Enbrel is currently licensed and for which GP2015 is eligible for licensure.

Although the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) is the lead division for this application, clinical and statistical input pertaining to the indication of plaque psoriasis was obtained from the Division of Dermatology and Dental Products (DDDP) during the course of the BLA review.

2. Background

The BPCI Act

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

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

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

To support a demonstration of biosimilarity, FDA recommends that applicants use a stepwise approach to developing the data and information needed. At each step, the applicant should evaluate the extent to which there is residual uncertainty about the biosimilarity of the proposed product to the reference product and identify next steps to try to address that uncertainty. The underlying presumption of an abbreviated development program is that a molecule that is shown to be structurally and functionally highly similar to a reference product is anticipated to behave like the reference product in the clinical setting(s). The stepwise approach should start with extensive structural and functional characterization of both the proposed biosimilar product and the reference product, as this analytical characterization

serves as the foundation of a biosimilar development program. Based on these results, an assessment can be made regarding the analytical similarity of the proposed biosimilar product to the reference product and, once the applicant has established that the proposed biosimilar meets the analytical similarity prong of the biosimilarity standard, the amount of residual uncertainty remaining can be assessed with respect to both the structural/functional evaluation and the potential for clinically meaningful differences. Additional data, such as nonclinical and/or clinical data, can then be tailored to address these residual uncertainty(-ies).

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

Reference Product

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

Relevant Regulatory History

The development of GP2015 was done outside the US. The first interaction with the FDA about the GP2015 development program occurred at a Biosimilar Biological Product Development (BPD) Type 2 meeting held on 9 July 2012. A second BPD Type 2 meeting was held on 19 December 2012. Additional interactions occurred to discuss the initial Pediatric Study Plan (iPSP). At the BPD Type 2 meetings, FDA provided general guidance on the proposed comparative clinical study design including primary endpoint and similarity margin to support a filing of the 351(k) BLA. The FDA also provided product quality, non-clinical, and clinical comments, including the following recommendations to the Applicant regarding clinical development:

- Provide a scientific rationale with supportive data to establish a bridge between US-licensed Enbrel and EU-approved Enbrel. A 3-way PK similarity study was recommended.

- Assess safety and immunogenicity in the setting of patients who undergo a single transition from comparator Enbrel to GP2015 to provide a descriptive comparison with patients who continue on comparator Enbrel.

There were no pre-BLA interactions to discuss the details of the format and content of the BLA.

This BLA was originally submitted on July 30, 2015. On April 28, 2016, during the review cycle, Sandoz submitted additional data to address the observed differences in *in vitro* TNF-α neutralization, as discussed in the section on CMC/Product Quality below. This submission was considered a major amendment leading to a 3-month extension of the review timelines.

3. CMC/Product Quality

CMC Reviewer: Peter L. Adams, Ph.D.; Application Technical Lead: Marjorie Shapiro, Ph.D.
CMC Statistical Reviewer: Meiyu Shen, Ph.D.; CMC Statistical Supervisor: Yi Tsong, Ph.D.
OBP Director: Steven Kozlowski, M.D.
Microbiology Reviewers: Reyes Candau-Chacon, Ph.D. and Candace Gomez-Broughton, Ph.D.; Acting Branch Chief: Patricia Hughes, Ph.D.
Facilities Reviewer: Zhong Li, Ph.D.; Branch Chief: Peter Qiu, Ph.D.
CDRH Reviewer: Sara Mollo

- **General product quality considerations**

GP2015 drug substance (DS) is a TNF Receptor-Fc Fusion protein produced in Chinese hamster ovary (CHO) cells. It is a homo-dimer containing 934 amino acid residues with a molecular mass of ~125 kDa. The N-terminal portion of the molecule is the TNF receptor followed by the Hinge Region, CH2 and CH3 domains of a human IgG1 molecule. It contains 29 intra- and inter-chain disulfide bonds. It contains the typical N-glycan structure and heterogeneity of an antibody in the Fc portion and has 2 N-glycosylation sites and multiple O-glycosylation sites on the TNFR portion of the molecule. The DS is manufactured at Sandoz GmbH, Langkampfen, Austria in large scale bioreactor culture followed by a DS purification process that includes various steps designed to isolate and purify the protein product. Residual levels of process-related impurities, such as host cell proteins (HCP), host cell DNA (hcDNA) and other process-related impurities specific to the GP2015 process, were evaluated in GP2015 DS. Data were provided that demonstrate that the manufacturing process of GP2015 DS is able to reduce these impurities to very low levels (e.g., ppm for HCP and pg/mg for hcDNA), consistent with industry standards for biotechnology products, as determined by the product quality review team. Although there were no changes in the scale of the manufacturing process for GP2015 DS, the process was optimized during the clinical development program to improve purity and yield. To rule out the possibility of evolution or drift in product quality over time, Sandoz provided data demonstrating comparable product quality of GP2015 DS that

were manufactured over the course of process development. The data support a GP2015 DS expiration dating period of (b) (4) months at (b) (4) °C.

GP2015 drug product (DP) was developed as a solution for injection in a pre-filled syringe or autoinjector with strengths, dosage forms, and routes of administration (25 mg/0.5 mL or 50 mg/ mL) previously approved for US-licensed Enbrel for use in the treatment of the same indications as those approved for US-licensed Enbrel. The GP2015 formulation differs from that of US-licensed Enbrel. The GP2015 formulation includes a citrate buffer, whereas the US-licensed Enbrel formulation includes a phosphate buffer[3]. The drug product manufactured for commercial launch was also shown to be comparable to the drug product manufactured by the clinical process. The shelf life for both 25 and 50 mg PFS and AI is 24 months at 2-8°C plus 28 days at 25±2°C. The GP2015 DP is manufactured at Novartis Pharma Stein AG, Switzerland, and the combination product at (b) (4).

Of note, US-licensed Enbrel is also available in a multiple-use vial as a lyophilized powder for reconstitution with Sterile Bacteriostatic Water for Injection. At this time, there is no GP2015 DP developed as a lyophilized drug product or a dose adjustable dosage form to allow for dosing and administration to patients with JIA who weigh less than 63 kg. To provide for such dosing, Sandoz will be required to develop an age-appropriate dosage form, as discussed under Section 11 Pediatrics below.

The GP2015 final DS and DP processes are validated, and the resultant product is of a consistent quality. The controls put in place for the manufacture of GP2015 drug substance and GP2015 drug product meet regulatory requirements. However, the product quality team recommends that the Applicant develops and implements an analytical method for release and stability testing of GP2015 DS and DP that can adequately assess levels of hydrophobic variants, including wrongly bridged disulfide bond variants, as detailed in Recommended Comments to Applicant section below in this memorandum. I concur with this recommendation.

The microbiology review team noted that microbial retentive studies were not done under worst-case conditions to demonstrate microbial retentivity of the sterilizing filters (b) (4) To address this finding, the team recommended a post-marketing commitment (PMC) for a repeat microbial retention study using the approach detailed in the section on Recommendation for other Postmarketing Requirements and Commitments at the end of this memorandum. I concur with this recommended PMC. With this PMC, the CMC microbiology review team concluded that the drug product is recommended for approval from sterility assurance and product quality microbiology perspective. I concur with this recommendation.

[3] US-licensed Enbrel labeling approved on March 25, 2015, at http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/103795s5548lbl.pdf, retrieved May 26, 2016.

An assessment of the manufacturing facilities took place on March 3-7, 2016, by a team of Agency inspectors. The FDA team verified that the drug substance and drug product sites are acceptable from a good manufacturing practice (GMP) perspective. This submission is recommended for approval from facilities assessment perspective and I agree.

- **Analytical Similarity Assessment**

To determine whether GP2015 is highly similar to US-licensed Enbrel, and to establish the adequacy of the analytical portion of the scientific bridge between GP2015, US-licensed Enbrel, and EU-approved Enbrel, Sandoz evaluated and compared analytical data from multiple lots of each of the three products. The analytical comparison of GP2015 with US-licensed Enbrel was used to support the Applicant's demonstration that GP2015 is highly similar to US-licensed Enbrel, notwithstanding minor differences in clinically inactive components. Pairwise comparisons of GP2015, US-licensed Enbrel, and EU-approved Enbrel were used to support the analytical portion of the scientific bridge between the three products to justify the relevance of the comparative data generated using EU-approved Enbrel from some clinical and nonclinical studies. The FDA performed independent confirmatory statistical analysis of the submitted data, which is presented in further detail later in this section. Overall, 19 lots of GP2015 drug product (DP), 34 lots of US-licensed Enbrel DP and 50 lots of the EU-approved Enbrel DP were analyzed, although not all lots were assessed using each test. In addition, 18 lots of GP2015 drug substance (DS) were also analyzed, but results for GP2015 DS and GP2015 DP were not combined for the assessment of analytical similarity. Importantly, 8-9 lots of GP2015 DP, 11-13 lots of US-licensed Enbrel and 11-12 lots of the EU-approved Enbrel were used for analysis with critical assays that directly measure the primary mechanism of action of the product, TNF-α binding and neutralization. The number of lots analyzed using each assay was chosen by Sandoz, based on their assessment of the variability of the analytical method and availability of material.

The expiration dates of the US-licensed Enbrel lots and EU-approved Enbrel lots that were analyzed spanned approximately 8 years (2008 – 2016). The GP2015 DP lots that were used for analysis were manufactured between 2011 and 2014.

The analytical similarity exercise used a comprehensive range of methods which included orthogonal methods measuring the same critical quality attribute (CQA) from different perspectives. Many assays were designed to specifically address and measure potential mechanisms of action of etanercept, including TNF-α binding and neutralization, TNF-β neutralization, and Fc-mediated functions. TNF-α neutralization was studied by two methods: an NF-κB reporter gene assay where GP2015, US-licensed Enbrel or EU-approved Enbrel neutralize the ability of TNF to induce NF-κB expression; and the ability of GP2015, US-licensed Enbrel or EU-approved Enbrel to inhibit TNF-α mediated apoptosis. All methods were validated or qualified prior to the time of testing and were demonstrated to be suitable for their intended use.

  - Primary and Higher Order Structure

The primary structure of GP2015, US-licensed Enbrel, and EU-approved Enbrel, as assessed by peptide map data obtained using four different sets of enzymes, demonstrated that the chromatographic profile (peptide map) and primary amino acid sequence matches that of US-licensed Enbrel and EU-approved Enbrel. No additional peptides or missing peptides were detected in the comparison among the three products.

The N-terminal sequence was determined using reducing peptide mapping in combination with mass spectrometry. The analysis confirmed that the first thirty-four amino acids of GP2015 (LPAQVAFTPYAPEPGSTCRLREYYDQTAQMCCSK) are identical to the first thirty-four amino acids of US-licensed Enbrel and EU-approved Enbrel and are derived from TNFR2. In addition, the N-terminal heterogeneity was highly similar among the products. The C-terminal sequence and C-terminal heterogeneities were also highly similar among the products and confirmed to be the C-terminal sequence of an IgG1 antibody.

