CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761042Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	BLA 351(k)
Application Number(s)	761042 Related IND: 114187
Priority or Standard	Standard
Submit Date(s)	30-JUL-2015
Received Date(s)	30-JUL-2015
BsUFA Goal Date	30-AUGUST-2016
Division/Office	CDER/OND/DDDP
Reviewer Name(s)	Gary T Chiang MD, MPH; Rachel L Glaser MD
Review Completion Date	27-JUL-2016
Established Name	etanercept
(Proposed) Trade Name	ERELZI and ERELZI Sensoready Pen
Applicant	Sandoz Inc.
Formulation(s)	PFS and Autoinjector
Dosing Regimen	RA, AS, PsA: 50 mg once weekly PsO: 50 mg twice a week for 3 months, then once weekly JIA: 0.8 mg/kg once weekly, no more than 50 mg once weekly
Applicant Proposed Indication(s)/Population(s)	RA, AS, PsA, PsO, polyarticular JIA
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	• RA, • AS, • PsA, • PsO, • Polyarticular JIA in patients aged 2 years or older and weigh >63 kg

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Glossary

AC	advisory committee
ADA	anti-drug antibodies
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
AI	autoinjector
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AS	ankylosing spondylitis
ATE	average treatment effect
BDRM	blind data review meeting
BLA	biologics license application
BPCI	Biologics Price Competition and Innovation Act
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COX-2	cyclooxygenase 2
CRF	case report form
CRO	contract research organization
CSR	clinical study report
DMARD	disease modifying anti-rheumatic drug
DLQI	Dermatology Life Quality Index
ECG	electrocardiogram
EOS	end of study
EQ-5DTM	EuroQol 5-Dimension Health Status Questionnaire
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
HAQ-DI	Health Assessment Questionnaire-Disability Index
ICH	International Conference on Harmonization
IGA	Investigator's Global Assessment
IgG1	type-1 human immunoglobulin
IMP	investigational medicinal product
IND	Investigational New Drug
IRT	interactive response technology
ISR	injection site reaction
JIA	juvenile idiopathic arthritis
LT-α	lymphotoxin α

MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effect model repeated measures
MTX	methotrexate
NSAID	nonsteroidal anti-inflammatory drug
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PASI	Psoriasis Area and Safety Index
PFS	prefilled syringe
PHS	Public Health Service Act
PI	prescribing information
PK	pharmacokinetics
PPS	per protocol set
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PsA	psoriatic Arthritis
PsO	plaque psoriasis
RA	rheumatoid arthritis
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SOC	system organ class
TEAE	treatment emergent adverse event
TNF	tumor necrosis factor
TNFR	tumor necrosis factor receptor
TP1	treatment period 1
TP2	treatment period 2
US	United States

1 Executive Summary

1.1. Product Introduction

Sandoz has submitted a biologics license application (BLA) under section 351(k) of the Public Health Service Act (PHS Act) for GP2015, a proposed biosimilar biological product to US-licensed ENBREL (etanercept). Etanercept is a recombinant human tumor necrosis factor receptor Fc (TNFR:Fc), a fully human dimer of two molecules of the extracellular portion of p75 TNFR fused to the Fc portion of a type-1 human immunoglobulin (IgG1). It binds both tumor necrosis factor α (TNF-α) and lymphotoxin α (LT-α) with high affinity. The proposed formulations include a pre-filled syringe and an autoinjector indicated for treatment of:

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

1.2. Conclusions on the Totality of the Evidence

This 351(k) Biological Licensing Application (BLA 761042) seeks approval of the product GP2015 (proposed trade name: ERELZI) which is a proposed biosimilar to US-licensed Enbrel

(etanercept, a TNF-α inhibitor). The Biologics Price Competition and Innovation Act (BPCI Act) created an abbreviated licensure pathway under section 351(k) of the PHS Act for biological products shown to be "biosimilar" to or "interchangeable" with an FDA-licensed biological product. Section 351(k) of the PHS Act defines the terms "biosimilar" or "biosimilarity" to mean that the proposed 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." Both parts of the statutory definition need to be met to demonstrate biosimilarity, but the foundation of the data demonstrating biosimilarity is extensive structural and functional characterization to support a demonstration that the products are highly similar.

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. The product quality review has determined that the 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 (European Union (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.

From a clinical standpoint, the clinical pharmacology, efficacy, safety, and immunogenicity data submitted to this 351(k) BLA from the clinical development program of GP2015, support the demonstration of no clinically meaningful difference between GP2015 and US-licensed Enbrel in the indication studied, i.e., plaque psoriasis (PsO).

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.

1.3. Benefit-Risk Assessment

APPEARS THIS WAY ON ORIGINAL

Benefit-Risk Summary and Assessment

ERELZI (a proposed biosimilar to etanercept) is being developed for the following indications:

- Rheumatoid Arthritis - reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis (RA). ERELZI can be initiated in combination with methotrexate (MTX) or used alone.
- Polyarticular Juvenile Idiopathic Arthritis - reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis (JIA) in patients ages 2 and older.
- Psoriatic Arthritis - reducing signs and symptoms, inhibiting the progression of structural damage of active arthritis, and improving physical function in patients with psoriatic arthritis (PsA). ERELZI can be used in combination with methotrexate (MTX) in patients who do not respond adequately to MTX alone.
- Ankylosing Spondylitis - reducing signs and symptoms in patients with active ankylosing spondylitis (AS).
- Plaque Psoriasis - treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis (PsO) who are candidates for systemic therapy or phototherapy.

The clinical development program of GP2015 provides evidence of similar efficacy between GP2015 and EU-approved Enbrel in moderate to severe plaque psoriasis. Safety analysis showed a similar incidence of adverse events, serious adverse events, adverse events leading to treatment discontinuations, and deaths between the biosimilar product and the comparator Enbrel. Rates of immunogenicity were low with treatment with both GP2015 and EU-approved Enbrel. The established scientific bridge justifies the relevance of the comparative clinical data with EU-approved Enbrel to support a demonstration of biosimilarity to US-licensed Enbrel. The results from the GP2015 clinical program support a conclusion of no clinically meaningful differences between GP2015 and US-licensed Enbrel in the studied indication.

Extrapolation of Data to Support Biosimilarity to Non-studied Indications

In addition to the indications studied in the clinical program, Sandoz is seeking licensure for rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and juvenile idiopathic arthritis for which they have not submitted clinical data. To support the demonstration of biosimilarity of GP2015 to US-licensed Enbrel for the non-studied indications, Sandoz has provided a scientific justification for the proposed extrapolation of data to support that there are no clinically meaningful differences between

GP2015 and US-licensed Enbrel for RA, PsA, AS, and JIA. The justification addresses issues for the tested and extrapolated indications/conditions of use outlined in Guidance for Industry: "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009", April 2015.

2 Therapeutic Context

2.1. Analysis of Conditions

Psoriasis (PsO)
Psoriasis is a common chronic skin disorder most frequently characterized by well-demarcated erythematous plaques with silver scale. Chronic plaque psoriasis is the most common variant of psoriasis. Patients with chronic plaque type psoriasis usually present with symmetrically distributed cutaneous plaques. The scalp, extensor elbows, knees, and back are common sites for involvement. The extent of involvement can range from limited localized disease to involvement of the majority of the body surface area. Involvement of intertriginous areas (inverse psoriasis), the ear canal, umbilicus, palms, soles, or nails also may be present.

Rheumatoid Arthritis (RA)
Rheumatoid arthritis is a symmetric polyarthritis, frequently affecting the small joints of the hands and feet. Patients may present with joint pain, joint swelling, and morning stiffness. Serologic tests for rheumatoid arthritis include rheumatoid factor and cyclic citrullinated peptide antibodies. Inflammatory markers may be elevated. Uncontrolled inflammation can lead to erosive radiographic changes of the joints. Extraarticular manifestations can affect the lungs, eyes, skin, and other organs.

Polyarticular Juvenile Idiopathic Arthritis (JIA)
Polyarticular Juvenile Idiopathic Arthritis is a childhood-onset inflammatory arthritis affecting ≥ 4 joints during the first 6 months of disease. Patients may be rheumatoid factor positive or negative. Extraarticular manifestations can also be present.

Psoriatic Arthritis (PsA)
Psoriatic arthritis, classified as a seronegative spondyloarthropathy, is a form of inflammatory arthritis that may involve both peripheral and axial joints. PsA affects approximately 15% of patients with psoriasis. A minority of patients with PsA do not have associated psoriatic skin disease. Patients may also present with symptoms of PsA prior to the onset of skin disease.

