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RESEARCH**

APPLICATION NUMBER:

761042Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sarah Yim, M.D. Supervisory Associate Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) Badrul Chowdhury, M.D., Ph.D. Director, DPARP
Subject	Division Director Summary Review
NDA/BLA # / Supplement #	BLA 761042/original
Applicant Name	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 / Established (USAN) Name	Erelzi, Erelzi Sensoready Pen / GP2015 ¹ , etanercept-szss
Dosage Forms / Strength	50 mg/mL solution in a single-use prefilled syringe (PFS), 50 mg/mL solution in a single-use prefilled pen injector, 25 mg/0.5 mL solution in a single-use PFS
Proposed Indication(s)	1. Rheumatoid Arthritis (RA) 2. Ankylosing Spondylitis (AS) 3. Psoriatic Arthritis (PsA) 4. Plaque Psoriasis (PsO) 5. Polyarticular Juvenile Idiopathic Arthritis (PJIA)
Action:	<i>Approval</i>

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Cross-Discipline Team Leader Rev.	Nikolay Nikolov, MD
Office of Biotechnology Products (OBP)	Peter Adams, PhD; Marjorie Shapiro, PhD; Kathleen Clouse-Strebel, PhD; Steven Kozlowski, MD
CMC statistics	Meiyu Shen, PhD; Yi Tsong PhD
Product Quality Microbiology	Reyes Candau-Chacon, PhD; Candace Gomez- Broughton, PhD; Patricia Hughes PhD
Immunogenicity	Brian Janelsins, PhD; Jee Chung, PhD
Facilities Inspections	Zhong Li, PhD; Peter Qiu PhD
OBP labeling	Jibril Abdus-Samad, PharmD
Project Manager, OPRO/OPQ	Keith Olin, PharmD
CDRH	Sarah Mollo, Alan Stevens

¹ In this document, we generally refer to Sandoz' 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-szss."

Medical Officer Review	DPARP: Rachel Glaser, MD; DDDP: Gary Chiang, MD, MPH; David Kettl, MD
Biostats Review	DDDP: Kathleen Fritsch, PhD; Mohamed Alosch, PhD
Pharmacology Toxicology Review	Andrea Benedict, PhD; Carol Galvis, PhD
Clinical Pharmacology Review	Yunzhao Ren, MD, PhD; Ping Ji, PhD
Clinical inspections, OSI	Roy Blay, PhD; Janice Pohlman, MD, MPH; Kassa Ayalew, MD, MPH
Division of Medication Error Prevention and Analysis	Carlos Mena-Grillasca, RPh; Mishale Mistry, PharmD, MPH; Lubna Merchant, MS, PharmD
Division of Medical Policy Programs—patient labeling	Nyedra Booker, PharmD, MPH; Marcia Williams, PhD; LaShawn Griffiths, MSHS-PH, BSN, RN
OPDP	Adewale Adeleye, PharmD, MBA

OND=Office of New Drugs

OPRO=Office of Programs and Regulatory Operations

CDRH=Center for Devices and Radiological Health

OSI=Office of Scientific Investigations

CMC=Chemistry, Manufacturing, Controls

OPQ=Office of Pharmaceutical Quality

DDDP=Division of Dermatology and Dental Products

OPDP=Office of Prescription Drug Promotion

1. Introduction

This is a 351(k) biologic license application (BLA) submitted by Sandoz, Inc. for GP2015, a proposed biosimilar to Enbrel (etanercept). Sandoz is seeking licensure of GP2015 (tradename “Erelzi”) for the same indications previously approved for US-licensed Enbrel, on the basis of the following:

- Analytical data intended to support the following purposes:
 - A demonstration that GP2015 can be manufactured in a well-controlled and consistent manner, leading to a product that is sufficient to meet required quality standards
 - A demonstration that GP2015 and US-licensed Enbrel are highly similar
 - Provide the analytical element of the scientific bridge to justify the relevance of comparative data that were generated using European Union (EU)-approved Enbrel to support a demonstration of biosimilarity of GP2015 to US-licensed Enbrel.
- The clinical pharmacology program for GP2015 included four pharmacokinetic (PK) studies (Studies 101, 102, 103, and 104), a cross-study PK comparison of US-licensed Enbrel and EU-approved Enbrel from studies 101 and 102 (Report 105), and a steady-state assessment of PK in patients with chronic plaque psoriasis (PsO). The clinical pharmacology studies served the following purposes:
 - To support the PK similarity of GP2015 and US-licensed Enbrel, and
 - To provide the PK element of the scientific bridge to justify the relevance of comparative data generated using EU-approved Enbrel to support a demonstration of biosimilarity of GP2015 to US-licensed Enbrel.
 - Study 103 provided evidence for the PK comparability of GP2015 administered via prefilled syringe (PFS) and autoinjector (AI) to support approvability of the AI as well as the PFS, in this application.
 - To provide information on steady state PK (from the clinical study, Study 302, in patients with plaque psoriasis).

- Study 302, a comparative clinical study in 531 patients with chronic moderate to severely active PsO who were treated with GP2015 or EU-approved Enbrel, intended to support a demonstration of no clinically meaningful differences between GP2015 and US-licensed Enbrel. This is a randomized, double-blind, parallel group study with two treatment periods. In treatment period 1 (TP1), patients were randomized 1:1 to GP2015 or EU-approved Enbrel at a dose of 50 mg subcutaneously (SC) twice weekly for 12 weeks. The primary endpoint for TP1 was the proportion of patients achieving a Psoriasis Area and Severity Index 75% improvement (PASI 75) at Week 12. This was followed by treatment period 2 (TP2), where patients in each arm were re-randomized to either continue on their current treatment or begin alternating intervals of treatment. After TP2, patients continued on their last assigned treatment for a further 22 weeks (total of 52 weeks), to further evaluate the efficacy, long-term safety, and immunogenicity of the various treatment arms from TP2.
- A scientific justification for extrapolation of biosimilarity to other indications which were not studied in the GP2015 development program but for which US-licensed Enbrel is licensed and for which Sandoz is also seeking licensure, i.e., rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (pJIA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS).

Of note, Sandoz elected to design Study 302 with multiple switches (b) (4) this application seeks approval of GP2015 as a biosimilar, (b) (4). FDA generally does not expect sponsors to submit data regarding multiple switches to support an application for a proposed biosimilar, but has asked for a descriptive assessment of the safety and immunogenicity of patients transitioning from Enbrel to GP2015 as part of the safety data in support of this BLA.

2. Background

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

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

animal studies, and a clinical study or studies, unless FDA determines, in its discretion, that certain studies are unnecessary in a 351(k) application (see section 351(k)(2) of the PHS Act).

The foundation of an abbreviated development program for biosimilars is extensive structural and functional characterization of both the proposed biosimilar product and its reference product which demonstrates that the products are highly similar analytically. Residual uncertainties about the clinical relevance of small differences in the comparative analytical characterization may be addressed by comparative human pharmacokinetic (PK) and, if applicable, pharmacodynamic data, clinical immunogenicity, safety, and effectiveness data. However, unlike a stand-alone development program (i.e., BLAs submitted under section 351(a) of the Public Health Service Act), a demonstration of efficacy and safety in each clinical indication is not expected. It is under this relatively new paradigm that Sandoz seeks licensure of GP2015.

Sandoz largely conducted the development of GP2015 outside of the U.S. FDA recommendations were discussed at Biosimilar Product Development (BPD) Type 2 meetings in July and December 2012. At these meetings, FDA provided general advice on the proposed comparative clinical study design, including primary endpoint and similarity margin, and recommended 3-way PK and analytical data to establish a scientific bridge between US-licensed Enbrel and EU-approved Enbrel, since EU-approved Enbrel was going to be used in the comparative clinical study. As part of the safety evaluation, FDA also recommended that Sandoz assess safety and immunogenicity in the setting of patients who undergo a single transition from Enbrel to GP2015, compared to patients who continue on Enbrel. As of the time of this review, GP2015 had not yet been approved or marketed in any country.