The disulfide bonding pattern of etanercept is complex. Each TNFR2 arm of etanercept contains eleven intrachain disulfide bonds and each Fc portion contains 2 intrachain disulfide bonds for a total of 26 intrachain disulfide bonds. In addition there are three interchain disulfide bonds in the IgG1 Fc hinge region. Analysis by non-reducing peptide mapping using RP-HPLC separation followed by mass spectrometry confirmed the expected presence of all interchain and intrachain disulfide bonds in each of the three products. However, etanercept is known to also contain incorrect disulfide bond variants that can affect the potency of the product[4]. Using non-reducing peptide mapping, Sandoz quantified the levels of peptide T7, which contains the incorrect disulfide bond Ex.3 in GP2015, US-licensed Enbrel and EU-approved Enbrel. GP2015 contains lower levels of this incorrect disulfide bond relative to US-licensed Enbrel and EU-approved Enbrel (Table 1).

Table 1. Descriptive Statistics for the T7 Peptide Data of GPP2015, US-licensed Enbrel, and EU-approved Enbrel

Product	Number of batches	Sample mean, %	Sample standard deviation, %	Min, %	Max, %
GP2015	9	1.21	0.11	1.1	1.4
US-licensed Enbrel	13	2.15	0.36	1.7	2.7
EU-approved Enbrel	11	2.21	0.31	1.7	2.8

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

In addition, the Applicant provided data demonstrating a correlation between levels of the T7 peptide and potency, where lots with higher levels of the T7 peptide had lower potency in the TNF-α neutralization assay. The relationship between incorrect disulfide bonds and potency is discussed in detail in the section describing biological activity below.

[4] US Patent 7,294,481, 2007, at http://www.google.com/patents/US7294481, retrieved May 26, 2016: Goswami. S. et al., Antibodies, 2013, 2:452-500.

Using multiple methods, including far and near UV circular dichroism (CD), Fourier Transform Infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC), Hydrogen/Deuterium Exchange (HDX), 1D-NMR, and X-ray crystallography Sandoz demonstrated that secondary and tertiary structures of GP2015 and US-licensed Enbrel were similar.

- Glycan Structures

Etanercept is a glycoprotein containing up to 28 O-glycans and 2 N-glycans on the TNFR portion of the molecule and one N-glycan on the Fc region. LC-ESI-MS was used to determine the site occupancy of the O-glycans and all three products were shown to be similar regarding the core structures and variants detected at each site.

The N-glycan structures were determined for the intact molecules, as well as for the Fc and TNFR portions of etanercept after digestion with the enzyme IdeS, which cleaves in the Fc hinge region. GP2015 was found to have slightly lower levels of sialylated species G2SA (6.1 – 6.6%) relative to US-licensed Enbrel and EU-approved Enbrel (8.0 – 10.7% and 7.5 – 10.9%, respectively). However, the location of the N-glycan structures in TNFR2 does not interfere with TNF binding.

Small differences were also noted in the levels of high mannose forms Man 5, Man 6 and Man8 (~2.2% for GP2015 and ~8% for US-licensed Enbrel and EU-approved Enbrel). High mannose glycan structures can alter the PK of a molecule through binding to cell surface mannose binding proteins. However, PK similarity, discussed in section Clinical Pharmacology/Biopharmaceutics was established for GP2015 and US-licensed Enbrel, which addresses the residual uncertainty in the differences in high mannose glycans between GP2015 and US-licensed Enbrel.

- Protein Content

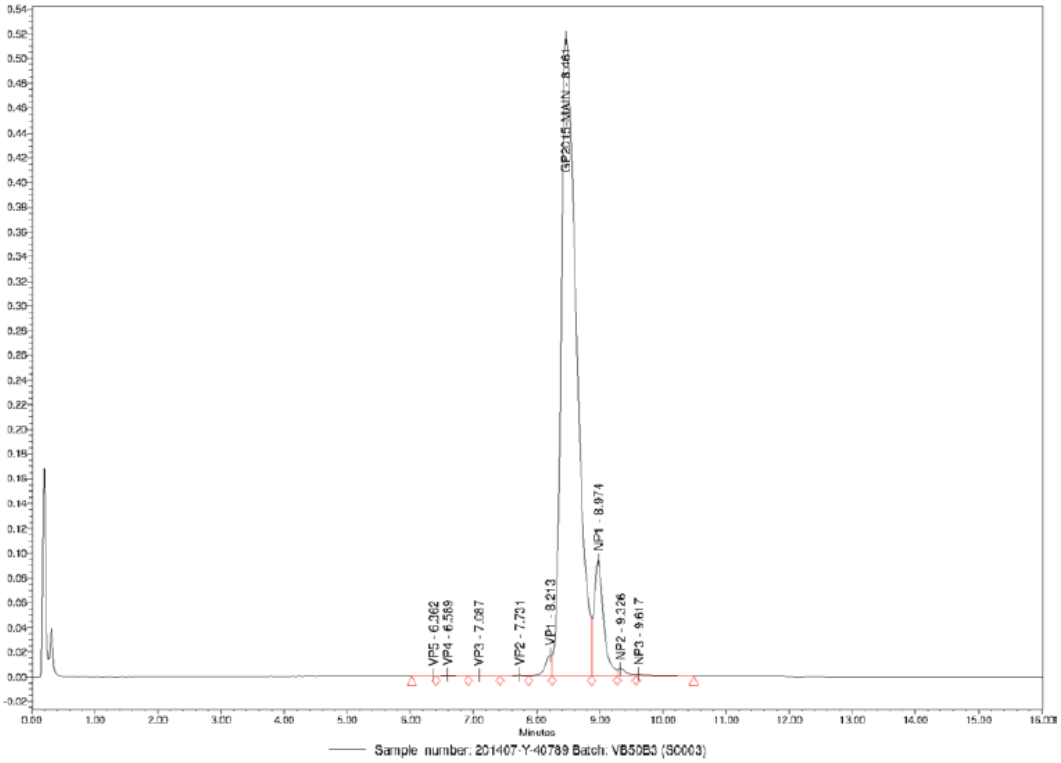
US-licensed Enbrel is filled in pre-filled syringes at 50 mg etanercept per mL in two strengths: 25 mg/0.5mL and 50 mg/mL. The drug product manufacturing process of GP2015 was designed to match the protein content of US-licensed Enbrel, within reasonable manufacturing tolerances. The data provided in the submission confirm that total protein amounts in the 25 mg/0.5 mL and 50 mg/mL pre-filled syringes of GP2015, US-licensed Enbrel and EU-approved Enbrel met pre-specified acceptance criteria.

- Hydrophobic Variants

Some product variants differ in hydrophobicity and can be separated by reversed-phase HPLC (RP-HPLC). Figure 1 shows the RPC profile of GP2015. The peak following the main peak, termed “post-peak” contains a variety of product-related species, but the major species in this peak contains misfolded protein due to incorrect disulfide bond formation. GP2015 has lower levels of the “post-peak” compared with US-licensed Enbrel and EU-approved Enbrel,

consistent with lower levels of the T7 peptide. Table 2 provides the descriptive statistics. The differences in levels of the RPC "post-peak" in GP2015 compared with US-licensed Enbrel and EU-approved Enbrel could affect the outcomes of measures of potency, which is discussed in detail in the section describing biological activity below.

Figure 1. RPC-Chromatogram of GP2015



Source: Figure from the Sandoz 351(k) BLA submission

Table 2. Descriptive Statistics for the RPC "Post-Peak" Data of GPP2015, US-licensed Enbrel, and EU-approved Enbrel

Product	# of lots	Sample mean, %	Sample standard deviation, %	Min, %	Max, %
GP2015	19	10.73	0.62	9.6	11.8
US-licensed Enbrel	21	16.16	1.91	10.2	17.4
EU-approved Enbrel	26	17.54	2.01	12.3	19.8

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

- Biological Activity and Mechanisms of Action

A number of bioassays were designed and qualified to evaluate potential etanercept functions, including critical quality attributes such as binding and neutralization of TNF-α, neutralization of TNF-β (lymphotoxin), as well as Fc effector functions.

TNF-alpha neutralization (assessed using RGA reporter gene assay) and TNF-alpha binding (assessed using surface plasmon resonance) are considered the primary mechanism of action of etanercept for all the indications being sought for licensure and were selected as the highly critical quality attributes to be evaluated by equivalence testing.

TNF-α binding

Data on TNF-alpha binding between GP2015 and the reference product met the criteria for statistical equivalence (Table 3) and support a demonstration that GP2015 is highly similar to US-licensed Enbrel. In addition, TNF-α binding between GP2015 and EU-approved Enbrel and between US-licensed Enbrel and EU-approved Enbrel met the criteria for statistical equivalence, which supports the analytical portion of the scientific bridge for non-clinical and clinical studies conducted with EU-approved Enbrel.

Table 3. Equivalence Testing Results for the TNF-α Binding

Comparison	# of lots	Mean difference	90% confidence interval for mean difference	Equivalence margin	Equivalent
GP2015 vs. US	(8, 11)	-0.125	(-3.11, 2.86)	(-3.80, 3.80)	Yes
GP2015 vs. EU	(8, 12)	-0.542	(-3.94, 2.94)	(-6.57, 6.57)	Yes
EU vs. US	(12, 11)	0.417	(-2.14,2.98)	(-3.80, 3.80)	Yes

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

TNF-α neutralization assay – Reporter Gene Assay

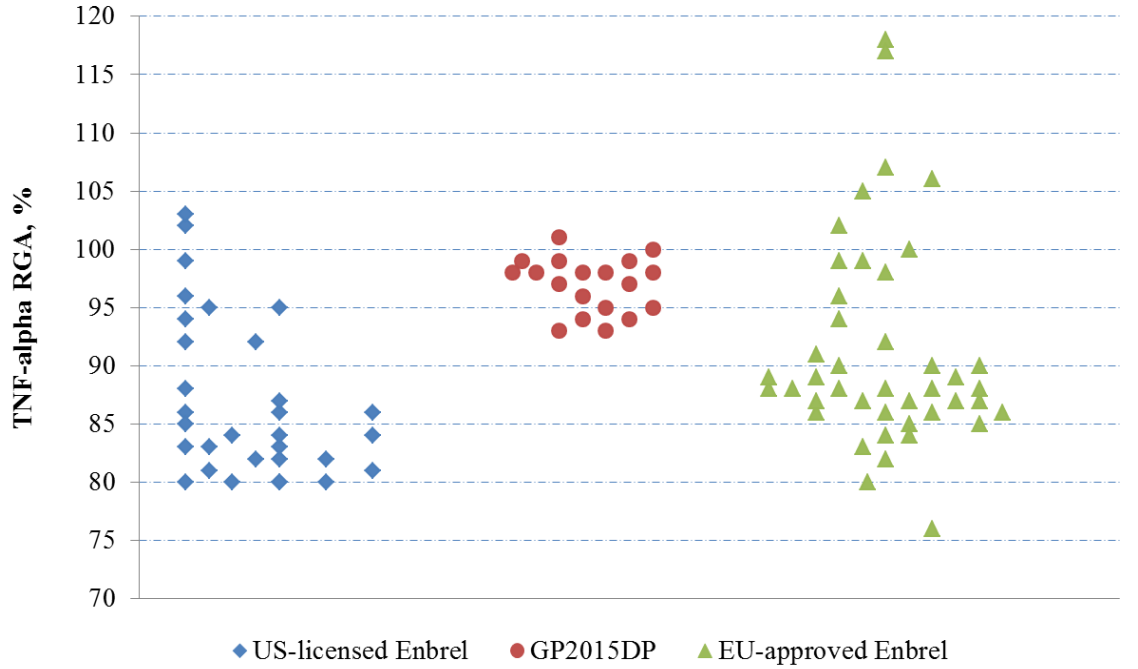
For TNF-alpha neutralization, GP2015 and US-licensed Enbrel did not meet the criteria for equivalence, although TNF-α neutralization between GP2015 and EU-approved Enbrel and between US-licensed Enbrel and EU-approved Enbrel met the criteria for statistical equivalence (Table 4). However, all the GP2015 lots were within the quality range (mean ± 3SD) of US-license Enbrel, but average mean potency for GP2015 was higher than for US-license Enbrel (Figure 2).