Ankylosing Spondylitis (AS)
Ankylosing spondylitis, also classified as a seronegative spondyloarthropathy, is a form of inflammatory arthritis that predominantly affects axial joints and entheses, areas where tendons and ligaments attach to the bones. Peripheral arthritis can also be present. It typically presents in young adulthood and is more common in males.

2.2. Analysis of Current Treatment Options

Available therapies may be approved for treatment of more than one condition. Currently approved non-biologic and biologic systemic therapies and the indications for which they are approved are listed in Table 1 and Table 2, respectively.

Plaque Psoriasis
The available approved systemic treatments for moderate to severe PsO in candidates for systemic therapy or phototherapy is described in Table 1 and Table 2 below. While multiple topical therapies are available, and may be used in combination with systemic treatments, topical therapies are not typically used alone for patients with psoriasis of moderate to severe severity. Phototherapy involves exposure to UVB (including narrowband) or to UVA in combination with the photosensitizer, Psoralen, a photochemotherapy that goes by the acronym PUVA. Phototherapy requires frequent office visits (e.g. three times per week) and carries an increased risk of squamous cell carcinoma (of the skin).

Rheumatoid Arthritis
Many effective therapies are approved for the treatment of patients with RA including nonsteroidal anti-inflammatory drugs (NSAIDs) and selective cyclooxygenase-2 (COX-2) inhibitors, corticosteroids, disease modifying anti rheumatic drugs (DMARDs) and biologics. Currently approved non-biologic and biologic systemic therapies for RA are listed in Table 1 and Table 2, respectively.

Polyarticular Juvenile Idiopathic Arthritis (JIA)
Similar to RA, effective therapies for the treatment of patients with JIA include NSAIDs, selective COX-2 inhibitors, corticosteroids, DMARDs, and biologics. Currently approved non-biologic and biologic therapies for polyarticular JIA are listed in Table 1 and Table 2 below.

Psoriatic Arthritis (PsA)
The first-line therapy for the treatment of psoriatic arthritis is typically the off-label use of small molecular immunomodulators (DMARDs, such as methotrexate (MTX), sulfasalazine, and leflunomide). NSAIDs and corticosteroids are also used. The TNF-inhibitors, infliximab, etanercept, adalimumab, certolizumab, and golimumab, as well as the IL-12/IL-23 inhibitor, ustekinumab, have been approved for treatment of active psoriatic arthritis. More recently, apremilast, a small molecule phosphodiesterase 4 inhibitor, and secukinumab, an IL-17 inhibitor, were also approved for treatment of active psoriatic arthritis. Currently approved therapies for treatment of adult patients with psoriatic arthritis are listed in Table 1 and Table 2.

Ankylosing Spondylitis (AS)

Initial treatment for AS typically includes the use of NSAIDs. Sulfasalazine may be used off-label for management of peripheral arthritis. For persistent axial symptoms, patients may be treated with TNF-inhibitors or secukinumab, an IL-17 inhibitor. Currently approved therapies for treatment of adult patients with ankylosing spondylitis are listed in Table 1 and Table 2.

Table 1: US-licensed Non-Biologic DMARDs by Indication

Product Name (Trade Name) [Applicant] {year}	***Mechanism of Action***	**Approved Indications**					
		RA	**PsA**	**AS**	**pJIA**	**PsO**	**Other**
Sulfasalazine (AZULFIDINE) [Pfizer]{1950}	*Anti-inflammatory and/or immunomodulator*	X			X		UC
Methotrexate sodium (METHOTREXATE SODIUM) [Multiple] {1953}	*Folate anti-metabolite*	X			X	X	Oncology indications
Hydroxychloroquine (PLAQUENIL) [Sanofi-Aventis]{1955}	*Unknown*	X					SLE, Malaria
Prednisone [Multiple sponsors]{1955}	*Anti-inflammatory and other unspecified mechanisms*	X					Many
Azathioprine (IMURAN) [Prometheus Labs]{1968}	*Anti-metabolite*	X					Renal transplant
Penicillamine (CUPRIMINE) [Aton]{1970}	*Unknown*	X					Wilson's Disease, cystinuria
Auranofin (RIDAURA) [Prometheus Labs]{1985}	*Unknown*	X					
Cyclosporine (NEORAL) (SANDIMMUNE) [Novartis]{1990, 1995}	T-cell inhibitor	X				X	Organ rejection, KCS
Acitretin (SORIATANE) (Stiefel){1996}	*Retinoid*					X	
Leflunomide (ARAVA) [Sanofi-Aventis]{1998}	*Anti-metabolite*	X					
Tofacitinib (XELJANZ) [Pfizer] (2012)	*JAK kinase inhibitor*	X					
Apremilast (Otezla) [Celgene] {2014}	*PDE4 inhibitor*		X			X	
*Year = Year of first approval	UC=Ulcerative Colitis, CD=Crohn's Disease, SLE=Systemic Lupus Erythematosis, KCS=Keratoconjunctivitis sicca						

Table 2: US-Licensed Biologic DMARDs by Indication

Product Name (Trade Name) [Applicant] {year}	Description and *Mechanism of Action*	Approved Indications					
		RA	PsA	AS	pJIA	PsO	Other
Etanercept (ENBREL) [Immunex/Amgen] {1998}	Fusion protein consisting of TNF-R and human IgG1 Fc *TNF inhibitor*	X	X	X	X	X	
Infliximab (REMICADE) [Centocor] {1999}	Chimeric IgG1 k mAb *TNF inhibitor*	X	X	X		X	CD, UC, Pediatric CD/UC
Anakinra (KINERET) [Amgen] {2001}	Recombinant polypeptide *IL-1 receptor antagonist*	X					NOMID
Adalimumab (HUMIRA) [Abbott] {2002}	Human IgG1 k mAb *TNF inhibitor*	X	X	X	X	X	CD, UC, Pediatric CD, HS, Uveitis
Abatacept (ORENCIA) [Bristol Myers Squibb] {2005}	Fusion protein consisting of CTLA-4 and human IGg1 Fc *T cell activation inhibitor*	X			X		
Rituximab (RITUXAN) [Genentech and Biogen] {2006}	Chimeric murine/human IgG1 k mAb *Anti CD20, B cell depletor*	X					GPA, MPA, NHL, CLL
Golimumab (SIMPONI) [Centocor] {2009}	Humanized IgG1 k mAb *TNF inhibitor*	X	X	X			UC
Certolizumab Pegol (CIMZIA) [UCB Inc] {2009}	Humanized Fab fragment *TNF inhibitor*	X	X	X			CD
Ustekinumab (STELARA) [Centocor Ortho Biotech] {2009}	Humanized IgG1 k mAb *IL-12, IL-23 antagonist*		X			X	
Tocilizumab (ACTEMRA) [Genentech/Roche] {2010}	Humanized IgG1 k mAb *IL-6 receptor inhibitor*	X			X		SJIA
Golimumab (SIMPONI ARIA) [Janssen Biotech] {2013}	Humanized IgG1 mAb *TNF inhibitor*	X					
Secukinumab (Cosentyx) [Novartis] {2015}	Humanized IgG1 mAb *IL-17 inhibitor*		X	X		X	
Year = Year of first approval	CD=Crohn's Disease, UC=Ulcerative Colitis, NOMID=Neonatal Onset Multisystem Inflammatory Disease, GPA=Granulomatosis with Polyangiitis, MPA=Microscopic Polyangiitis, NHL=Non-Hodgkin's Lymphoma, CLL=Chronic Lymphocytic Leukemia, SJIA= Systemic Juvenile Idiopathic Arthritis, HS=Hidradenitis Suppurativa						

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

GP2015 has not been licensed or marketed in the US.