3. CMC/Device

Manufacturing and Product Quality Evaluation

Drug substance

GP2015 drug substance (DS) is a TNF Receptor-Fc fusion protein produced in Chinese Hamster Ovary (CHO) cells and consisting of 467 amino acids that includes the extracellular domain of TNFR2 (1-235) and IgG1 Fc region (236-467). The Fc region is truncated and includes the human IgG1 hinge, CH2 and CH3 domains of the Fc region. The TNF receptor contains both O- and N-linked glycans and the Fc portion contains the typical immunoglobulin N-linked glycan. The molecule forms a homo-dimer and contains 29 intra- and inter-chain disulfide bonds. GP2015 binds to both soluble TNF- α and TNF- β (also known as lymphotoxin- α) as well as membrane-bound TNF- α . GP2015 binding to soluble TNF hinders the ability of TNF to bind its receptors on the surface of cells, resulting in inhibition of downstream effects. While etanercept can be shown to have complement dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC) activities, both of these activities are low relative to anti-TNF monoclonal antibodies and even lower when compared to antibodies whose primary mechanism of action (MOA) includes effector

function. Thus, antibody effector function does not contribute to the overall mechanism of GP2015.

The drug substance manufacturing process, detailed in the product quality reviews, is well-controlled. The DS is manufactured at Sandoz GmbH, Langkampfen, Austria. Submitted data support an expiration dating period of (b) (4) months at (b) (4) °C.

Drug product

GP2015 will be supplied as 25 mg/0.5 mL solution for injection and 50 mg/mL solution for injection in PFS, and as a 50 mg/mL solution for injection in AI. The 50 mg PFS and AI have an overfill of (b) (4)% and 25 mg PFS has an overfill of (b) (4)% to ensure an accurate extractable volume to supply the appropriate dose. Excipients include 50 mM citrate buffer, 29 mM sucrose, 26 mM NaCl, 25 mM L-Lysine. The DP is stored in 1 mL (b) (4) glass syringes (b) (4). The staked hypodermic needle is stainless steel (b) (4) and the 27g x 1/2" needle is glued to the glass syringe body. There is a rubber needle shield in a rigid (b) (4) needle shell. The plunger stopper is comprised of (b) (4) rubber. 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 drug product (DP) is manufactured at Novartis Pharma Stein AG, Switzerland. The combination product (DP in the device) is made at (b) (4).

Microbiology

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. Refer to Section 13 for the final agreed-upon PMC.

Device Evaluation

The Center for Devices and Radiological Health (CDRH) performed an evaluation of the design of the device constituent parts of the prefilled syringe (PFS) with needle safety device and the autoinjector (AI) configurations. The configurations include a PFS with 27g 1/2 inch staked needle with a Becton-Dickinson "UltraSafe" passive needle guard, in two strengths—25 mg/0.5mL and 50 mg/mL. The AI is based on (b) (4) developed by (b) (4) for Novartis Pharma, which is a disposable, fixed-dose, single-use needle-based injection system. The evaluation covered the intended design and design control information for the subject device constituent parts. The CDRH reviewer determined the devices' design verification, controls, and performance met requirements and the PFS and AI are acceptable for approval. The (b) (4) AI (b) (4) is already marketed in the US as part of the Cosentyx (secukinumab) product, also from Novartis and approved for plaque psoriasis, psoriatic arthritis and ankylosing spondylitis. Because these populations are similar to those proposed for approval in this BLA, the Division of Medication Error Prevention and Analysis

(DMEPA) concluded that the Cosentyx Sensoready pen human factors validation data referenced in this submission can be relied on to support the proposed Erelzi autoinjector.

CDRH recommended several PMC pertaining to the break loose, glide force (BLGF) of the PFS, tests for injection depth and audible and visual feedback (b) (4), and transport validation testing for a new folding box and transport carton (u) (4). See Section 13 for final agreed-upon PMC.

Facilities Inspections

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 considered adequate for approval from a facilities assessment perspective.

Analytical Similarity Evaluation

The analytical similarity evaluation included comprehensive methods that assessed the primary structure and post-translational modifications, higher order structure, size variants, hydrophobic variants, charge variants and glycoform variants. Comparative analytical data was evaluated from multiple lots of GP2015, US-licensed Enbrel, and EU-approved Enbrel. Comparative data between GP2015 and US-licensed Enbrel were used to assess the analytical similarity of GP2015. TNF- α neutralization (reporter gene assay) and TNF- α binding (surface plasmon resonance) were identified as methods to be evaluated by statistical equivalence testing. Pairwise comparisons of GP2015, US-licensed Enbrel, and EU-approved Enbrel were used to support the analytical element of the scientific bridge between the three products, to justify the relevance of the comparative data generated using EU-approved Enbrel in some clinical and nonclinical studies.