Table 4. Equivalence Testing Results for the *in vitro* TNF-α Neutralization RGA of GP2015, US-licensed Enbrel, and EU-approved Enbrel

Comparison	# of lots	Mean difference	90% confidence interval for mean difference	Equivalence margin	Equivalent
GP2015 vs. US	(19,31)	10.01	(7.62, 12.36)	(-10.28, 10.28)	No
GP2015 vs. EU	(19,43)	5.62	(3.15, 8.59)	(-13.50, 13.50)	Yes
EU vs. US	(43,31)	4.39	(1.32, 7.46)	(-10.28, 10.28)	Yes

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

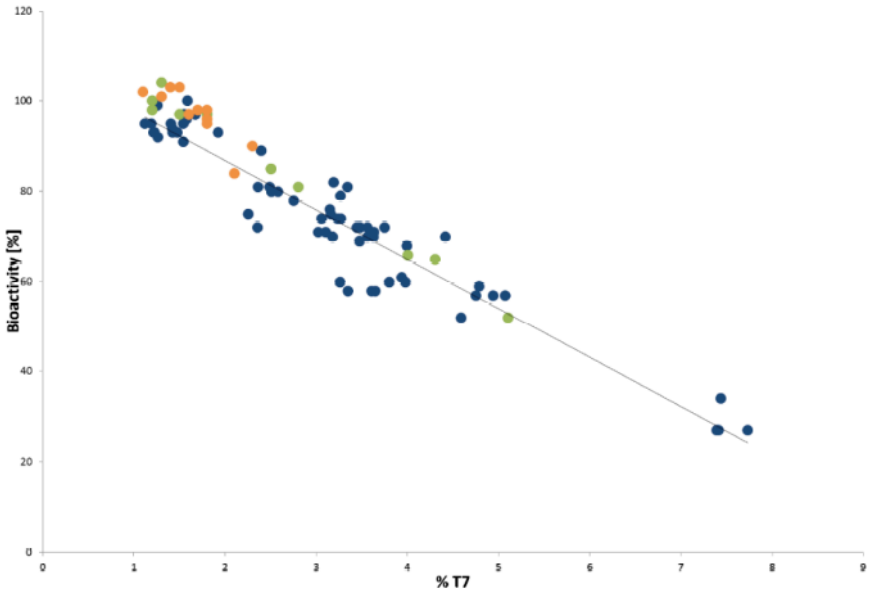
Figure 2. TNF-α RGA of GP2015, US-licensed Enbrel, and EU-approved Enbrel



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

The reason for the lack of a demonstration of equivalence was due to differences in the presence of the product related impurity identified by reverse phase chromatography termed "post peak" (see Figure 1 above). US-licensed Enbrel, as well as EU-approved Enbrel contain higher levels of this hydrophobic variant than GP2015 as described in Table 2 above. This hydrophobic variant is known to have reduced potency relative to the main peak. The "post peak" contains wrongly bridged disulfide bonds. Sandoz identified 4 wrongly bridged disulfide bonds that can occur between 5 different cysteine residues in the TNFR portion of the molecule. Sandoz demonstrated a correlation between the presence of one of the wrongly bridged disulfide bonds, termed the T7 peptide, with a reduction of potency in the TNF-neutralization assay as shown in Figure 3. Thus, a structure function relationship was established between wrongly bridged disulfide bonds and potency in the TNF-alpha neutralization assay.

Figure 3. Structure-Function Relationship Between the T7 Peptide and Bioactivity



Source: Figure from the Sandoz 351(k) BLA submission

Most disulfide bonds are structural and are important for the correct folding of a protein. However, some disulfide bonds are allosteric, which control the function of a protein when they are reduced or oxidized *in vivo* in the blood. Examples of proteins with allosteric disulfide bonds include antibodies and other proteins, tissue factor and viral glycoproteins responsible for viral entry into cells. Reports in the literature also provide evidence that TNFR1, TNFR2 and other members of the TNFR family contain allosteric disulfide bonds.

Therefore, during the review cycle, Sandoz was asked to provide data that would demonstrate that the wrongly bridged disulfide bonds in could refold *in vivo*. In response Sandoz provided data for an *in vitro* system using mild redox conditions that mimic the *in vivo* environment. These data demonstrated a reduction of levels of wrongly bridged disulfide bonds and restoration of potency in GP2015 process intermediates that contain high levels of the T7 peptide, US-licensed Enbrel and EU-approved Enbrel lots.

Based on these data and knowledge of the levels of the T7 peptide in a subset of GP2015, US-licensed Enbrel, and EU-approved Enbrel, a computed potency model was developed taking into account the correct refolding of the disulfide bonds that is expected to occur *in vivo*. Using the computed potency model, GP2015 and US-licensed Enbrel met statistical equivalence for TNF-alpha neutralization (Table 5). In addition, comparisons between GP2015 and EU-approved Enbrel, and US-licensed Enbrel and EU-approved Enbrel also met the criteria for statistical equivalence. Based on these data, the product quality review team concluded, and I agree, that differences in levels of post-peak hydrophobic variant do not preclude a conclusion that GP2015 is highly similar to US-licensed Enbrel. Furthermore, the comparisons support the analytical portion of the scientific bridge for non-clinical and clinical studies conducted with EU-approved Enbrel.

Table 5. Equivalence Testing Results for the *in vitro* TNF-α Neutralization RGA of GP2015, US-licensed Enbrel, and EU-approved Enbrel Based on the Computed Potency Model

Comparison	# of lots	Mean difference	90% confidence interval for mean difference	Equivalence margin	Equivalent
GP2015 vs. US	(9,13)	-1.25	(-5.08, 2.59)	(-11.20, 11.20)	Yes
GP2015 vs. EU	(9,11)	-5.74	(-9.66, -1.81)	(-10.41, 10.41)	Yes
EU vs. US	(11,13)	4.49	(-0.57, 9.55)	(-11.20, 11.20)	Yes

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

Fc Function

Fc function was assessed by ADCC and CDC bioassays, as well as by binding to C1q, Fcγ receptors and FcRn using SPR. Although there were some differences between GP2015 and US-licensed Enbrel and EU-approved Enbrel in the ADCC and CDC bioassays, data provided were consistent with published literature showing that these activities for etanercept are low relative to anti-TNF mAbs. In addition, the binding affinities of GP2015 and US-licensed Enbrel and EU-approved Enbrel for C1q, Fcγ Receptors and FcRn were similar.

- Aggregates and Process-related Substances and Impurities

Biopharmaceuticals typically contain very low levels of protein aggregates (<1%) at release, which increase with the age of the product. They are measured and controlled at lot release and by long term stability studies. Small amounts of aggregation are present in both GP2015 and US-licensed Enbrel. Aggregation is typically detected and quantified by the size-exclusion chromatography assay (SEC-HPLC). The average level of aggregates in US-licensed Enbrel quantified by Sandoz's SEC-HPLC assay was 2.1%, while GP2015 was 0.4%. Overall, GP2015 has lower levels of aggregates compared with US-licensed Enbrel. This may be in part due to differences in the ages of the lots at the time they were tested, but some aged GP2015 lots also had lower levels of aggregates compared with US-licensed Enbrel. From a product quality standpoint, high levels of aggregation may impact product immunogenicity when administered to patients, but levels up to 3% at the end of shelf life are typical for biotechnology products. The three products all achieved acceptably low levels of residual impurities (data not shown).

- Comparative Stability Studies

Sandoz evaluated comparative stability of GP2015, US-licensed Enbrel, and EU-approved Enbrel in several stability studies including thermal stability at 25°C for 6 months and 40°C for 1.5 months and forced degradation studies using high and low pH, oxidizing conditions, exposure to light and mechanical stress. The products were evaluated for the accumulation of high and low molecular weight species (SE-HPLC and non-reducing CE-SDS), changes in hydrophobic variants (RP-HPLC), acidic variants (capillary zone electrophoresis), or loss of

potency (TNF-α neutralization). The product quality review team concluded that the stability patterns of the three products were similar across all studies.

Conclusions on Analytical Similarity Assessment

In summary, the GP2015 product was evaluated and compared to US-licensed Enbrel, and EU-approved Enbrel in a battery of biochemical, biophysical and functional assays. The exercise also included assays that addressed each potential mechanism of action. The evidence submitted supports the conclusion that GP2015 is highly similar to US-licensed Enbrel. The amino acid sequences of GP2015 and US-licensed Enbrel are identical. A comparison of the secondary and tertiary structures, and the impurity profiles, of GP2015 and US-licensed Enbrel support the conclusion that the two products are highly similar. TNF-α binding and neutralization activities, reflecting the primary mechanism of action of US-licensed Enbrel are similar, supporting a conclusion that GP2015 has the same mechanism of action as US-licensed Enbrel.

Some tests indicate that subtle shifts in glycosylation (afucosylation and high mannose) exist and are likely an intrinsic property of the GP2015 product due to the manufacturing process. Afucosylation is associated with ADCC activity specifically through binding FcγRIIIa and high mannose glycans (which contribute to the total afucosylated glycoforms) can also impact PK. However, consistent with literature, GP2015 and the reference product have low ADCC activity relative to anti-TNF mAbs and another mAb whose major MOA includes ADCC. In addition, the binding to FcγRIIIa by SPR was highly similar. The residual uncertainty of ~6% difference in high mannose forms was addressed by the PK similarity between GP2015 and US-licensed Enbrel, as discussed in the section on Clinical Pharmacology below. Thus, based on the extensive comparison of the functional, physicochemical, protein and higher order structure attributes, the product quality review team concluded that GP2015 is highly similar to US-licensed Enbrel, notwithstanding minor differences in clinically inactive components. I concur with this conclusion. Further, the data submitted by Sandoz, support the conclusion that GP2015 and US-licensed Enbrel have the same mechanisms of action for specified indications, to the extent that the mechanisms of action are known or can reasonably be determined.

In addition, the three pairwise comparisons of GP2015, US-licensed Enbrel, and EU-approved Enbrel met the pre-specified criteria for analytical similarity. Sandoz provided a sufficiently robust analysis for the purposes of establishing the analytical component of the scientific bridge among the three products to justify the relevance of comparative data generated from clinical and non-clinical studies that used EU-approved Enbrel, to support a demonstration of biosimilarity of GP2015 to US-licensed Enbrel.

- **Devices**

The device constituent parts, pre-filled syringe (PFS) with needle safety device (NSD) and the autoinjector (AI) configurations, of the proposed drug-device combination products were reviewed by the Center for Devices and Radiological Health (CDRH).