US-licensed reference product, Enbrel, is an inhibitor of tumor necrosis factor alpha (TNF-α) binding and is licensed in the US to Immunex Corp, Thousand Oaks, CA, and marketed by Amgen Inc, and Pfizer Inc. It is available for the treatment of (dates of approval):

- Rheumatoid Arthritis (RA) (November 2, 1988)
- Polyarticular Juvenile Idiopathic Arthritis (JIA) in patients aged 2 years or older (May 27, 1999)
- Psoriatic Arthritis (PsA) (January 15, 2002)
- Ankylosing Spondylitis (AS) (July 24, 2003)
- Plaque Psoriasis (PsO) (April 30, 2004)

The US Enbrel (etanercept) label was updated on 25-MAR-2015 and contains an updated boxed warning describing serious infections and malignancies:

SERIOUS INFECTIONS

- Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens. (5.1)
- Enbrel should be discontinued if a patient develops a serious infection or sepsis during treatment. (5.1)
- Perform test for latent TB; if positive, start treatment for TB prior to starting Enbrel. (5.1)
- Monitor all patients for active TB during treatment, even if initial latent TB test is negative. (5.1)

MALIGNANCIES

- Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including Enbrel. (5.3)

In addition to the boxed warning on the label, the WARNINGS AND PRECAUTIONS section of the label provides for warnings on serious infections, neurological events, malignancies, post-marketing reports of heart failure or worsening of heart failure, hematologic events, hepatitis B reactivation, allergic reactions, interference with immunizations, autoimmunity and the formation of autoantibodies, and immunosuppression.

3.2. Summary of Presubmission/Submission Regulatory Activity

The development of GP2015 was conducted outside the US. On 9-JUL-2012, Sandoz met with the Agency for a Type B Pre-IND meeting to discuss the proposed development plan for GP2015. The Agency reviewed the meeting package and provided extensive comments regarding the biosimilar pathway. In addition to providing guidance on the analytical assessment, the Agency discussed the appropriate pathway to clinical study comparability.

On 19-DEC-2012, a teleconference was held with the Applicant to discuss the proposed statistical package for the clinical trial. It was agreed that the study design for the clinical study was adequate and the primary endpoint to evaluate clinically meaningful differences between GP2015 and the US-licensed or EU-approved Enbrel would be Psoriasis Area and Safety Index (PASI) 75 response at week 12 with a proposed equivalence margin of 18%.

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

3.3. Foreign Regulatory Actions and Marketing History

GP2015 is not marketed in any other countries.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations (OSI) was consulted to conduct routine applicant/monitor inspection for GP2015, a proposed biosimilar to US-licensed Enbrel. A single clinical comparative study (302) was conducted to support a determination of no clinically meaningful differences, and provides the foundation for extrapolation to all indications sought for the biosimilar.

The clinical study provided only 5 sites (out of 71) that enrolled more than 8 subjects per arm—one in Estonia and 4 in Poland. Poland sites enrolled the most subjects (190 out of 531). Randomization was stratified on weight and prior therapy (but not center), so randomization could be unbalanced within a center.

The largest center enrolled 35 subjects (19 to Enbrel and 16 to GP2015). All subjects had data at Week 12, and all 35 subjects were PASI 75 responders (Center 4809 / Dr. Grazyna Pulka / Krakow, Poland). This site was selected to be inspected by OSI based on the size of enrollment.

The next largest center enrolled 30 subjects (20 to Enbrel and 10 to GP2015). Twenty-nine (29) subjects had data at Week 12, and 79% (15/19) had a PASI 75 response on Enbrel and 10/10 had a PASI 75 response on GP2015 (Center 3704 / Dr. Kulli Kingo / Tartu, Estonia). This site was also selected for inspection.

The third largest center enrolled 26 subjects (13 per arm). Twenty-three (23) subjects had data at Week 12, and 83% (10/12) had a PASI 75 response on Enbrel and 11/11 had a PASI 75 response on GP2015 (Center 4813 / Dr. Jolanta Weglowska / Wroclaw, Poland).

The three sites described above were selected to be inspected. In addition, an Applicant inspection of Hexal, Inc, a subsidiary of Sandoz, Inc. was conducted.

The Applicant submitted an error report to the BLA dated January 14, 2016, to provide notice of inconsistencies in the data for prior psoriasis medications in Study 302. The report notes that some members of the clinical team misunderstood the protocol's provision to list concomitant treatments within 6 months prior to baseline for treatments for any other indication, while all treatments for psoriasis without time restriction were to be entered in the electronic case report form (eCRF). This led to erroneous requests by the CRO asking sites to remove concomitant medication/therapy stopped before 6 months prior to baseline, without specifying that this would not apply for psoriasis treatments. Subject stratification was to be based on documentation of prior psoriasis treatment. OSI was unable to confirm the reliability of reported concomitant psoriasis treatment and adherence to the protocol-specified randomization stratification scheme. The study was otherwise conducted according to the protocol and other data generated by the sites inspected appeared acceptable in support of the respective indication.

OSI inspections of the clinical sites and the Applicant did not identify major deficiencies in data quality and integrity. Based on review of inspectional findings for the clinical investigators and the Applicant, the study data collected appear reliable in support of the BLA. See discussion regarding stratification analyses under section Efficacy Results-Primary Analysis below.

4.2. Product Quality

GP2015 is a proposed biosimilar product to US-licensed Enbrel. An analytical similarity program was designed utilizing the proposed biosimilar, GP2015, US-licensed Enbrel, and EU-approved Enbrel. The program had two goals: first, an analytical comparison of the proposed biosimilar to

US-licensed Enbrel was needed to demonstrate findings that it is "highly similar" to the US-licensed Enbrel notwithstanding minor differences in clinically inactive components; and second, a comparison of US-licensed Enbrel to EU-approved Enbrel was needed to establish the analytical component of the scientific bridge to justify the relevance of data generated using EU-approved Enbrel as the comparator in some clinical and non-clinical studies. To support a determination that GP2015 is highly similar to the reference product, Sandoz submitted an extensive analytical similarity package consisting of multiple orthogonal physicochemical and biological assays. Highly critical quality attributes include amino acid identity, higher order structure, in vitro TNF-α neutralization, and TNF-α binding. GP2015 shares the same 934 amino acid primary sequence as the reference molecule and is also synthesized as a dimeric, secreted, soluble protein with post-translational dimerization of the Fc region via two disulfide bonds. 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. 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. In vitro TNF-α neutralization activity of GP2015 was not statistically equivalent to US-licensed Enbrel as assessed in the reporter gene assay. Etanercept is known to contain incorrect disulfide bond variants that can affect the potency of the product[1]. GP2015 contains lower levels of incorrect disulfide bonds at peptide T7 relative to US-licensed Enbrel and EU-approved Enbrel. At the request of the Agency, 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. Sandoz provided evidence of refolding of the wrongly bridged variants under redox conditions in vitro. Using a computed potency model developed by Sandoz to determine the adjusted potency based on the level of T7 peptide, a comparison of the relative TNF-α neutralization of GP2015, US-licensed Enbrel, and EU-approved Enbrel were determined to be equivalent. This additional information represented a major amendment. TNF-α neutralization was also assessed by a cell based apoptosis method which determined GP2015 was within the quality range set by US-licensed Enbrel. TNF-α binding was determined to be statistically equivalent for GP2015, US-licensed Enbrel, and EU-approved Enbrel. Assessment of TNF-ß neutralization by reporter gene assay fell within the quality range set by US-licensed Enbrel as well.

[1] 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.

Tests indicated 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 antibody-dependent cell-mediated cytotoxicity (ADCC) activity specifically through binding FcγRIIIa and high mannose glycans (which contribute to the total afucosylated glycoforms) can also impact PK. GP2015 was demonstrated to have lower ADCC activity relative to US-licensed Enbrel and EU-approved Enbrel, due to lower levels of afucosylated Fc glycan structures on GP2015. However, consistent with literature, GP2015 and the reference product have low ADCC activity relative to anti-TNF mAbs and another mAb whose major mechanism of action (MOA) includes ADCC. ADCC is not considered to be a mechanism of action of etanercept. As discussed below, PK similarity 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.

The results of these comparisons show that the three products met the pre-specified criteria for analytical similarity, including statistical criteria for the critical potency bioassay, TNF-α neutralization, and TNF-α binding. Thus, a pair-wise analytical comparison of GP2015 to US-licensed Enbrel supports the conclusion that GP2015 is highly similar to US-licensed Enbrel. Further, an adequate analytical bridge between EU-approved Enbrel, US-licensed Enbrel, and GP2015 was established as part 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.

Refer to the review by Dr. Adams, Ph.D. for detailed analysis of the CMC findings.

4.3. Clinical Microbiology

No issues have been identified by the clinical microbiology review team as of the time of this review.

4.4. Nonclinical Pharmacology/Toxicology

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 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 reasonably similar to that of EU-approved Enbrel in cynomolgus

monkeys and rabbits. Further, the efficacy of GP2015 in Tg197 transgenic mice (i.e., reduced development of arthritis-related pathology) was similar to that of EU-approved Enbrel.