TNF- α Binding Assay Results

Data on TNF- α binding with GP2015 and Enbrel met criteria for statistical equivalence, supporting a finding 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 element of the scientific bridge for nonclinical and clinical studies conducted with EU-approved Enbrel.

TNF α Neutralization Assay Results, Post-Peak Variants and Wrongly-Bridged Disulfide Bonds

For TNF- α neutralization, GP2015 and US-licensed Enbrel did not meet statistical criteria for equivalence, although GP2015 was statistically equivalent to EU-approved Enbrel, and US-licensed Enbrel was statistically equivalent to EU-approved Enbrel. All GP2015 lots were

within the quality range (mean $\pm$ 3 standard deviation) of US-licensed Enbrel; however, the average mean potency of GP2015 was higher than for US-licensed Enbrel. The reason for the data not meeting equivalence criteria was determined by Office of Biotechnology Products (OBP) reviewers to be due to differences in a product-related impurity identified by reverse phase chromatography termed, “post peak.” GP2015 contains lower levels of this post-peak, which is due to a hydrophobic variant known to have reduced potency relative to the main peak. The post-peak was determined to contain 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 showed 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- α neutralization assay.

Some disulfide bonds are allosteric, and control the function of a protein when they are reduced or oxidized in vivo in blood. Therefore, it was considered possible that the differences in results of the ex vivo TNF- α neutralization assay would not translate into an actual difference in potency between the molecules in vivo. To address this question, Sandoz was asked to provide data to support the supposition that the wrongly bridged disulfide bonds could refold in vivo.

Sandoz submitted these data on April 28, 2016, and this was considered a major amendment. Data were provided 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. Using the computed potency model, GP2015 and US-licensed Enbrel met the criteria for statistical equivalence. In addition, using the computed potency model, GP2015 and EU-approved Enbrel, and US-licensed Enbrel and EU-approved Enbrel, met the criteria for statistical equivalence.

Therefore, the differences in levels of post-peak hydrophobic variant do not preclude a conclusion that GP2015 is highly similar to US-licensed Enbrel.

Similarity of Other Quality Attributes

The amino acid sequences of GP2015 and US-licensed Enbrel are identical. A multitude of other quality attributes, including secondary and higher order structure, Fc (effector) function, and other structural/functional characteristics were assessed by quality range analysis and by qualitative comparisons. These attributes also support a finding that GP2015 is highly similar to US-licensed Enbrel, notwithstanding minor differences in clinically inactive components. Analytical data on glycan structure showed small differences in the levels of high mannose forms, but these small differences were considered not to be relevant in light of the lack of differences in PK (Section 4 below). There was also a small difference in the amount of afucosylated glycoforms, but this was not considered relevant in light of the low antibody-

dependent cellular cytotoxicity (ADCC) activity of etanercept in general, and the lack of differences in binding to Fc γ RIIIa.

Summary

In summary, reviewers from OBP, Office of Compliance, and Center for Devices and Radiological Health have reviewed the product quality, manufacturing, and device aspects and have determined the submitted data are adequate to support approval. Additionally, FDA reviewers from the Office of Biotechnology Products (OBP) and Office of Biostatistics (OB) have evaluated the analytical similarity of GP2015, US-licensed Enbrel, and EU-approved Enbrel and have determined that 1) GP2015 is analytically highly similar to US-licensed Enbrel, and 2) Sandoz provided an adequate analysis for the purposes of establishing the analytical element of the scientific bridge among the three products to justify the relevance of comparative data generated from clinical and nonclinical studies that used EU-approved Enbrel, to support a demonstration of biosimilarity of GP2015 to US-licensed Enbrel.

4. Nonclinical Pharmacology/Toxicology

The pharmacology and toxicology studies submitted in support of the BLA included pharmacology studies in Tg197 mice (which constitutively express human TNF- α 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 showed comparable exposures, safety, and efficacy between GP2015 and EU-approved Enbrel. There are no outstanding pharmacology/toxicology issues.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology program in this application served several purposes:

- 1) To evaluate the pharmacokinetic (PK) similarity between GP2015 and US-licensed Enbrel (Study 102)
- 2) To provide the PK element of the scientific bridge between GP2015, US-licensed Enbrel and EU-approved Enbrel (Studies 101 and 104, along with Report 105, which is a cross-study comparison of Studies 101 and 102)
- 3) To demonstrate the PK comparability of GP2015 administered via prefilled syringe or autoinjector (Study 103).
- 4) To provide information on steady state PK (from the clinical study, Study 302, in patients with plaque psoriasis).