The GP2015 drug product is filled in a PFS with a 27 ½ Gauge stacked needle with BD UltraSafe Passive Needle Guard (NSD) in two strengths, 25 mg/0.5 mL and 50 mg/mL. Both strengths use the identical primary container materials. They only differ in the filling volume and are identified by (b) (4). After assembly the strength can be differentiated amongst others by the label, the color of the device constituent parts and the secondary packaging.

The auto-injector is based off of the (b) (4) developed by (b) (4). on behalf of Novartis Pharma (b) (4). It is a disposable, fixed dose, single dose needle-based injection system with automated functions according to ISO 11608-1.

The CDRH review team concluded that (1) design controls and verification activities are adequate, (2) the devices conform with the referenced international and FDA-recognized consensus standards, (3) the devices meet essential performance requirements, the ISO 11608-1 Dose Accuracy Specifications, (4) the sponsor has established and conducted appropriate device design risk management activities, (5) the devices were demonstrated to be biocompatible according to the level of patient contact.

The CDRH review team recommended approval of the combination product based on review of the device constituent with three post-market commitments as detailed in the section on Recommendation for other Postmarketing Requirements and Commitments at the end of this memorandum. The recommended PMCs pertain to the injection depth and the test items related to the audible and visual feedback into the lot release testing for commercial batches of (b) (4), implementation of specifications based on recently validated a method for measurement of BLGF (break loose, glide force), and transport validation prior to the launch of the product. I concur with CDRH recommendations.

With respect to the proposed (b) (4) autoinjector, the applicant also submitted human factors study data gathered for Cosentyx Sensoready pen platform. The BLA for Cosentyx (secukinumab) is held by Novartis and the Sensoready pen platform was approved as part of BLA 125504 on January 21, 2015. Of note, Sandoz is a Novartis company. Because the Cosentyx human factor study included the same comparable state and patient populations as those proposed for Erelzi (with the exception of JIA), as a scientific matter, DMEPA concluded that the Cosentyx Sensoready pen human factors validation data referenced in this submission can be appropriately relied on to support the development of the Erelzi autoinjector. I concur with this conclusion.

- **Facilities review/inspection**

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for Sandoz GmbH (FEI 3004828473) and Novartis Pharma Stein AG (FEI 3002653483) proposed for GP2015 DS and DP manufacture.

All proposed manufacturing and testing facilities are acceptable on the basis of their currently acceptable CGMP compliance status and recent relevant inspectional coverage. This submission is recommended for approval from a facilities assessment perspective.

4. Nonclinical Pharmacology/Toxicology

Pharm-Tox Reviewer: Andrea Benedict, Ph.D.; Supervisor: Carol Galvis, Ph.D.

The GP2015 nonclinical development program was adequate to support clinical development. The pharmacology and toxicology studies submitted in support of the BLA included pharmacology studies in Tg197 mice (which constitutively express human TNFα and develop polyarthritis) 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. 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 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. The nonclinical pharmacology, pharmacokinetic, and repeat-dose toxicity data submitted support a demonstration of the similarity (i.e., comparable achieved exposures, safety, and efficacy) between GP2015 and EU-approved Enbrel from the nonclinical Pharmacology and Toxicology perspective. There are no outstanding issues from the nonclinical Pharmacology and Toxicology perspective.

In summary, the animal studies submitted demonstrate the similarity of GP2015 to EU-approved Enbrel in terms of the pharmacologic, pharmacokinetic, and repeat-dose toxicity profiles. The Pharmacology and Toxicology team concluded, and I agree, that the results of these animal studies can be taken together with the data from the analytical bridging studies (refer to the CMC section for details) to support a demonstration that GP2015 is biosimilar to US-licensed Enbrel. No residual uncertainties have been identified by this discipline.

5. Clinical Pharmacology/Biopharmaceutics

Clinical Pharmacology Reviewer: Yunzhao Ren, M.D., Ph.D.
Clinical Pharmacology Team Leader: Ping Ji, Ph.D.

- **General clinical pharmacology/biopharmaceutics considerations**

Description of Relevant Clinical Pharmacology Studies

The clinical pharmacology program of GP2015 to evaluate the pharmacokinetic (PK) similarity between GP2015 and US-licensed Enbrel and to assess the PK element of the scientific bridge between GP2015, US-licensed Enbrel and EU-approved Enbrel included three PK studies (Studies 101, 102, and 104) in healthy subjects, a cross-study PK comparison (Report 105), and steady state PK assessment in patients with chronic PsO (Study 302) (Table 6).

Table 6. Key Design Features of GP2015 Clinical Studies

Study ID	Design	Objectives	Subjects	Treatments	Endpoints
Clinical Pharmacology Studies					
Study 101	R, DB, SD, 2-way cross-over	PK, safety, and immunogenicity	57 healthy subjects	SD 50 mg SC: • GP2015 • EU-Enbrel	C_{max}, AUC_t and AUC_{inf}
Study 102	R, DB, SD, 2-way cross-over	PK, safety, and immunogenicity	54 healthy subjects	SD 50 mg SC: • GP2015 • US-Enbrel	C_{max}, AUC_t and AUC_{inf}
Study 104	R, DB, SD, 2-way cross-over	PK, safety, and immunogenicity	54 healthy males	SD 50 mg SC: • GP2015 • EU-Enbrel	C_{max}, AUC_t and AUC_{inf}
Report 105	A cross-study comparison of studies 101 and 102				
Study 103	R, OL, SD 2-way cross-over	PK, safety, and immunogenicity	57 healthy males	SD GP2015 50 mg SC: • Autoinjector • Prefilled syringe	C_{max}, AUC_t and AUC_{inf}
Comparative Clinical Study					
Study 302	R, DB, PG TP1 (Wk 0-12)	Efficacy, safety, immunogenicity, PK	531 PsO patients	50 mg SC twice weekly: • GP2015 • EU-Enbrel	PASI 75
	R, DB, PG TP2 (switching) (Wk 12-30)	Safety, immunogenicity, PK	PsO patients re-randomized	50 mg SC Q weekly: • cont'd GP2015 • switched GP2015 • cont'd EU-Enbrel • switched EU-Enbrel	Safety, Immunogenicity

Each of the three PK studies was conducted as randomized, two-way crossover studies to assess PK, safety, and immunogenicity. In these studies, healthy subjects received one single dose of 50 mg subcutaneously (SC) of study drug followed by a washout period of at least 35 days and were then crossed over to receive another single dose of 50 mg SC of the comparator product. As described in the draft guidance for Industry entitled, "Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product,"[12] a single-dose,

[12] Guidance for Industry "Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference

randomized study is generally the preferred design for PK similarity assessments. A cross-over design is appropriate for GP2015/etanercept because it has a relatively short half-life and low immune response rate. Additionally, conducting the study in healthy subjects is reasonable, as it is more sensitive in evaluating the product similarity due to lack of potentially confounding factors such as underlying and/or concomitant disease and concomitant medications. The 50 mg SC dose is relevant as it is consistent with the approved dose of US-licensed Enbrel.

- Study 102 was the pivotal clinical pharmacology study designed to evaluate PK similarity, safety, and immunogenicity of GP2015 and US-licensed Enbrel.

- Both Study 101 and Study 104 were designed to compare the PK profiles of GP2015 and EU-approved Enbrel. Study 104 was conducted on request by the European Regulatory Authorities to support the demonstration of PK similarity of GP2015 to the EU-approved Enbrel, as in Study 101, the pre-specified acceptance criteria were met for C_{max} but not for AUC_{0-t} and AUC_{0-inf}.

- A pre-specified cross-study comparison was conducted to establish the PK bridge between US-licensed Enbrel (from Study 102) and EU-approved Enbrel (from Study 101) (Report 105). In addition to the analytical bridging data, the PK comparison provided in the report and the PK similarity data from Studies 101, 102, and 104 comprised the bridging data to scientifically justify the relevance of the comparative data from the clinical development program with EU-approved Enbrel. For additional considerations on the use of data generated using non-US-approved comparator product, refer to section 2, (under "Reference Product") above. A cross-study comparison was justified because both Study 101 and 102 had identical study design, eligibility criteria, demographic and baseline characteristics of the study population, GP2015 product lot, and bioanalytical method. The two studies were performed during an overlapping time period.

- The supportive PK similarity assessment in the setting of repeat dosing was conducted in patients with moderate to severe chronic plaque-type psoriasis (Study 302). The Study 302 was designed as a multi-center, randomized, double-blind, parallel group, comparative clinical efficacy, safety, and immunogenicity study between GP2015 and EU-approved Enbrel. Sparse PK samples from 147 patients were collected for trough concentrations at Week 2, 4, 8, and 12.

The PK samples in the clinical pharmacology studies were analyzed with validated ELISA method. The bioanalytical assays used in the PK studies provided total protein concentration measurement and were not able to distinguish the disulfide bond correctly-bridged variant and wrongly-bridged variant. Of note, the Applicant submitted data from one additional PK study,

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Product." May 2014.
http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM397017.pdf

Study 103, designed to assess PK similarity between two delivery devices following a single dose of GP2015.

Results of Clinical Pharmacology Studies

Study 102: GP2015 vs US-licensed Enbrel

Study 102 was a single center, randomized, double-blind, two-way crossover study with two treatment periods comparing a single-dose 50 mg SC injection of the test product GP2015 and US-licensed Enbrel in 54 healthy subjects. The pairwise comparisons of GP2015 and US-licensed Enbrel met the pre-specified acceptance criteria for PK similarity (90% CIs for the ratios of geometric mean of $AUC_{0\text{-}inf}$, $AUC_{0\text{-}tlast}$, and C_{max} within the interval of 80% to 125%) as summarized in Table 7. As discussed in the section on Analytical Similarity Assessment above, the analytical data on glycan structure showed small differences in the levels of high mannose forms Man 5, Man 6 and Man8 (~2.2% for GP2015 and ~8% for US-licensed Enbrel and EU-approved Enbrel). High mannose glycan structures may alter the PK of a molecule though binding to cell surface mannose binding proteins. However, PK similarity was demonstrated for GP2015 and US-licensed Enbrel, which addresses the residual uncertainty in the differences in high mannose glycans between GP2015 and US-licensed Enbrel and which supports a demonstration of biosimilarity between GP2015 and US-licensed Enbrel.

Table 7. Statistical Analysis of the PK Parameters of GP2015 and US-Licensed Enbrel in Study 102

Parameter	N	GP2015[1]	US-Enbrel[1]	Ratio (GP2015/US-Enbrel)[2]
$AUC_{0\text{-}t}$ (µg·h/mL)[1]	53	369.761	414.962	0.8911 (0.8308, 0.9557)
$AUC_{0\text{-}inf}$ (µg·h/mL)[1]	54	390.286	439.656	0.8877 (0.8320, 0.9471)
C_{max} (µg/mL)[1]	54	2.028	2.146	0.9450 (0.8695, 1.0271)

Source: FDA analysis of data from Sandoz 351(k) BLA submission
[1] Least-squares geometric means
[2] Ratio (90% CI)

Studies 101 and 104: GP2015 vs EU-approved Enbrel

Study 101 was a single center, randomized, double-blind, two-way crossover study with two treatment periods comparing a single-dose 50 mg SC injection of the test product GP2015 and comparator EU-approved Enbrel in healthy subjects. The pairwise comparison of GP2015 and EU-approved Enbrel was within the pre-specified criteria for C_{max} but not for $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ as summarized in Table 8.