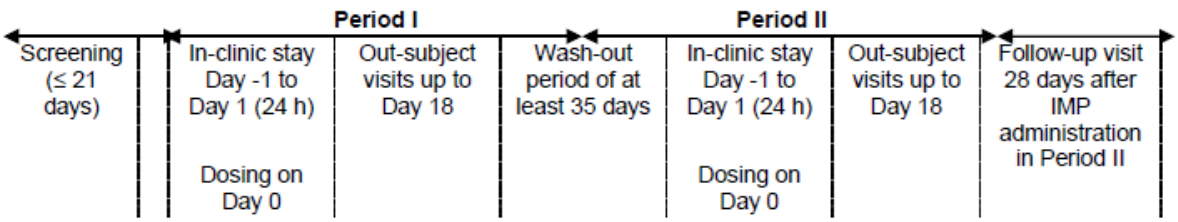
The nonclinical pharmacology, pharmacokinetic, and repeat-dose toxicity data submitted support a demonstration of the similarity (i.e., comparable achieved exposures, safety, and efficacy) between GP2015 and EU-approved Enbrel from the nonclinical pharmacology and toxicology perspective. Refer to the review by Dr. Bennedict, Ph.D. for detailed analysis of the pharmacology/toxicology findings.

4.5. Clinical Pharmacology

The clinical pharmacology program of GP2015 was designed to evaluate the 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. The GP2015 clinical development program included four PK studies (Studies 101, 102, 103, and 104), a cross-study PK comparison between US-licensed Enbrel and EU-approved Enbrel from studies 101 and 102 (Report 105), and a steady state PK assessment in patients with chronic PsO (Study 302).

Each of the PK studies was conducted as a randomized two-way crossover study with a design to assess PK similarity, and descriptive safety, and immunogenicity. In these studies, healthy subjects received a 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. Studies 101 and 102 were designed to evaluate PK similarity and safety of GP2015 and US-licensed Enbrel, and GP2015 and EU-approved Enbrel, respectively. Figure 1 illustrates the study design for Studies 101 and 102. Studies 103 and 104 were of similar crossover design with at least a 35 day wash-out period, but included longer in-clinic stays of 120 hours and 48 hours, respectively. Specified criteria for PK similarity would be met when the 90% CIs for the ratios of geometric means of Cmax, AUCt, and AUCinf were within the margins of 0.8 and 1.25 in Studies 101, 103, and 104. Of note, the assessment in Study 102 included Cmax and AUCt only.

Figure 1: Study Design, Studies 101, 102



Source: Applicant's 351(k) submission; Summary of Clinical Pharmacology Studies

As described in the draft guidance for Industry entitled, "Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product," a single-dose, randomized study is generally the preferred design for PK similarity assessments. A cross-over design is appropriate for etanercept, however, 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. The PK samples in the clinical pharmacology studies were analyzed with a 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.

In Study 102, the pairwise comparisons of GP2015 and US-licensed Enbrel met the pre-specified acceptance criteria for PK similarity. In Study 101, the lower bound of the confidence interval for AUCt and AUCinf fell just below 0.8 (0.7835 and 0.7815 respectively), and the pre-specified criteria were not met for the comparison of GP2015 and EU-approved Enbrel. The Applicant explains that a post hoc analysis that included the operator as a fixed effect to the ANOVA model demonstrated PK similarity between GP2015 and EU-approved Enbrel. The pre-specified cross study comparison, Report 105, met the pre-specified criteria between US-licensed Enbrel and EU-approved Enbrel.

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 through 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.

Sandoz subsequently submitted the results of Study 104, a repeat PK study of similar design and methodology as Study 101. The study was requested by the European regulatory authorities. 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 the 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 AUCt, AUCinf, and Cmax met the pre-specified acceptance criteria for PK similarity.

Study 103 was a randomized, open-label, two-way cross-over study to compare the PK and safety of GP2015 administered by autoinjector (AI) and prefilled syringe (PFS) in healthy adult males. This study was not intended to assess similarity between GP2015 and the reference product. It is discussed further under section 4.6 Devices and Companion Diagnostic Issues and contributes to the discussion in the safety section.

A BRC meeting held on November 19, 2015 to discuss the interpretation of the PK similarity assessments submitted by Sandoz in support of the BLA. The discussion at the BRC meeting centered on the acceptability of the cross-study comparison between studies 101 and 102, and the adequacy of the PK bridge between US-licensed and EU-approved Enbrel to support the relevance of the clinical data generated using EU-approved Enbrel in Study 302 to support a demonstration of biosimilarity between GP2015 and US-licensed Enbrel. Given the identical study design and conduct of Studies 101 and 102, and the pre-specified criteria for the cross-study Report 105, the BRC agreed that the approach used for the PK similarity assessments in the GP2015 program was acceptable. Further, based on the results of the cross-study Report 105, the BRC also agreed that the PK component of the scientific bridge between US-licensed Enbrel and EU-approved Enbrel is sufficiently justified. PK similarity between GP2015 and EU-approved Enbrel was also supported by the results from Study 104. Of note, systemic exposures of both GP2015 and EU-approved Enbrel in Study 104 were approximately two-fold higher than those in Studies 101 and 102; however, this difference was explained by the different bioanalytical assay used in Study 104, compared to Studies 101 and 102.

For further detail on the clinical pharmacology findings, refer to the review by Dr. Ren.

4.5.1. Mechanism of Action

Etanercept is a dimeric fusion protein, consisting of an extracellular ligand-binding portion of the human p75 tumor necrosis factor receptor (TNFR) which is linked to the Fc domain of human IgG1. It binds to and neutralizes pro-inflammatory cytokines TNF-α and lymphotoxin-α by preventing binding to natural cell surface receptors and subsequent signal transduction.

4.5.2. Pharmacodynamics

N/A

4.5.3. Pharmacokinetics

See section 4.5 above.

4.6. Devices and Companion Diagnostic Issues

Sandoz proposes two presentations for administration of GP2015, an autoinjector (50 mg/1.0 mL) and a prefilled syringe (25 mg/0.5 mL and 50 mg/1.0 mL). The AI and PFS presentations were reviewed by Center for Devices and Radiological Health (CDRH). The AI is based on the (b) (4) developed by (b) (4) on behalf of Novartis Pharma. The device is designed for a prefilled 1 ml long syringe with a staked 0.5 inch needle with rigid needle shield. The AI does not have a fluid path and does not have contact with the drug or biologic contained within the prefilled syringe. The AI components for GP2015, as well as for the approved product secukinumab, (b) (4), differing in drug product and fill volume specification. The Applicant conducted those tests that could be impacted by the drug/fill volume. The design requirements for the PFS and AI were felt to be adequate for the intended use of the products. The human factors study performed for the secukinumab AI was felt appropriate for the combination product in RA patients and no additional human factors studies were required.

The PFS with needle safety device and AI were used in the clinical evaluations of the drug and the devices have been validated for intended use. The two presentations were compared in Study 103, a randomized, open-label, two-way cross-over study to compare the PK and safety of GP2015 administered by AI and PFS in healthy adult males. The 90% CI of the primary PK endpoints of AUClast, AUCinf, and Cmax fell within the prespecified interval of 0.8 and 1.25, demonstrating PK similarity between the two presentations.

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 3: Summary of the Clinical Development Program of GP2015

Study ID	Design	Objectives	Subjects	Treatments	Endpoints
Clinical Pharmacology Studies					
Study 102	R, DB, 2-way cross-over	PK, safety, and immunogenicity	54 healthy subjects (42m/15f)	SD 50 mg SC: • GP2015 • US-Enbrel	C_{max}, AUC_t and AUC_{inf}
Study 101	R, DB, 2-way cross-over	PK, safety, and immunogenicity	57 healthy subjects (33m/21f)	SD 50 mg SC: • GP2015 • EU-Enbrel	C_{max}, AUC_t and AUC_{inf}
Study 104	R, DB, 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, DB, 2-way cross-over	PK, safety, and immunogenicity	51 healthy males	SD 50 mg SC: • GP2015 PFS • GP2015 AI	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 (329m/202f) GP2015: N-264 (157m/107f) Enbrel/EU: N=267 (172m/95f)	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: • GP2015 cont'd • GP2015 switch • EU-Enbrel cont'd • EU-Enbrel switch	Safety, Immunogenicity

Source: Adapted from Applicant 351(k) BLA submission

5.2. Review Strategy

The clinical development program for GP2015 consists of the five controlled clinical studies listed in Table 3. The following studies provide the primary evidence to support the

demonstration of no clinically meaningful differences between GP2015 and US-licensed Enbrel.