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. This study was the pivotal clinical pharmacology study evaluating the PK similarity of GP2015 and US-licensed Enbrel. 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-inf} , $AUC_{0-tlast}$, and C_{max} within the interval of 80% to 125%).

Both Study 101 and Study 104 were designed to compare the PK profiles of GP2015 and EU-approved Enbrel. In Study 101, the pre-specified PK acceptance criteria were met for C_{max} but not for AUC_{0-t} and AUC_{0-inf} . Therefore, Study 104 was conducted at the request of the European Regulatory Authorities, and was performed at a later time, using a different assay. In Study 104, the pairwise comparisons of GP2015 and EU-approved Enbrel did meet pre-specified acceptance criteria for C_{max} , AUC_{0-t} , and AUC_{0-inf} .

To support the scientific bridge between GP2015, US-licensed Enbrel, and EU-approved Enbrel, the sponsor provided data for the remaining pairwise comparison by performing a cross-study comparison (Report 105) of EU-approved Enbrel from Study 101 and US-licensed Enbrel from Study 102, as these two studies were performed contemporaneously and with similar methods. 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-inf} , $AUC_{0-tlast}$, and C_{max} within the interval of 80% to 125%) in this analysis.

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

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.

In summary, the Office of Clinical Pharmacology has determined that an adequate PK bridge has been demonstrated between GP2015, US-licensed Enbrel, and EU-approved Enbrel. Importantly, 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.

6. Clinical Microbiology

Not applicable. Refer to Section 3 for Product Quality microbiology information.

7. Clinical/Statistical-Efficacy

Sandoz submitted one comparative clinical study in patients with plaque psoriasis (Study 302). 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. As discussed above, analytical and PK bridging data justify the relevance of comparative data acquired with EU-approved Enbrel to support a demonstration of no clinically meaningful differences with US-licensed Enbrel. The design of Study 302 includes equal randomization to either GP2015 or EU-approved Enbrel for 12 weeks in treatment period 1 (TP1), followed by re-randomization of patients achieving at least a PASI50 response to one of 4 groups:

1a) Patients on GP2015 continue on GP2015.

1b) Patients on GP2015 transition to EU-approved Enbrel for 6 weeks, then go back to GP2015 for 6 weeks, then receive EU-approved Enbrel through the remainder of the study.

2a) Patients on EU-approved Enbrel continue on EU-approved Enbrel.

2b) Patients on EU-approved Enbrel transition to GP2015 for 6 weeks, then go back to EU-approved Enbrel for 6 weeks, then receive GP2015 for the remainder of the study.

The period of switching lasted from Week 12 to Week 30 (treatment period 2=TP2); then patients remained on their last assigned treatment from Week 30 through Week 52 (Extension period).

Of the 531 subjects enrolled, 264 were randomized to the GP2015 arm and 267 randomized to the EU-approved Enbrel arm. 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).

Of note, the design of Study 302 includes multiple switching periods during TP2 (weeks 12 to 30). The focus of the FDA review was TP1 and the first 6 weeks of TP2, including patients who underwent a single transition from EU-approved Enbrel to GP2015. However, because additional data were provided by Sandoz, FDA did review the pooled safety and immunogenicity data from multiple switches. See Section 8 below.

Study 302 Results

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 the 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.

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 $\pm 18\%$. 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. The primary analysis was also supported by sensitivity analyses accounting for missing data. The clinical and statistical review teams are in agreement that these results support the demonstration of no clinically meaningful differences between GP2015 and US-licensed Enbrel.

8. Safety

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.