Table 8. Statistical Analysis of the PK Parameters of GP2015 and EU-approved Enbrel in Study 101

Parameter	N	GP2015[1]	EU-Enbrel[1]	Ratio (GP2015/EU-Enbrel)[2]
AUC_{0-t} (µg·h/mL)	49	335.150	392.619	0.8536 (0.7830, 0.9307)
AUC_{0-inf} (µg·h/mL)	49	353.338	416.506	0.8583 (0.7803, 0.9223)
C_{max} (µg/mL)	50	1.808	1.982	0.9124 (0.8247, 1.0094)

Source: FDA analysis of data from Sandoz 351(k) BLA submission
[1] Least-squares geometric means
[2] Ratio (90% CI)

Study 104 was a single center, randomized, double-blind, two-way crossover study with two treatment periods comparing a single-dose 50 mg SC injection of the test product GP2015 and comparator EU-approved Enbrel in healthy males. It is a repeat study, on request by the European Regulatory Authorities, and has the same study design and methodology as Study 101. Notable differences include that only male subjects (n=54) were enrolled in Study 104 whereas both males (n=23) and females (n=23) were enrolled in the study 101; the batches of both GP2015 and EU-approved Enbrel were different between two studies; and the bioanalytical methods were different between two studies, although both methods were validated. The modifications implemented in Study 104 were intended to reduce the PK variability observed in Study 101. The pairwise comparisons of GP2015 and EU-approved Enbrel for AUC_{0-t}, AUC_{0-inf}, and C_{max} met the pre-specified acceptance criteria for PK similarity as summarized in Table 9.

Table 9. Statistical Analysis of the PK Parameters of GP2015 and EU-approved Enbrel in Study 104

Parameter	N	GP2015	EU-Enbrel	Ratio (GP2015/EU-Enbrel)[2]
AUC_{0-t} (µg·h/mL)[1]	54	632.662	644.007	0.9824 (0.9449, 1.0214)
AUC_{0-inf} (µg·h/mL)[1]	54	680.945	706.883	0.9633 (0.9264, 1.0016)
C_{max} (µg/mL)[1]	54	3.416	3.087	1.1066 (1.0500, 1.1664)

Source: FDA analysis of data from Sandoz 351(k) BLA submission
[1] Least-squares geometric mean
[2] Ratio (90% CI)

The two-fold difference in exposure between Study 104 and Study 101 observed for GP2015 and EU-approved Enbrel could be due to different bioanalytical methods used in the two studies, however, other factors cannot be ruled out.

Report 105: EU-approved Enbrel and US-licensed Enbrel

The PK comparison between EU-licensed Enbrel from study 101 and US-licensed Enbrel from Study 102 was conducted and summarized in Report 105. This statistical comparison was pre-defined and outlined as a pre-specified objective of both protocols. The sample size used in the data analysis was pre-determined from the two study protocols 101 and 102 and appears sufficient to assess similarity between these two products. The pairwise comparisons of EU-approved Enbrel and US-licensed Enbrel met the pre-specified acceptance criteria for PK

similarity (90% CIs for the ratios of geometric mean of $AUC_{0\text{-inf}}$, $AUC_{0\text{-tlast}}$, and C_{max} within the interval of 80% to 125%) as summarized in Table 10.

Table 10. Statistical Analysis of the PK Parameters of EU-approved Enbrel and US-Licensed Enbrel in Report 105

Parameter	EU-Enbrel	US-Enbrel	Ratio (EU-Enbrel/US-Enbrel)[2]
$AUC_{0\text{-t}}$ (µg·h/mL)[1]	392.632 (N=49)	415.237 (N=53)	0.9456 (0.8397, 1.0647)
$AUC_{0\text{-inf}}$ (µg·h/mL)[1]	416.484 (N=49)	439.738 (N=54)	0.9471 (0.8451, 1.0615)
C_{max} (µg/mL)[1]	1.980 (N=50)	2.146 (N=54)	0.9222 (0.8026, 1.0596)

Source: FDA analysis of data from Sandoz 351(k) BLA submission
[1] Least-squares geometric means (subject number)
[2] Ratio (90% CI)

Study 103: PK Study Comparing GP2015 Exposure Between Pre-filled Syringe and Autoinjector Presentations

Study 103 demonstrated that PK is comparable between GP2015 administered via a pre-filled syringe and the proposed marketed autoinjector presentation as the 90% CIs for the geometric mean ratios (autoinjector/pre-filled syringe) of systemic exposure (i.e., $AUC_{0\text{-t}}$, $AUC_{0\text{-inf}}$, and C_{max}) are all within 80-125%.

Study 302: Supportive PK in Patients After Repeat Dosing

In comparative clinical Study 302, pre-dose PK samples were collected from 147 patients at Day 1, and at Weeks 2, 4, 8, and 12 during treatment period 1. The mean trough serum concentrations were generally comparable at each time point between GP2015 and EU-approved Enbrel at steady state.

Clinical Pharmacology Conclusions

Overall, the submitted clinical pharmacology data are adequate to:

1) Demonstrate similarity of exposure between GP2015 and US-licensed Enbrel. The PK studies, conducted in healthy subjects, are considered sensitive to detect clinically significant differences in exposure among the products. Single-dose PK similarity pre-specified margins were met in comparison of GP2015 to US-licensed Enbrel, GP2015 to EU-approved Enbrel, and US-licensed Enbrel to EU-approved Enbrel. The demonstration of similar exposure supports a finding of PK similarity between GP2015 and US-licensed Enbrel.
2) Establish the PK component of the scientific bridge to justify the relevance of the comparative data generated using EU-approved Enbrel to support a demonstration of the biosimilarity of GP2015 to US-licensed Enbrel.

The Office of Clinical Pharmacology has determined that PK similarity has been demonstrated between GP2015 and US-licensed Enbrel, and the results from the PK studies add to the

totality of evidence to support a demonstration of no clinically meaningful differences between GP2015 and US-licensed Enbrel. I concur with this recommendation. The PK studies have not raised any new uncertainties and the clinical pharmacology data support a demonstration of biosimilarity between GP2015 to US-licensed Enbrel.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Primary Statistical Reviewer for DDDP: Kathleen Fritsch, Ph.D.,
Statistical Team Leader for DDDP: Mohamed Alosh, Ph.D.

Overview of the Clinical Program

Sandoz Inc. submitted one comparative clinical study in patients with plaque psoriasis (Study 302). Of note, the comparative clinical efficacy data are derived from a clinical study using EU-approved Enbrel as the comparator. However, Sandoz has provided sufficient analytical and clinical PK bridging data (Studies 101, 102, and 104, and Report 105) between GP2015, US-licensed Enbrel, and EU-approved Enbrel. These data justify the relevance of the comparative data generated using EU-approved Enbrel to support a demonstration of no clinically meaningful differences between GP2015 to US-licensed Enbrel.

Study 302 is a randomized, double blind comparative clinical study of GP2015 and EU-approved Enbrel in subjects age 18 years and older with chronic moderate-to-severe plaque psoriasis. Of the 531 subjects enrolled, 264 were randomized to the GP2015 arm and 267 randomized to the EU-approved Enbrel arm. The study provided data on subjects who underwent a transition from EU-approved Enbrel to GP2015 after Week 12. The primary endpoint was the proportion of subjects at Week 12 achieving at least a 75% reduction from baseline in the Psoriasis Area Severity Index (PASI 75). The proportion of subjects achieving PASI 75 at Week 12 was similar in both the GP2015 and EU-approved Enbrel arms (70.5% vs. 71.5% in the full analysis population; the exact 90% confidence interval for the difference was (-8.3, 6.0)). The confidence interval was within the pre-specified margin of ± 18%. The results of the supportive endpoints (mean percent change in PASI and the Investigator's Global Assessment) were consistent with the results of the primary endpoint. The enrolled population in Study 302 was comparable to the populations enrolled in two historical placebo-controlled trials of Enbrel: Leonardi (2003)[5] and Papp (2005)[6]. One notable difference was the geographic location: the historical Enbrel studies were conducted in the US, Canada, and

[5] Leonardi CL et al, N Engl J of Med. 2003; 349:2014-22.
[6] Papp KA et al, Br J of Dermatol. 2005; 152:1304-12.

Western Europe, while Study 302 was conducted in Europe and South Africa, with most centers in Eastern Europe. The PASI 75 response rates in Study 302 were higher than in the historical studies (71.5% vs. 49%). While differences in the populations between the geographic locations could have contributed to the higher response rate in Study 302, that higher rate does not represent a loss of efficacy relative to the historical studies and does not negatively impact the assay sensitivity of the study. Further, we did not identify issues with the quality of study conduct or the integrity of the study data.

Of note, the study design of Study 302 includes multiple switching periods during treatment period 2 (weeks 12 and 30). We note that the data to support a demonstration of biosimilarity that is the focus of the FDA review of this application includes treatment period 1 in subjects who undergo a single transition from the reference product to GP2015. While there are additional data that Sandoz has presented involving multiple switches, that data generally is not expected as a part of demonstrating biosimilarity. However, because the data were provided by Sandoz, FDA did review the pooled safety and immunogenicity data from the multiple switches.

Brief Description of Efficacy Endpoints

The primary endpoint in Study 302 was PASI 75 at Week 12. The PASI score is derived from assessments for erythema, plaque elevation, and scaling over four body regions (head, trunk, upper limbs, and lower limbs). PASI scores can range from 0 to 72. PASI 75 is defined as at least a 75% reduction from baseline in the PASI score. The key secondary endpoint was percent change in PASI averaged across TP1. Additional secondary endpoints included percent change in PASI at each visit and IGA success (clear or almost clear) at each visit.

Discussion on Similarity Margin

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

The pre-specified similarity margin for the difference in proportions was ±18%. The Applicant justified the choice of an 18% similarity margin noting that 18% maintains 60% of the observed treatment effects relative to placebo (45-46%) reported in Leonardi (2003)[7] (49% for Enbrel vs. 4% for placebo) and Papp (2005)[8] (49% for Enbrel vs. 3% for placebo). Under the design characteristics used by the Applicant (proposed sample size of approximately 546 subjects with an expected PASI 75 response rate of 49%), a 90% confidence interval would be the point estimate for the treatment difference plus or minus approximately 7%[9].

[7] Leonardi CL et al, N Engl J of Med. 2003; 349:2014-22.
[8] Papp KA et al, Br J of Dermatol. 2005; 152:1304-12.
[9] Normal approximation to the binomial: $\pm 1.645\sqrt{2(0.49)(0.51)/273}$

Study Conduct

Treatment groups in the Study 302 were generally balanced with respect to demographics and baseline characteristics. The study was conducted in Europe and South Africa with most enrollments in Eastern Europe. None of the study sites were in the US. The average baseline disease PASI score was 22.5, average BSA was 30.7 and 71% of subjects had moderate and 29% severe disability on the IGA, consistent with the intended population of patients with moderate-to-severe chronic plaque psoriasis.

Study 302 randomized 531 subjects: 264 to GP2015 and 267 to EU-approved Enbrel. The discontinuation rate prior to Week 12 was low (see Table 11); 3% of GP2015 and 4.5% of EU-approved Enbrel subjects withdrew. The most common reason for study discontinuation was 'subject decision.' A greater number of EU-approved Enbrel subjects than GP2015 subjects (1.9% vs. 0.8%) discontinued due to subject decision. Similar numbers of subjects withdrew due to adverse events.