- Study 302 is the comparative clinical study that provides the comparative clinical efficacy and safety data for GP2015 as compared to EU-approved Enbrel in plaque psoriasis.
- Study 102, is a single-dose, 2-way crossover study in healthy subjects providing PK and safety data to directly compare GP2015 and US-licensed Enbrel.
- Study 101 and Study 104, are of generally similar design to Study 102, and provide PK and safety data to directly compare GP2015 and EU-approved Enbrel.
- Report 105 provides pre-specified cross-study comparative clinical pharmacology data between US-licensed Enbrel and EU-approved Enbrel.
- Study 103 is a supportive PK study comparing GP2015 administered by PFS and AI, that provides additional safety data.

Together, Studies 102, 101, 104, and Report 105 support the PK component of the scientific bridge between GP2015, EU-approved Enbrel, and US-licensed Enbrel, and justify the relevance of the comparative data generated using EU-approved Enbrel in Study 302 to support a demonstration of no clinically meaningful differences between GP2015 and US-licensed Enbrel.

Evaluation of the single comparative clinical study, 302, in plaque psoriasis provides evidence to further support a demonstration of no clinically meaningful differences. The similarity margin of ± 18% was selected based on response rates in published literature on double-blind, placebo controlled studies with etanercept in similar populations (Leonardi et al 2003, Papp et al 2005) in which the observed effect size was 45-46%. The 18% similarity margin was selected to preserve at least 60% of the treatment effect relative to placebo in the historical studies. The similarity margin was discussed and agreed upon with the Agency prior to conduct of the clinical trial. The primary endpoint, PASI 75 response, was assessed at Week 12. The safety data from Weeks 12 to 18 follows the first transition from EU-approved Enbrel to GP2015 and includes an evaluation of immunogenicity and longer term safety data. The original submission included efficacy and safety data through Week 12. The Applicant provided safety data up to Week 30 in a supplemental safety report. This review will focus on the safety, immunogenicity, and efficacy comparisons for the initial 12 week period of the study; as well as the safety and immunogenicity for the transition period (from Week 12 to Week 18), and for the entirety of treatment period 2, Week 12-30. As the study is ongoing and limited data from the extension period, i.e. beyond Week 30, are available, data from the extension period is not included in this review. Of note, the submitted safety database is adequate to support a substantial review of the application and the safety data from the ongoing extension period is not considered necessary for the assessment of whether clinically meaningful differences exist between GP2015 and US-licensed Enbrel. Studies 102, 101, and 104, provide additional comparative safety and immunogenicity data and these studies, in addition to Study 103, contribute towards the safety database.

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. A Randomized, Double-Blind, Multi-Center, Study to Demonstrate Equivalent Efficacy and to Compare Safety and Immunogenicity of a Biosimilar Etanercept (GP2015) and Enbrel in Patients with Moderate to Severe Chronic Plaque-type Psoriasis.

6.1.1. Study Design

Overview and Objective

To demonstrate equivalent efficacy of GP2015 and EU-approved Enbrel in patients with moderate to severe chronic plaque-type psoriasis with respect to PASI 75 response rate at Week 12.

Secondary objectives in Treatment Period 1:

- To compare PASI 50, PASI 75, and PASI 90 response rates of GP2015 and Enbrel
- To compare the response of patients treated with GP2015 and Enbrel over time based on the PASI score
- To compare the response rates of GP2015 and Enbrel determined by the Investigator's Global Assessment (IGA) of disease activity
- To compare the health-related quality of life during treatment with GP2015 and Enbrel by the Dermatology Life Quality Index (DLQI) and the EuroQol 5-Dimension Health Status Questionnaire (EQ-5DTM)
- To compare the functional ability by the Health Assessment Questionnaire-Disability Index (HAQ-DI©) only in patients with a medical history of PsA
- To compare the clinical safety and tolerability of GP2015 and Enbrel as assessed by vital signs, clinical laboratory variables, electrocardiogram (ECG), and adverse events (AEs) monitoring
- To compare injection site reactions (ISRs)
- To compare the pharmacokinetics (PK) of GP2015 and Enbrel in terms of trough serum concentrations in a subset of 100 patients
- To compare immunogenicity as determined by measuring the rate of anti-drug antibody (ADA) formation against GP2015 and Enbrel

Secondary objectives in Treatment Period 2:

- To compare efficacy, safety, and immunogenicity of pooled data from patients undergoing repeated switches (Groups 1b and 2b) with those from patients continually treated with GP2015 (Group 1a) and Enbrel (Group 2a)

- To compare efficacy, safety, and immunogenicity of data from patients continually treated with GP2015 (Group 1a) versus those of patients continually treated with Enbrel (Group 2a)

Objectives in the Extension Period:

- To compare efficacy, long term safety, and immunogenicity of pooled data from patients undergoing repeated switches and continue with the last treatment after week 30 for further 22 weeks (Groups 1b and 2b) with those from patients continually treated with GP2015 (Group 1a) and Enbrel (Group 2a) for 52 weeks
- To compare efficacy, long term safety, and immunogenicity of data from patients constantly treated with GP2015 (Group 1a) versus those of patients continually treated with Enbrel (Group 2a) after week 30 up to week 52

Of note, the multiple "switching" study design was selected by the Applicant. The Agency does not consider the multiple switches necessary for studies supporting a demonstration of no clinically meaningful differences and biosimilarity. However, for proposed biosimilars to TNF-inhibitors, such as GP2015, descriptive data comparing safety and immunogenicity between patients undergoing a single transition from Enbrel comparator product to GP2015 and those continuing on Enbrel comparator product, is expected. These data were included in the Week 12 to Week 18 safety analyses.

Trial Design

This is a multi-center, randomized, double-blind study, in 531 subjects with moderate to severe chronic plaque-type psoriasis treated for up to 52 weeks as detailed in **Error! Reference source not found.**.

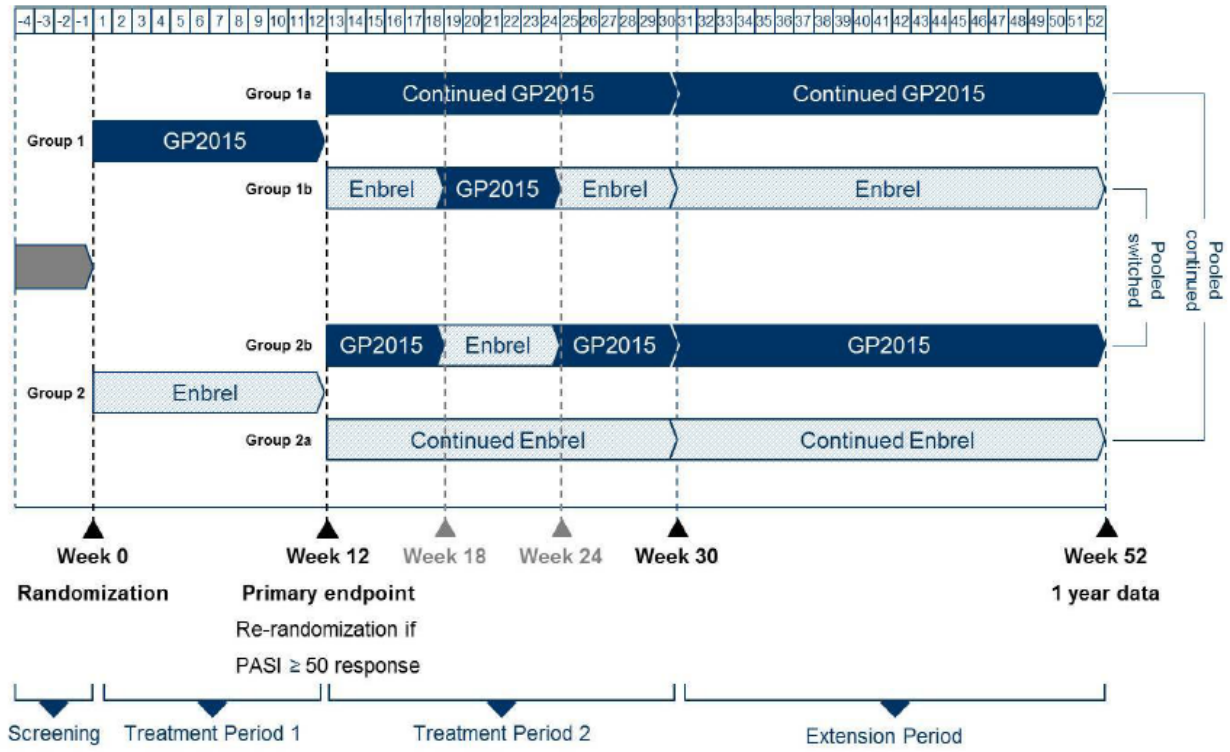
After an initial screening period of a minimum of two weeks and a maximum of four weeks duration, patients were randomized by interactive response technology (IRT) to two groups to receive either GP2015 (Group 1) or EU-Enbrel (Group 2) for 12 weeks (Treatment Period 1, TP1). Patient randomization was stratified by body weight (< 90 kg or ≥ 90 kg) and prior systemic therapy (no prior systemic therapy, any prior systemic therapy including biologic immunomodulating agents but no prior treatment with a TNF antagonist, or prior treatment with a TNF antagonist).