Safety Summary

In the GP2015 clinical program, the overall incidences of treatment-emergent adverse events (AEs), serious adverse events (SAEs), and AEs leading to discontinuation or treatment interruption, infections, injection site reactions, were similar between GP2015 and the comparator products. In Study 302, there was a single death—a patient in Treatment Period 1 (TP1) on EU-approved Enbrel who had hypertension and diabetes and died of cardiopulmonary failure. The number of SAEs was low and similar between groups (4/264 [1.5%] in the GP2015 group and 3/267 [1.1%] in the EU-approved Enbrel group), as were the discontinuations due to adverse events (5/264 [1.9%] in the GP2015 group and 4/267 [1.5%] in the EU-approved Enbrel group). There were no notable differences in AE or SAEs in patients who stayed on EU-approved Enbrel vs. those who underwent a transition from EU-approved Enbrel to GP2015.

Immunogenicity Summary

Immunogenicity was assessed throughout the GP2015 clinical program, including in studies 101 (GP2015 and EU-approved Enbrel), 102 (GP2015 and US-licensed Enbrel), 103 (GP2015 via PFS or AI), and 104 (GP2015 and EU-approved Enbrel) following single-dose administration in healthy subjects, and in Study 302 following repeat-dose monotherapy in patients with plaque psoriasis.

In the healthy subject single-dose 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 anti-drug antibodies (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.

Summary

In summary, no new safety signals were identified with GP2015 compared to the known adverse event profile of US-licensed Enbrel. Immunogenicity data from populations without concomitant immunosuppressive therapy (healthy subjects after a single dose and repeat-dose in plaque psoriasis patients) suggest there is not 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, the safety and immunogenicity data support a demonstration of no clinically meaningful differences between GP2015 and US-licensed Enbrel.

9. Advisory Committee Meeting

An Arthritis Advisory Committee (AAC) meeting was held for this application on July 13, 2016. This meeting included experts in product quality assessment, clinical pharmacology, rheumatology, and dermatology, as well as patient, consumer, and industry representatives. The Committee discussed the analytical data for GP2015 and generally agreed that GP2015 was highly similar to US-licensed Enbrel. The Committee also discussed the clinical data with GP2015 in plaque psoriasis, and generally agreed there were no clinically meaningful differences between GP2015 and US-licensed Enbrel in this indication. The Committee then discussed the scientific justification for extrapolating conclusions of biosimilarity to additional indications that had not been studied. Panel members generally agreed that extrapolation was justified. For the voting question, panelists were asked whether, based on the totality of the evidence, GP2015 should receive licensure as a biosimilar product to US-licensed Enbrel for each of the indications for which US-licensed Enbrel is currently licensed and for which Sandoz is seeking licensure (i.e., rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis). The Committee voted 20 to 0 in favor of licensure of GP2015 for these indications.

10. Pediatrics

As a proposed biosimilar, this application for GP2015 triggers the requirements of the Pediatric Research Equity Act (PREA) for every indication for which licensure is sought. The GP2015 pediatric plan was discussed at the Pediatric Review Committee (PeRC) meeting of March 09, 2016. PeRC agreed with the applicant's current request for waivers and deferrals.

11. Other Relevant Regulatory Issues

- **Inspections:** No issues precluding approval were found on inspection of the manufacturing facilities or of selected clinical sites.
- **Financial Disclosure:** No issues.

12. Labeling

The proprietary name for GP2015 will be Erelzi. FDA has determined that the use of a distinguishing suffix in the nonproprietary name is necessary to distinguish this product from Enbrel (etanercept). The nonproprietary name for GP2015 will be etanercept-szzs. Of note, FDA's determination does not constitute or reflect a decision on a general naming policy for biological products, including biosimilars. FDA issued draft guidance on Nonproprietary Naming of Biological Products in August 2015, and the Agency is carefully considering the comments submitted to the public docket as we move forward in finalizing the draft guidance. As a result, the nonproprietary name is subject to change to the extent that it is inconsistent with any general naming policy for biological products established by FDA. Were the name to change, FDA intends to work with Sandoz to minimize the impact this would have to its manufacture and distribution of this product.

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

13. Decision/Action/Risk Benefit Assessment

- **Regulatory Action**

The action on this biologics license application will be Approval.

- **Assessment of Biosimilarity**

Section 351(i) of the PHS Act defines the terms "biosimilar" or "biosimilarity" to mean that "the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product" (see section 351(i)(2) of the PHS Act).