Table 11. Patient Disposition in Treatment Period 1 (Week 1-12), Study 302

	GP2015	EU-Enbrel
Subjects Randomized	264	267
Discontinued Treatment Period 1	8 (3.0%)	12 (4.5%)
Adverse event	4 (1.5%)	3 (1.1%)
Death	--	1 (0.4%)
Lost to follow-up	1 (0.4%)	--
Non-compliance with study treatment	--	1 (0.4%)
Physician decision	--	1 (0.4%)
Protocol deviation	1 (0.4%)	--
Subject decision	2 (0.8%)	5 (1.9%)
Injection site reaction	--	1 (0.4%)

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

The randomization in Study 302 was stratified on prior systemic psoriasis therapy and weight. The Agency investigated why so many of the stratification values entered by the investigators into the randomization system did not match the data recorded about prior therapies. It was determined that the protocol did not provide sufficient guidance to the individual investigators on what types of therapies were to be considered prior systemic therapies for psoriasis or what time frame should be used to determine if prior therapies had been used. The sensitivity analyses to account for the differences in adequately capturing and classifying prior systemic psoriatic therapies were consistent with the primary analyses and did not impact the conclusions of the study. No other significant issues with study conduct were identified.

Study Results

Study 302 met the similarity criteria for the primary endpoint of PASI 75 at Week 12 in both the full analysis set and the per protocol population. The exact confidence intervals for the difference in PASI 75 response were within the pre-specified similarity margin of ±18% (see Table 12). Because of the concerns with how the prior therapy information was collected for the stratification and randomization, FDA recommends presenting the results using the analysis specified in the protocol (exact confidence intervals) rather than using the analysis specified in the statistical analysis plan (confidence intervals based on a logistic regression model with terms for body weight and prior therapy). For the full analysis population (FAS), missing data was imputed as non-response. Because only 4% of subjects had missing data at Week 12, even when subjects with missing data are handled in opposite ways (such as all successes on one arm and as all failures on the other) it does not change the conclusion for similarity.

Table 12. Exact Confidence Intervals for the Risk Difference of PASI 75 Response Rates, Study 302

Population	GP2015	EU-approved Enbrel	Difference	90% Conf. Int.
FAS	70.5% (n=264)	71.5% (n=267)	-1.1%	(-8.3%, 6.0%)
PPS	73.6% (n=239)	75.5% (n=241)	-1.9%	(-9.4%, 5.6%)

Source: FDA analysis of data from Sandoz's 351(k) BLA submission
FAS = full analysis set (missing data imputed as non-response), PPS = per protocol set

In addition, the results of the analyses using the various definitions of the prior therapy classification (the ones used in the randomization stratification, and the re-classified 'actual' results used in the Week 12 and Week 30 study reports) lead to similar results as the exact confidence interval (data not shown).

The results for the secondary endpoints of percent change in PASI at Week 12 and IGA success (clear or almost clear) were consistent with the primary endpoint. The mean percent change in PASI at Week 12 was -82.6% for GP2015 and -81.7% for EU-approved Enbrel. The proportion of IGA responders was 58.2% for GP2015 and 55.1% for EU-approved Enbrel.

- **Discussion of statistical and clinical efficacy reviews with explanation for CDTL's conclusions**

In summary, the Applicant has provided statistically robust comparative efficacy data demonstrating similar efficacy between GP2015 and EU-approved Enbrel in patients with moderate-to-severe plaque psoriasis. The primary analysis was supported by the analysis of key secondary endpoints and sensitivity analyses accounting for the missing data. The statistical review team concluded that the results from the GP2015 clinical program support a demonstration of no clinically meaningful differences between GP2015 and US-licensed Enbrel in the indication studied. I concur with this conclusion.

- **Includes discussion of notable efficacy issues both resolved and outstanding**

None.

8. Safety

Primary Clinical Reviewer for DDDP: Gary Chiang, M.D., M.P.H.; Clinical Team Leader DDDP: David Kettl, M.D.
Primary Clinical Reviewer for DPARP: Rachel Glaser, M.D.; Clinical Team Leader for DPARP: Nikolay Nikolov, M.D.

- **Studies contributing to safety analyses**

The comparative safety and immunogenicity data with repeat dosing were derived from the single comparative clinical study in plaque psoriasis (Study 302). The safety population included 531 subjects, of whom 143 (95.3%) were exposed to GP2015 for at least 24 weeks. Patients with plaque psoriasis received 50 mg SC twice weekly for the first 12 weeks, then 50 mg SC weekly up to 52 weeks of GP2015 or EU-approved Enbrel. Additional safety and immunogenicity data with single dosing were provided from the PK studies 101, 102, and 104. A summary of the studies contributing to the primary safety analyses may be found in Table 6 above. As noted earlier, the majority of the safety data are derived from clinical studies using the EU-approved Enbrel. However, Sandoz has provided comparative analytical data and clinical PK bridging data between the US-licensed and EU-approved Enbrel to justify the relevance of comparative data, including safety data generated using EU-approved Enbrel to support a demonstration of no clinically meaningful differences between the GP2015 and US-licensed Enbrel.

- **General discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests.**

In the GP2015 clinical program, the overall incidences of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and AEs leading to discontinuation or treatment interruption, infections, injection site reactions, were similar between GP2015 and the comparator products. The incidence of adverse events, serious adverse events, adverse events of special interest, and death in the comparative clinical study 302 in patients with plaque psoriasis are summarized in Table 13. No new safety signals were identified in the GP2015 group compared to the known adverse event profile of US-licensed Enbrel.

Table 13. Summary of Adverse Events in Treatment Periods 1 and 2 Through Week 30, Study 302

	Treatment Period 1		Treatment Period 2			
Number of patients with:	**GP2015 N=264 n (%)**	**EU-Enbrel N=267 n (%)**	**Cont'd GP2015 N=150 n (%)**	**Cont'd EU-Enbrel N=151 n (%)**	**Switched EU-Enbrel N=96 n (%)**	**Switched GP2015 N=100 n (%)**
At least 1 TEAE	99 (38)	96 (36)	47(31)	52 (34)	35 (37)	32 (32)
Serious Adverse Events	4 (2)	3 (1)	1 (<1)	2 (1)	3 (3)	3 (3)
Discontinuation due to AE	5 (2)	4 (2)	1 (<1)	2 (1)	5 (5)	1 (1)
Treatment interruption due to AE	3 (1)	6 (2)	6 (4)	6 (4)	2 (2)	3 (3)
Deaths	--	1 (0.4)	--	--	--	--
AESI	9 (3)	5 (2)	7 (5)	3(2)	2 (2)	3 (3)

Continued GP2015: GP2015 continued from Period 1
Continued Enbrel: EU-Enbrel continued from Period 2
Switched GP2015: Switched to treatment sequence EU-Enbrel>GP2015>EU-Enbrel in Period 2
Switched Enbrel: Switched to treatment sequence GP2015>EU-Enbrel>GP2015 in Period 2
Patients experiencing multiple events are counted once within each treatment group
Source: FDA analysis of data from Sandoz's 351(k) BLA submission

Death

A single death occurred in the EU-approved Enbrel treatment group. This 58 year old Caucasian male subject who had concomitant conditions that included diabetes and hypertension, died of cardiopulmonary failure not suspected related to the study drug. There were no other deaths in the GP2015 clinical program.

Nonfatal Serious Adverse Events (SAE)

The proportion of patients who experienced at least one SAE was similar between the two treatment groups, GP2015 and EU-approved Enbrel, during treatment period 1 in Study 302 (Table 13). There was no notable difference in the incidence of SAEs in those patients who underwent a transition from EU-approved Enbrel to GP2015 as compared to those who continued on EU-approved Enbrel, nor in those that continued on GP2015 and those that transitioned from GP2015 to EU-approved Enbrel in treatment period 2. The types of SAE did not identify any new safety concerns. None of the SAEs were reported in more than one patient.

Discontinuations due to Adverse Events

Adverse events leading to discontinuation were rare overall and did not cluster within any specific system organ class (SOC). The proportion of patients discontinuing due to an adverse event was similar between the GP2015 and EU-approved Enbrel treatment groups in treatment period 1 and did not appear to increase in treatment period 2 following the transition from EU-approved Enbrel to GP2015

Adverse Events of Special Interest (AESI)

AESI were defined by preferred terms encompassing all of the special warnings and precautions given on the label for Enbrel. These included infections, serious infections, pneumonia, tuberculosis (TB), injection site reactions, anaphylaxis, congestive heart failure (CHF), serious hepatobiliary events, drug induced liver injury, malignancy and lymphoma, among other events. A similar proportion of patients in both treatment groups reported TEAEs of special interest; 9 subjects (3.4%) and 5 subjects (1.9%) in the GP2015 and EU-approved Enbrel treatment groups had at least one TEAE of special interest, respectively in treatment period 1. A higher proportion of patients in the GP2015 treatment group (5 patients (1.9%) experienced AESI in the neoplasms as compared with the EU-approved Enbrel treatment group (1 patient (0.4%). The reported neoplasms were of varied types and reported early in treatment, and thus, not attributed to study treatment. The single malignant event was a malignant melanoma that was resected prior to initiation of study treatment.

In treatment period 2, a similar proportion of patients in the continued GP2015, continued EU-approved Enbrel, switched EU-approved Enbrel, and switched GP2015 treatment groups reported AESI (7 patients (4.7%), 3 patients (2.0%), 2 patients (2.1%), and 3 patients (3.0%) respectively). The most commonly affected SOCs were infections and infestations and skin and subcutaneous tissue disorders. One patient in the continued GP2015 group reported a melanocytic nevus. Analysis of the safety data of patients who underwent a single transition from EU-approved Enbrel to GP2015 between weeks 12 and 18, as compared to those who continued treatment with EU-approved Enbrel did not reveal any increase in adverse events.

Common AE

Adverse events in the Infections and Infestations SOC were the most common adverse events in the GP2015 development program with event rates similar between GP2015 and the comparator products. The most frequently reported infections included upper respiratory tract infection and nasopharyngitis. The common adverse event profile remained consistent during treatment period 2 and similar between subjects who underwent a single transition from EU-approved Enbrel to GP2015 and those who continued on EU-approved Enbrel.

Laboratory Abnormalities, Vital Signs and Electrocardiograms (ECGs)

No unexpected laboratory findings were reported in GP2015 clinical program.

- **Immunogenicity**

Immunogenicity Reviewer: Brian Janelsins, Ph.D.
Immunogenicity Team Leader: Jee Chung, Ph.D.

Immunogenicity was assessed throughout the GP2015 clinical program, including in studies 101, 102, 103, and 104 following single dose administration in healthy subjects, and in Study 302 following repeat dosing as a monotherapy in patients with plaque psoriasis.

Immunogenicity assays to screen and confirm the presence of binding anti-drug antibodies (ADAs) and to determine the neutralizing capability of confirmed positive ADAs were developed, validated, and used to determine the clinical immunogenicity rates between GP2015 and EU-approved Enbrel. As previously discussed in this memorandum, the applicability of the data generated with the EU-approved Enbrel, including immunogenicity data, is supported by the analytical and clinical pharmacology bridging data between GP2015, US-licensed Enbrel and EU-approved Enbrel generated by the Applicant.