Patients who achieved at least a PASI 50 response at Week 12 were re-randomized to continue to Treatment Period 2 (TP2). The reassignment at Week 12 was not stratified. Patients who did not achieve at least a PASI 50 response at the end of TP1 did not continue treatment. Approximately 75% of the patients in each group were to remain on their initial treatment throughout the study, while approximately 25% of the patients were to receive alternating

treatment with GP2015 or EU-approved Enbrel for periods of 6 consecutive weeks, i.e. switching after Week 12 and again switching back to the original treatment after Week 18 followed by a third switch of treatment regimens after Week 24. After adjustment of the re-assignment ratio, the actual randomization ratio between continuous versus alternating treatment arms was approximately 3:2.

After completion of TP2, patients received treatment for an additional 22 weeks during the Extension Period. They continued the last treatment received during TP2 through the Extension Period.

Figure 2: Study Design 302



Source: Applicant's 351(k) submission; Study 302, Week 30 Clinical Study Report

The eligible patient population consisted of adult male and female patients at least 18 years of age with active, but clinically stable chronic plaque-type psoriasis of at least 6 months duration, involving at least 10 percent of the body surface area (BSA), having a minimal PASI score of 10 (indicating moderate-to-severe psoriasis), an IGA score of 3 or greater, and having previously received phototherapy or systemic therapy for psoriasis at least once or were candidates to receive such therapy in the opinion of the investigator.

Study Endpoints

Efficacy assessments:

- PASI 50, 75, and 90 response rates
- % change in PASI from baseline
- Change in IGA
- Proportion of IGA responders (proportion of patients achieving clear (0) or almost clear (1) disease state)
- Change in Dermatology Life Quality Index (DLQI) from baseline
- Proportion of patients achieving DLQI of 0 or 1
- EuroQol 5-Dimension Health Status Questionnaire (EQ-5D)
- Health Assessment Questionnaire-Disability Index (HAQ-DI) and pain VAS (for PsA assessment)

Safety assessments:

- Physical examination and vital signs
- ECG
- Laboratory assessments: hematology, clinical chemistry, urinalysis, pregnancy tests
- Assessment of ISRs
- Adverse events
- Immunogenicity

Statistical Analysis Plan

Raw data listings, summary tables, figures and statistical tests will be generated using the SAS® Version 9.2 or higher.

All clinical data, including laboratory and PK data will be provided as raw data output from an external database. CDISC SDTM 3.1.2 amendment 1 compliant SAS datasets will then be prepared.

The final SDTM files will also include variables indicating the actual and planned treatment assigned population flags for the various populations as well as all protocol deviations. Coding of corresponding data (e.g. by Medical Dictionary for Regulatory Activities [MedDRA] or World Health Organization [WHO]-drug dictionary) is included in the SDTM datasets.

Appropriate SAS programs will be prepared and validated according to (b) (4) standard operating procedures.

The following descriptive statistical parameters will be shown in summary tables:

- Continuous variables: n (valid cases), mean, standard deviation (SD), minimum, median, maximum. Quartiles will be presented as appropriate.

- Categorical variables: Count and percentage of each category. Percentages are routinely based on the total category count excluding the missing category if not otherwise mentioned. Percentages showing a rate relative to the total number of patients in this group are given in special tables (e.g. adverse event [AE] tables). Footnotes will specify the percent basis.

The same number of decimal places as in the raw data will be presented when reporting minimum and maximum, 1 more decimal place than in the raw data will be presented when reporting mean, median and quartiles, and 2 more decimal places than in the raw data will be presented when reporting SD.

The default significance level will be 5%; confidence intervals (CIs) will be 95% and all tests will be two-sided, unless otherwise specified in the description of the analysis.

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled and follow-up measurements will not be included in by-visit summaries. However unscheduled and follow-up measurements will be presented in the listings. In case of a retest (same visit number assigned), the last available measurement for that visit will be used for by-visit summaries.

Protocol Amendments & Study Conduct

Study 302 was amended 3 times. The first amendment was issued 10-SEP-2013, approximately 10 weeks after study start. In this amendment, based on advice from the European Health Authorities, a 95% confidence interval was applied to the primary endpoint, the sample size was increased (b) (4) to 546 randomized patients, and the reassignment scheme at Week 12 was changed to a ratio of 3:1 from a ratio of 1:1. In addition, the existing follow-up phase was modified to an extension phase of 22 weeks for all patients. The permitted concomitant and prohibited treatments sections of the protocol were updated to clarify these definitions. Amendment 2 was issued 13-NOV-2013, approximately 18 weeks after study start and contained non-substantial changes to correct inconsistencies and typographic errors. With amendment 3, issued 08-MAY-2014, after completion of recruitment, the re-assignment ratio of 6:1 was set to achieve a goal overall randomization ratio of 3:1 at Week 12 between the continuous versus the alternating treatment arms. Given the time point at which this was implemented, the actual randomization ratio was approximately 3:2. A decision to cease further recruitment of patients was made after 531 patients were randomized based on the low number of discontinued patients. Overall, the protocol amendments did not affect safety or efficacy results.

Data Quality and Integrity: Applicant's Assurance

A Blind Data Review Meeting (BDRM) evaluated any major protocol deviations. The review assured data quality and integrity.

During the BDRM the following criteria were defined as those resulting in major protocol deviations:

- Deviations of Inclusion/Exclusion criteria that effect the study outcome with regard to efficacy (exclusion from PPS) or PK (exclusion from PK)
- Missing PASI scores at baseline or week 12; discontinued patients will be included in the PPS if reason for discontinuation was "unsatisfactory therapeutic effect" after they have received drug for at least 4 weeks
- Compliance to study drug administration: if the patient has missed more than four doses of study drug administration out of which more than two doses are not allowed to be missed consecutively. However, a patient cannot miss two consecutive doses in the week before week 12
- Visit window: if the patient has deviated week 12 visit by more than 2 days out of visit window (4 days from planned visit day). However deviations at other planned visits prior to week 12 are acceptable and are considered as "Minor"
- Prohibited medication that may impact efficacy (exclusion from PPS) or PK (exclusion from PK)

Frequency and percentage of patients having major and minor protocol deviations (only for PPS) will be presented by deviation category, treatment group and overall for all patients in FAS. Patient having major and minor protocol deviations will be counted only once under the more severe deviation category. Protocol deviations will also be listed. The summary of protocol deviations will be based on the FAS.

6.1.2. Study Results

Compliance with Good Clinical Practices

All studies were conducted by Good Clinical Practice as described in International Conference on Harmonization (ICH) Guideline E6 and in accordance with the ethical principles outlined in the Declaration of Helsinki. The studies were conducted in compliance with the protocols. Informed consent, protocol, amendments, and administrative letters forms for each study and received Institutional Review Board/Independent Ethics Committee approval prior to implementation. The investigators conducted all aspects of these studies in accordance with applicable national, state, and local laws of the pertinent regulatory authorities. Written informed consent was obtained prior to the subject entering the studies (before initiation of protocol-specified procedures). The investigators explained the nature, purpose, and risks of

the study to each subject. Each subject was informed that he/she could withdraw from the study at any time and for any reason. Each subject was given sufficient time to consider the implications of the study before deciding whether to participate. Subjects who chose to participate signed an informed consent document

Financial Disclosure

The Applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on Financial Disclosure by Clinical Investigators. The Applicant submitted FDA Form 3454 certifying investigators and their spouses/dependents were in compliance with 21 CFR part 54. No potentially conflicting financial interests were identified.