A multitude of quality attributes, including primary, secondary and higher order structure, Fc (effector) function, and other structural/functional characteristics were assessed by quality

range analysis and by qualitative comparisons. Comparative TNF- α binding for GP2015 and US-licensed Enbrel met statistical equivalence criteria. These attributes support a finding that GP2015 is highly similar to US-licensed Enbrel, notwithstanding minor differences in clinically inactive components.

The applicant also provided additional data and information to address residual uncertainty surrounding apparent differences in comparative TNF α neutralization assay results, which did not meet statistical equivalence criteria, with GP2015 appearing slightly more potent in the assay. Sandoz demonstrated that the differences in assay results were likely due to lower levels of post-peak hydrophobic variant related to wrongly-bridged disulfide bonds, and that these bonds are likely to refold in vivo, restoring expected potency. Using a computed potency model where these disulfide bonds are refolded correctly, GP2015 and US-licensed Enbrel would meet statistical criteria for equivalence. Therefore the differences observed in the TNF- α neutralization assay do not preclude a conclusion that GP2015 is highly similar to US-licensed Enbrel.

Comparative PK data between GP2015 and US-licensed Enbrel met the acceptance criteria for PK similarity (90% confidence intervals for the ratios of geometric mean of AUC_{inf}, AUC_{last}, and C_{max} within the interval of 80% to 125%). Comparative analytical characterization data and PK similarity data between GP2015, US-licensed Enbrel, and EU-approved Enbrel provided a scientific justification for the relevance of comparative data with EU-approved Enbrel to support a demonstration of biosimilarity to US-licensed Enbrel. Therefore clinical efficacy, safety, and immunogenicity data from Study 302 in plaque psoriasis patients, which evaluated GP2015 and EU-approved Enbrel, supported a finding that there are no clinically meaningful differences between GP2015 and US-licensed Enbrel.

Therefore, based on the data available in this application, the statutory standards for biosimilarity have been met, and the application may be approved.

Extrapolation

The applicant sought licensure for all the indications for which US-licensed Enbrel is licensed, based on a development program that included data from a single comparative clinical study in PsO. To support extrapolation of the finding of biosimilarity to other conditions of use (i.e., RA, JIA, AS, PsA), the applicant provided a scientific justification. The primary mechanism of action (MOA) of etanercept is through inhibition of the 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 is the MOA for all the indications for which US-licensed Enbrel is licensed (i.e., RA, JIA, AS, PsA and plaque psoriasis). Therefore GP2015, US-licensed Enbrel and EU-approved Enbrel would be expected to act in a similar manner in the other conditions of use and no clinically meaningful differences between GP2015 and US-licensed Enbrel would be expected in RA, JIA, AS, and PsA, as well.

Additionally, there are no product-related attributes that would be expected to alter the PK/biodistribution of GP2015 and US-licensed Enbrel differently in the indications sought for

licensure. Since similar PK was demonstrated between GP2015 and US-licensed Enbrel in healthy subjects and between GP2015 and EU-approved Enbrel in patients with psoriasis, a similar PK profile would be expected between GP2015 and US-licensed Enbrel in patients with RA, JIA, AS, and PsA.

Furthermore, the immunogenicity of GP2015 and EU-approved Enbrel was similarly low in the GP2015 clinical program, and there no notable differences between patients treated with GP2015 and EU-approved Enbrel in the plaque psoriasis study following repeat-dosing without background immunosuppression. No ADA were observed in either GP2015 or US-licensed Enbrel groups after single-doses in healthy subjects in PK study 102. Accordingly, no clinically meaningful differences in immunogenicity would be expected between GP2015 and US-licensed Enbrel in patients with RA, JIA, AS and PsA.

In aggregate, the evidence supports that extrapolation of biosimilarity to RA, JIA, AS, and PsA is scientifically justified.

- **Postmarketing Risk Evaluation and Mitigation Strategies**

None.

- **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. PMR/PMC Schedule Milestones:

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

Final Report Submission: 12/2019

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: 12/2017

2. Repeat the microbial retention study using a more suitable surrogate solution. Attributes of the surrogate solution that are known to affect microbial retention (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: 9/2017

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: 10/2019

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: 10/2017

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: 9/2016

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SARAH K YIM

08/29/2016

BADRUL A CHOWDHURY

08/29/2016