In the healthy subject studies, 101, 102, and 103, all samples were negative for binding anti-etanercept antibodies. In study 104, three subjects who received GP2015 in period 1 and EU-approved Enbrel in period 2, had binding ADAs at the follow-up visit and a fourth subject had an indeterminate ADA result. The confirmed ADAs were below the lower limit of quantification and none of the ADAs were neutralizing.

In Study 302, immunogenicity data are available for all patients who were treated in treatment period 1 and treatment period 2. Binding ADAs were confirmed in 5 patients in the EU-approved Enbrel treatment arm. None of these antibodies were neutralizing. No patients in the GP2015 treatment arm developed ADAs. In treatment period 2, no additional patients developed ADAs up to Week 30. There was no increase in ADA at Week 18 in those patients who transitioned study treatment as compared to those who continued on the treatment to which they were originally randomized.

Based on the immunogenicity data from the single dose healthy subject studies, and the repeat dose study 302, there does not appear to be an increased risk of development of ADAs with treatment with GP2015 as compared to EU-approved Enbrel. Further, ADA formation did not increase following a single transition from EU-approved Enbrel to GP2015. Therefore, there are sufficient data supporting similar immunogenicity between GP2015, EU-approved Enbrel, and US-licensed Enbrel, and that immunogenicity adds to the totality of the evidence to support a demonstration of no clinically meaningful differences between GP2015 and US-licensed Enbrel. The immunogenicity review team recommends approval of the BLA from immunogenicity perspective and I agree with this recommendation.

- **Discussion of primary reviewer's comments and conclusions**

The DPARP and DDDP clinical review teams and I are in agreement that the submitted safety and immunogenicity data and analyses are adequate to support the conclusion of no clinically meaningful differences between GP2015 and US-approved Enbrel. The safety database submitted for GP2015 is adequate to provide a reasonable descriptive comparison between the two products. The analysis of the data indicates a safety profile similar to that of US-licensed Enbrel. There were no notable differences between GP2015 and EU-approved Enbrel in treatment-emergent adverse events, serious adverse events, adverse events leading to discontinuations, and deaths between the treatment groups. No new safety signals have been identified compared to the known adverse event profile of US-licensed Enbrel. The FDA safety analysis is consistent with the Applicant's.

- **Highlight differences between CDTL and review team with explanation for CDTL's conclusion**

None.

- **Discussion of notable safety issues (resolved or outstanding)**

None.

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

Sandoz seeks licensure for all indications for which US-licensed Enbrel is licensed (listed in Introduction section above). The GP2015 clinical program however, provides clinical efficacy and safety data from a clinical study in patients with PsO.

The Agency has determined that it may be appropriate for a biosimilar product to be licensed for one or more conditions of use (e.g., indications) for which the reference product is licensed, based on data from a clinical study(ies) performed in another condition of use. This concept is known as extrapolation. As described in the Guidance for Industry: "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009", if a biological product meets the statutory requirements for licensure as a biosimilar product under section 351(k) of the PHS Act based on, among other things, data derived from a clinical study or studies sufficient to demonstrate safety, purity, and potency in an appropriate condition of use, the potential exists for that product to be licensed for one or more additional conditions of use for which the reference product is licensed.[10] The Applicant needs to provide sufficient scientific justification for extrapolation, which should address, for example, the following issues for the tested and extrapolated conditions of use:

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

[10] Guidance for Industry "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009", April 2015
http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444661.pdf

As a scientific matter, the FDA has determined that differences between conditions of use with respect to the factors addressed in a scientific justification for extrapolation do not necessarily preclude extrapolation. Consistent with the principles outlined in the above FDA guidance, Sandoz has provided a justification for the proposed extrapolation of clinical data from studies in PsO to each of the other indications approved for US-licensed Enbrel for which Sandoz is seeking licensure, as summarized in this section.

First, Sandoz believes GP2015 is highly similar to US-licensed Enbrel based on extensive analytical characterization data, similar clinical pharmacokinetics, and similar efficacy, safety, and immunogenicity in an approved indication, as demonstrated in study GP15-302 in patients with plaque psoriasis.

Further, the additional points considered in the scientific justification for extrapolation of data to support a demonstration of biosimilarity in the indications for which Sandoz is seeking licensure (RA, JIA, PsA, and AS) include:

- The primary mode of action (MOA) of etanercept is through inhibiting binding of soluble TNF-α to cell-surface receptors and through binding transmembrane TNF-α, inhibiting subsequent signal transduction and adhesion molecule expression. The scientific literature indicates that this MOA is the primary MOA in RA, JIA, AS, PsA, and PsO. In contrast to monoclonal antibodies to TNF-α, complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity have not been considered to be clinically relevant mechanisms of etanercept. The data provided by Sandoz showed similar TNF-α binding and potency to neutralize TNFα, supporting analytical similarity pertinent to this MOA.

- The pharmacokinetic parameters of US-licensed Enbrel in patients with PsO were similar to those seen in patients with RA.[11] The estimated half-life of etanercept was about 100 hours and comparable in healthy subjects, JIA and RA patients. As a fusion glycoprotein and consisting entirely of human protein components, etanercept is expected to undergo proteolysis in patients across different diseases. There are no product-related attributes that would increase the uncertainty that the PK/biodistribution may differ between GP2015 and US-licensed Enbrel in the indications sought for licensure. Since similar PK was demonstrated between GP2015 and US-licensed Enbrel in healthy subjects and patients with psoriasis, a similar PK profile would be expected between GP2015 and US-licensed Enbrel in patients with RA, JIA, AS, and PsA.

- The immunogenicity of the US-licensed Enbrel was generally low (<10%).[23] In GP2015 clinical program, the ADA formation was also low and there were no notable differences between GP2015 and comparator Enbrel, both in patients with plaque psoriasis, following repeat dosing without background immunosuppression, which is a

[11] FDA-approved Enbrel labeling

reasonably sensitive setting, and in healthy subjects after single doses. Accordingly, similar immunogenicity would be expected between GP2015 and US-licensed Enbrel in patients with RA, JIA, PsA, and AS.

- Similar clinical safety profile with chronic dosing was demonstrated between GP2015 and EU-approved Enbrel in patients with plaque psoriasis, and following single doses in healthy subjects. As analytical and PK similarity was demonstrated between GP2015 and US-licensed Enbrel, a similar safety profile would be expected between GP2015 and US-licensed Enbrel in RA, JIA, PsA, and AS

In aggregate, the evidence indicates that the extrapolation of biosimilarity to the indications for which Sandoz is seeking licensure (RA, JIA, PsA, and AS) is scientifically justified.

10. Advisory Committee Meeting

An Advisory Committee (AC) meeting was determined to be necessary to obtain independent expert advice on issues related to analytical similarity assessment and extrapolation to non-studied indications. The AC meeting was convened on July 13, 2016.[12] The following is a brief summary of the questions to the committee and surrounding discussions.

1. **DISCUSSION:** Please discuss whether the evidence from analytical studies supports a demonstration that GP2015 is highly similar to US-licensed Enbrel, notwithstanding minor differences in clinically inactive components.

   Committee Discussion: *Most committee members agreed that the evidence from analytical studies supports a demonstration that GP2015 is highly similar to US-licensed Enbrel, notwithstanding minor differences in clinically inactive components. One committee member noted that excellent characterization information for GP2015 was presented, but because it is a very complex molecule, recommended a discriminating quality control program to make sure that it stays within specifications. Another committee member noted that in addition to the analytical data presented, the use of pharmacodynamic biomarkers would have been helpful to further support the demonstration that GP2015 is highly similar to US-licensed Enbrel. Please see the transcript for details of the committee discussion.*

2. **DISCUSSION:** Please discuss whether the evidence supports a demonstration that there are no clinically meaningful differences between GP2015 and US-licensed Enbrel in the studied condition of use (plaque psoriasis (PsO)).

[12] http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/ucm481975 htm

Committee Discussion: *Most committee members agreed that the evidence supports a demonstration that there are no clinically meaningful differences between GP2015 and US-licensed Enbrel in the studied condition of use (plaque psoriasis (PsO)). One committee member agreed that that the results of the single clinical study were good, but noted that the primary efficacy response rates were significantly higher in the comparative clinical study than in the two historic placebo controlled trials raising the question about the interpretability of the comparative clinical study. Please see the transcript for details of the committee discussion.*

3. **DISCUSSION:** Please discuss whether the totality of the data provides adequate scientific justification to support a demonstration of no clinically meaningful differences between GP2015 and US-licensed Enbrel for the following additional indications for which US-licensed Enbrel is licensed:
    - Rheumatoid Arthritis (RA)
    - Juvenile Idiopathic Arthritis (JIA)
    - Psoriatic Arthritis (PsA)
    - Ankylosing Spondylitis (AS)

    If not, please state the specific concerns and what additional information would be needed to support such a demonstration. Please discuss by indication, if relevant.

    Committee Discussion: *The committee members generally agreed that the totality of the data provides adequate scientific justification to support a demonstration of no clinically meaningful differences between GP2015 and US-licensed Enbrel for the following additional indications for which US-licensed Enbrel is licensed (RA, JIA, PsA and AS). Even though not concerned with the extrapolation to JIA, one committee member expressed concerns about the lack of an age-appropriate presentation for administration of GP2015 in pediatric patients with JIA. Please see the transcript for details of the committee discussion.*

4. **VOTE:** Does the totality of the evidence support licensure of GP2015 as a biosimilar to US-licensed Enbrel for the following indications for which US-licensed Enbrel is currently licensed and for which Sandoz is seeking licensure (RA, JIA, AS, PsA, PsO)?

    Please explain the reason for your vote.

    Vote Result: YES: 20 NO: 0 ABSTAIN: 0

    Committee Discussion: *The committee members unanimously agreed that the totality of the evidence support licensure of GP2015 as a biosimilar to US-licensed Enbrel for the following indications for which US-licensed Enbrel is currently licensed and for which Sandoz is seeking licensure (RA, JIA, AS, PsA, PsO). Some committee members recommended mandatory postmarketing surveillance to assess long-term safety. One committee member noted that nonmedical switching is a major concern that needs greater*

clarification from the Agency. One committee member noted that the labeling should clearly indicate that GP2015 is a biosimilar and is not an interchangeable product. Some committee members also stressed the importance of patient education on biosimilars and interchangeability Please see the transcript for details of the committee discussion.

The reader is also referred to the full transcript of the meeting.[13]

11. Pediatrics

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

Under the Pediatric Research Equity Act (PREA), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable. Section 505B(m) of the FD&C Act added by section 7002(d)(2) of the Affordable Care Act, provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a new "active ingredient" for purposes of PREA, and a pediatric assessment is required unless waived or deferred. Thus, if GP2015 is licensed as a biosimilar product, its approval would trigger PREA and Sandoz must address PREA requirements for every indication for which they are seeking licensure.