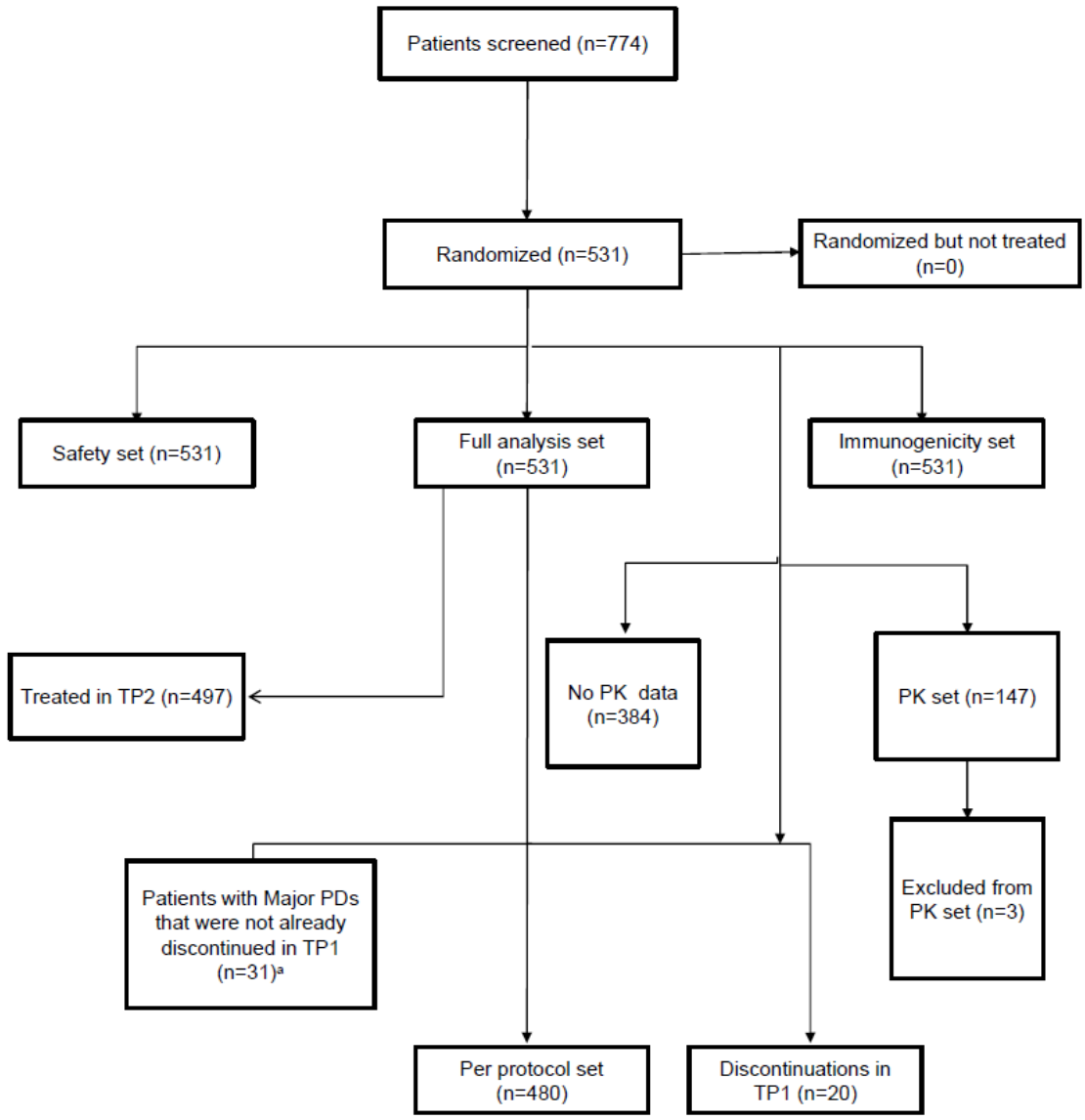
Data Quality and Integrity – Reviewers' Assessment

The databases for the studies required minimal data management prior to performing analyses. However, two requests for additional information were made during the review cycle. In the first request, the Agency requested statistical programs for creating the estimates and confidence intervals for the primary and key secondary analyses in Study 302, as the statistical analysis plan did not contain sufficient detail regarding the Applicant's models to replicate the analyses without the statistical programs. In the second request, the Agency requested additional datasets in a sufficiently usable form that included information on the recorded prior therapies for psoriasis (which was used to define a key factor in the analyses). The Applicant submitted the requested materials.

Patient Disposition

For the initial 12 week treatment period, a total of 774 subjects were screened at 74 study centers. Five-hundred thirty-one (531) subjects were randomized 1:1 to receive one of the treatments; 264 patients and 267 patients were randomized to receive GP2015 and EU-approved Enbrel, respectively.

Figure 3: Patient Disposition for Treatment Period 1, Study 302



Source: Applicant's 351(k) submission; Study 302, Week 30 Clinical Study Report

The majority (511 patients, 96.2%) of all randomized patients completed TP1 (initial 12 Weeks). The most common reasons for discontinuation were AEs and patient decision (1.3% each, total) as shown in Table 4. All other reasons for discontinuation were reported by not more than 1 patient (0.2% total) and no patients discontinued due to lack of efficacy. Thirty-four patients had major protocol deviations, but 3 of these patients discontinued during TP1. Consequently, 31 of the 511 patients who completed TP1 were excluded from the PPS due to major protocol deviations and the PPS thus comprised 480 patients.

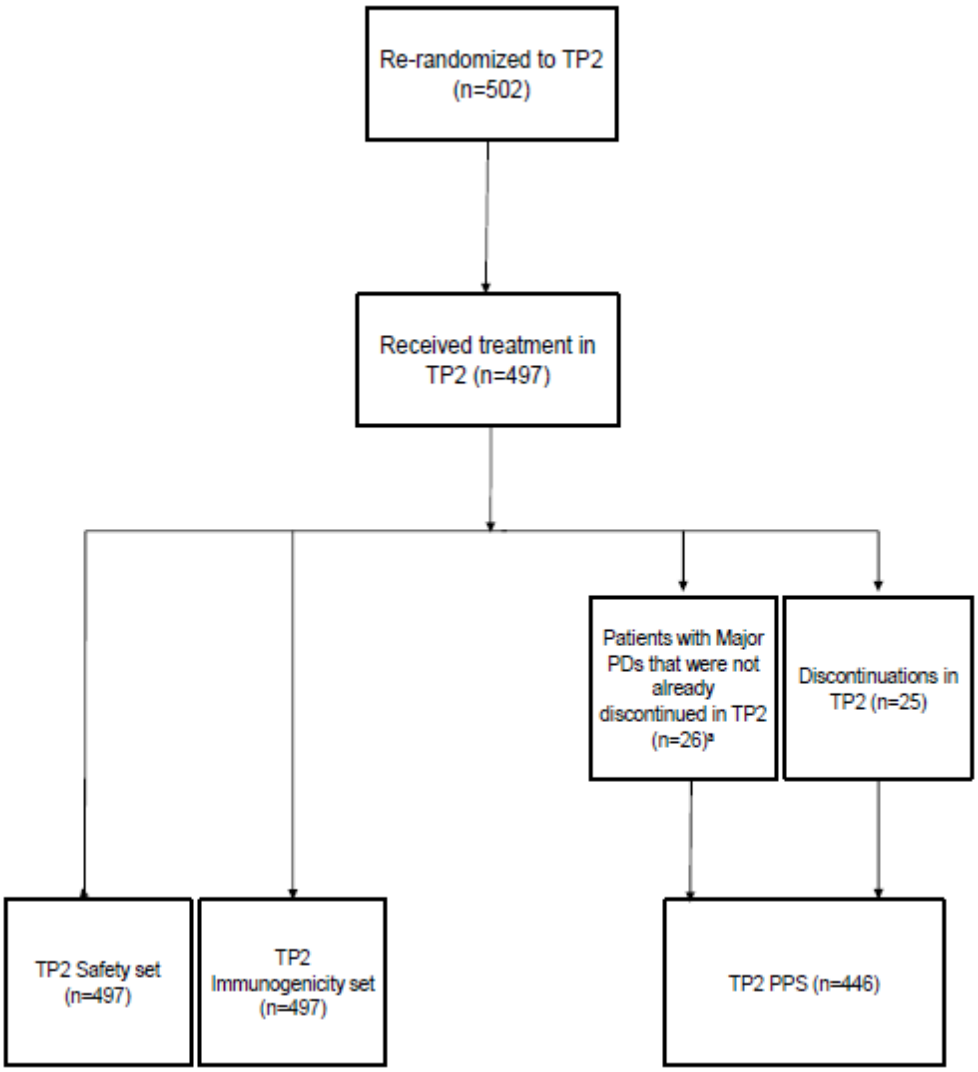
Table 4: Patient Disposition for Treatment Period 1, Study 302, (FAS)