Following revisions to the initial pediatric study plan (iPSP), based on Agency's feedback, Sandoz submitted an agreed iPSP to address the PREA requirements for the following indications as detailed below:

- Rheumatoid Arthritis (RA), Polyarticular juvenile idiopathic arthritis (JIA): Polyarticular JIA has been considered the condition of use to address PREA for products approved for RA. (b) (4) the GP2015 prefilled syringe with needle safety device and autoinjector presentations submitted in the BLA are not designed to allow for accurate administration of doses less than 50 mg, which impacts children who weigh less than 63 kg. For accurate weight-based dosing of patients 2 years of age or older that are less than 63 kg, a dose-adjustable presentation is required under PREA. Thus, Sandoz requested a deferral of the requirement to develop an age-appropriate presentation that can be used to accurately administer GP2015 to pediatric patients who weigh less than 63 kg to address PREA. The Applicant has also submitted requests for waiver of the requirement to submit a pediatric assessment for patients < 2

[13] http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM518367.pdf

years old because condition is rare in this age group and such studies would be impossible or highly impracticable.

- Ankylosing Spondylitis (AS), Psoriatic Arthritis (PsA): The Applicant has submitted requests for waiver of the requirement to submit a pediatric assessment for juvenile AS and juvenile PsA because the studies would be impossible or highly impracticable (b) (4) .

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

The GP2015 pediatric study plan was discussed at the Pediatric Review Committee (PeRC) meeting on March 09, 2016. The PeRC agreed with the requested waivers and deferrals for RA, JIA, AS and PsA and recommended that a PREA PMR be issued to develop an age appropriate presentation so that this product may be accurately administered to pediatric patients down to 2 years of age with pJIA. I agree with PeRC's recommendations.

12. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP)—**Not warranted, no issues.
- **Exclusivity or patent issues of concern**— The CDER Exclusivity Board (Board) has determined that there is no unexpired exclusivity under section 351(k)(7) of the Public Health Service (PHS) Act for Enbrel (etanercept) (BLA 103795; Amgen, Inc.) that would prohibit the submission, or approval, of any 351(k) application for a proposed biosimilar (or interchangeable) to Enbrel (etanercept).
- **Financial disclosures**—No issues.
- **Other GCP issues**—No issues.
- **OSI audits—**Three clinical sites that enrolled patients in the comparative clinical study 302 were selected for inspection. In addition, a sponsor inspection of Hexal, Inc., a subsidiary of Sandoz, Inc., was also conducted. OSI inspections of the clinical sites and the Applicant did not identify major deficiencies in data quality and integrity. The inspection findings supported the acceptability of the clinical data submitted to support the BLA.
- **Other discipline consults**—Not applicable
- **Any other outstanding regulatory issues**—Not applicable

13. Labeling

- **Proprietary name**

The Applicant initially submitted the proposed proprietary name, (b) (4) on July 30, 2015. However, the Division of Medication Error Prevention and Analysis (DMEPA) found the names, unacceptable due to orthographic and phonetic similarities, as well as shared product characteristics with the proprietary name, (b) (4)

Thus, the Applicant submitted the names, Erelzi and Erelzi Sensoready Pen, for review on November 25, 2015. The proposed proprietary names for GP2015 were Erelzi and Erelzi Sensoready Pen. These names have been reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) and by the Office of Prescription Drug Promotion (OPDP, formerly the Division of Drug Marketing and Advertising) and were found to be conditionally acceptable and the Applicant was informed on February 16, 2016.

- **Non-proprietary/Proper name**

FDA has determined that the use of a distinguishing suffix in the nonproprietary name for Sandoz's GP2015 is necessary to distinguish this proposed product from Enbrel (etanercept). As explained in FDA's draft Guidance for Industry, Nonproprietary Naming of Biological Products,[14] FDA expects that a nonproprietary name that includes a distinguishing suffix will facilitate safe use and optimal pharmacovigilance of biological products. FDA advised Sandoz to provide proposed suffixes in accordance with the draft guidance. FDA has not finalized a policy on the nonproprietary naming of biological products. Accordingly, DMEPA reviewed Sandoz's proposed suffixes against the criteria described in the draft guidance.

On August 5, 2016, Sandoz submitted a list of suffixes, in their order of preference, to be used in the nonproprietary name of GP2015 along with supporting analyses to demonstrate that the proposed suffixes satisfy the factors described in section V of the draft guidance. The DMEPA review concluded, and I agree, that Sandoz's proposed suffix "szzs" (etanercept-szzs) is acceptable and should be reflected in the product label and labeling accordingly.

Of note, FDA's determination does not constitute or reflect a decision on a general naming policy for biological products, including biosimilars. FDA issued draft guidance on Nonproprietary Naming of Biological Products in August 2015, and the Agency is carefully considering the comments submitted to the public docket as we move forward in finalizing the draft guidance.[15] As a result, the nonproprietary name is subject to change to the extent that it

[14] See the FDA draft guidance for industry on Nonproprietary Naming of Biological Products (August 2015). When final, this guidance will represent FDA's current thinking on this topic. The guidances referenced in this document are available on the FDA Drugs guidance Web page at http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf

[15] FDA has received several citizen petitions directed to the nonproprietary naming of biosimilar products. The citizen petition submitted by Johnson & Johnson requests that FDA require biosimilar products to bear

is inconsistent with any general naming policy for biological products established by FDA. Were the name to change, FDA intends to work with Sandoz to minimize the impact this would have to its manufacture and distribution of this product.

- **Address important issues raised by brief discussion of OPDP and OSE Division comments**

None

- **Physician labeling**

The applicant proposed a labeling closely mirroring the labeling of US-licensed Enbrel. In addition, the applicant proposed:

1) Inclusion in Section 3, a statement that healthcare providers should be advised that there is no dosage form for [GP2015] which allows weight-based dosing as it is required for pediatric patients weighing below 63 kg.
2) Labeling changes to conform to PLLR formatting.

The proposed labeling is generally consistent with the March 2016 Draft Guidance, Labeling for Biosimilar Products and the PLLR format notwithstanding differences in nomenclature. Of note, limited product-specific data are included in the proposed GP2015 labeling. The data for GP2015 development program were presented at the Arthritis Advisory Committee on July 13, 2016[16] and FDA's review of these data will be publically available after licensure as part of the FDA "action package" for the public to review.

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

As discussed above.

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

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

[16] http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/ucm481975 htm

As discussed above in the DMEPA review and recommendations, the proprietary name "Erelzi" and the non-proprietary name "etanercept-szzs" should be reflected in the product Patient labeling/Medication guide as appropriate.

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

The applicant proposed a Patient labeling/Medication guide closely tracking that of US-licensed Enbrel. The proprietary name "Erelzi" and the non-proprietary name "etanercept-szzs" should be reflected in the product Patient labeling/Medication guide as appropriate.

14. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

I recommend approval of the 351(k) BLA 761,042 for GP2015 to receive licensure as a biosimilar product to US-licensed Enbrel for each of the following indications for which US-licensed Enbrel is currently licensed and Sandoz is seeking licensure of GP2015: RA, JIA, PsA, AS, PsO.

- **Totality of the Evidence**

The conclusion of the comparison of the structural and functional properties of the clinical and commercial product lots of GP2015 and US-licensed Enbrel was that they were highly similar, notwithstanding minor differences in clinically inactive components.

Sandoz provided analytical and clinical pharmacology bridging data to scientifically justify the relevance of data obtained using EU-approved Enbrel to a demonstration of biosimilarity of GP2015 to the US-licensed Enbrel.

The submitted clinical pharmacology studies are adequate to (1) support the demonstration of PK similarity between GP2015 and US-licensed Enbrel, (2) establish the PK component of the scientific bridge to justify the relevance of the data generated using EU-approved Enbrel.

The results of the clinical development program indicate that Sandoz's data meet the requirement for a demonstration of "no clinically meaningful differences" between GP2015 and US-licensed Enbrel in terms of safety, purity, and potency in the indication studied. Specifically, the results from the comparative clinical efficacy, safety, and PK studies, which included chronic dosing regimens of GP2015 and EU-approved Enbrel in patients with PsO, and a single dose of 50 mg in healthy subjects of GP2015, EU-approved Enbrel, and US-licensed Enbrel, adequately supported the demonstration that there are no clinically meaningful differences between GP2015 and US-licensed Enbrel in PsO. Further, the single transition from EU-approved Enbrel to GP2015 during the second treatment period of GP15-302 in PsO patients did not result in different safety or immunogenicity profile. This would

support the safety of a clinical scenario where non-treatment naïve patients undergo a single transition to GP2015.

In considering the totality of the evidence submitted, the data submitted by the Applicant show that GP2015 is highly similar to US-licensed Enbrel, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between GP2015 and US-licensed Enbrel in terms of the safety, purity, and potency of the product.

The Applicant has also provided an extensive data package to address the scientific considerations for extrapolation of data to support biosimilarity to other conditions of use to support their request that GP2015 should receive licensure for each of the indications for which US-licensed Enbrel is currently licensed and for which GP2015 is seeking licensure.

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

Not applicable.

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

Postmarketing Requirement (PMR):

As currently presented, GP2015 prefilled syringe with needle safety device and autoinjector presentations are not designed to allow for accurate administration of doses less than 50 mg, which impacts children who weigh less than 63 kg. For accurate weight-based dosing of patients 2 years of age or older that are less than 63 kg, a dose-adjustable presentation is required under PREA. Therefore, I recommend a PREA PMR for the development of a presentation that can be used to accurately administer GP2015 to pediatric patients who weigh less than 63 kg.

1. Develop a presentation that can be used to accurately administer etanercept-szzs to pediatric patients who weigh less than 63 kg.

   Final Report Submission: December 2019

Postmarketing Commitments (PMC):

I concur with the post-marketing commitments recommended by the product quality, microbiology, and CDRH review teams as listed below:

1. Develop and implement an analytical method for release and stability testing of GP2015 drug substance and drug product that can adequately assess levels of hydrophobic variants, including wrongly bridged disulfide bond variants. Submit the

method final validation report and the release and stability acceptance criteria as a Prior Approval Supplement.

Final Report Submission: December 2017

2. Repeat the microbial retention study using a more suitable surrogate solution. Attributes of the surrogate solution that are known to affect microbial retention (e,g., surface tension, viscosity, ionic strength, etc.) should model the drug product as closely as possible while preserving viability of the challenge organism. Alternatively, use of a reduced exposure time or modified process conditions (e.g., temperature) may be appropriate. Provide the summary data, the associated report, and justification for any modifications to the study. Submit the final report as a Changes Being Effected in 30 days (CBE30) and include any change in filtration parameters based upon the study.

   Final Report Submission: September 2017

3. Use a validated method to measure break loose, glide force (BLGF) for (b) (4) drug product pre-filled syringes to generate data from commercial batches to define release specifications for BLGF. Submit the study report and specifications for BLGF including testing site in the annual report.

   Final Report Submission: October 2019

4. Develop methods for confirming the injection depth (e.g. needle length exposed for injection), audible feedback (e.g. occurrence of second click) and visual feedback (e.g. plunger fills the window and stops moving) for release testing. Define release specifications that meet design output specifications for injection depth, audible feedback, and visual feedback for lot release testing prior to launch of Erelzi. Submit the study report and release specifications in the annual report.

   Final Report Submission: October 2017

6. Complete transport validation testing to assess mechanical stress on the new folding box and transport carton prior to launch of Erelzi. Submit the final transport validation report.

   Final Report Submission: September 2016

- **Recommended Comments to Applicant**

None.

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/s/

NIKOLAY P NIKOLOV
08/29/2016