Disposition/Reason	GP2015 N=264 n (n%)	EU-Enbrel N=267 n (n%)	TOTAL N=531 n (n%)
Randomized	264 (100.0)	267 (100.0)	531 (100.0)
Completed TP1	256 (97.0)	255 (95.5)	511 (96.2)
Discontinued the study in TP1	8 (3.0)	12 (4.5)	20 (3.8)
Adverse events	4 (1.5)	3 (1.1)	7 (1.3)
Death	0	1 (0.4)	1 (0.2)
Lost to follow-up	1 (0.4)	0	1 (0.2)
Non-compliance with study	0	1 (0.4)	1 (0.2)
Physician decision	0	1 (0.4)	1 (0.2)
Protocol deviation	1 (0.4)	0	1 (0.2)
Patient decision	2 (0.8)	5 (1.9)	7 (1.3)
Injection site reaction	0	1 (0.4)	1 (0.2)

FAS=Full analysis set; TP= treatment period
Source: Applicant's 351(k) submission; Study 302, Week 30 Clinical Study Report

Of the 511 subjects who completed Week 12, 8 subjects did not achieve a PASI 50 response; however 3 of these patients continued to receive treatment. Of the 503 subjects who did achieve a PASI 50 response at Week 12, 7 subjects did not receive study drug in TP2 due to discontinuation (2 patients were not re-randomized, 1 patient discontinued at Week 12 due to an AE, and 4 patients were re-randomized but did not take any study drug in TP2). Additionally, 2 patients (achieved PASI 50 at Week 12) had no data beyond Week 12 because these were patients from Ukrainian sites and could not continue due to the war situation in their country.

Figure 4: Patient Disposition for Treatment Period 2, Study 302



Source: Applicant's 351(k) submission; Study 302, Week 30 Clinical Study Report

In treatment period 2 (Week 12-30), a total of 497 patients received treatment; 150 patients continued to receive GP2015, 151 patients continued to receive EU-approved Enbrel, 100 patients who received GP2015 in TP1 then transitioned to receive the treatment sequence Enbrel>GP2015>Enbrel (switched GP2015), and 96 patients who received Enbrel in TP1 transitioned to receive the treatment sequence GP2015>Enbrel>GP2015 (switched EU-approved Enbrel). The majority of re-assigned patients (472 patients, 95.0%) completed TP2. Patient disposition for TP2 is detailed in Figure 4. The most common reasons for discontinuation during TP2 were 'patient decision' (1.8%, total) and 'Adverse events' (1.4% total) (Table 5). There was no notable difference in the rate of discontinuation between

continued GP2015 and continued Enbrel groups (3.3% in each group) nor between pooled continued and pooled switched treatment groups (3.3% vs. 4.6%, respectively). One subject was unblinded, and a second subject was misrecorded as being unblinded, but subsequently confirmed not to have been unblinded. A total of 5 patients (1.0%) were discontinued in Ukraine where a study site was closed due to the war.

Table 5: Subjects Disposition for Treatment Period 2, Study 302, (FAS)

Disposition/Reason	Continued GP2015 N=150 n (n%)	Continued EU-Enbrel N=151 n (%)	Pooled Continued Treatments N=301 n (%)	Pooled Switched Treatments N=196 n (n%)	Total N=497 n (n%)
Re-Assigned	150 (100)	151 (100)	301 (100)	196 (100)	497 (100)
Discontinued the study in TP2	7 (4.7)	9 (6.0)	16 (5.3)	9 (4.6)	25 (5.0)
Patient decision	3 (2.0)	4 (2.6)	7 (2.3)	2 (1.0)	9 (1.8)
Adverse events	1 (0.7)	2 (1.3)	3 (1.0)	4 (2.0)	7 (1.4)
Study terminated for site by Applicant[1]	1 (0.7)	2 (1.3)	3 (1.0)	2 (1.0)	5 (1.0)
Lack of efficacy	1 (0.7)	0	1 (0.3)	1 (0.5)	2 (0.4)
Physician decision	1 (0.7)	0	1 (0.3)	0	1 (0.2)
Protocol deviation	0	1 (0.7)	1 (0.3)	0	1 (0.2)

TP2= treatment period 2
1 All 5 Subjects were enrolled at the same site in Ukraine.
Source: Applicant's 351(k) submission; Study 302, Week 30 Clinical Study Report

A total of 465 patients continued into the extension period, including 139 patients in the continued GP2015 treatment group, 141 patients in the continued EU-approved Enbrel group, 95 patients in the switched GP2015 group, and 90 patients in the switched EU-approved Enbrel treatment group. Data concerning completion of the extension period were not available for the majority of patients as of the cut-off date of 29-OCT-2014.

Protocol Violations/Deviations

A total of 34 patients (6.4%) had major protocol deviations during TP1 and the proportion of patients with major protocol deviations was balanced between the GP2015 (6.8%) and Enbrel (6.0%) groups, with the most common being violations of visit windows (13 patients, 2.4% total), violation of inclusion and exclusion criteria (12 subjects, 2.2% total) and use of prohibited medication (8 subjects, 1.5%). In addition, 4 subjects (0.8% total) showed non-compliance to study drug administration. Three (0.6% total) of these 4 subjects participated in the PK sub-study and were excluded from the PK analysis set.

Twenty eight patients (5.6%) were determined to have major protocol deviations in TP2. The proportion of patients with major protocol deviations was lower in the continued GP2015 (4.0%) treatment group than in the continued EU-approved Enbrel (8.6%) group. Use of prohibited medication (8 patients, 1.6% total) and violations of exclusion criteria (7 patients, 1.4% total) were the most common violations. The proportion of patients with major protocol deviations was generally similar between the pooled continued (6.3%) and pooled switched (4.6%) groups.

Table of Demographic Characteristics

The demographics of subjects were well balanced in characteristics. Baseline demographic characteristics, determined at the start of TP1, were also similar in the four treatment arms of TP2.

Table 6: Subject Demographics TP1, Study 302 (FAS)

Demographic Parameters (FAS)	Treatment Group		Total (N=531) n (%)
	GP2015 (N=264) n (%)	EU-Enbrel (N=267) n (%)	
Sex			
Male	157 (59.5)	172 (64.4)	329 (62.0)
Female	107 (40.5)	95 (35.6)	202 (38.0)
Age			
Mean years (SD)	42.1 (12.29)	42.7 (12.86)	42.4 (12.57)
Median (years)	41.0	42.0	41.0
Min, max (years)	18, 78	19, 75	18, 78
Weight Group, n (%)			
< 90kg	160 (60.6)	161 (60.3)	321 (60.5)
≥ 90kg	104 (39.4)	106 (39.7)	210 (39.5)
Weight (kg)			
Mean (SD)	86.3 (21.12)	85.9 (18.72)	86.1 (19.93)
Median	84.0	85.0	85.0
Range	47, 148.5	46.5, 158	46.5, 158
Race			
Caucasian	263 (99.6)	264 (98.9)	527 (99.2)
Black or African American	1 (0.4)	0	1 (0.2)
Asian	0	1 (0.4)	1 (0.2)
Unknown	0	1 (0.4)	1 (0.2)
Other	0	1 (0.4)	1 (0.2)
BMI (kg/m^2)			
Mean (SD)	28.561 (6.0953)	28.458 (5.4632)	28.509 (5.7809)
Median	27.74	28.24	27.78
Range	16.65, 48.44	17.44, 46.05	16.65, 48.44

BMI= Body Mass Index; SD= Standard Deviation; FAS= full analysis set
Source: Applicant's 351(k) submission; Study 302, Week 12 Clinical Study Report

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Baseline disease characteristics were recorded at the start of TP1. Overall, the baseline disease characteristics were will matched between GP2015 and EU-approved Enbrel in TP1, and between the 4 treatment arms in TP2. The groups were representative of the intended target population of moderate to severe plaque psoriasis. The baseline mean PASI score was 22.51

and the mean total BSA affected was 30.70%. The mean time since diagnosis of psoriasis was 17.69 years. Previous exposure to systemic therapy was reported by 39.7% of total patients, as defined in the Week 12 CSR, 40.6% in the Week 30 CSR, and 31.1% as defined in the amendment to the Week 30 CSR. There were no meaningful differences between the groups in previous exposure to biologic and non-biologic systemic therapies.

Medications that were used by ≥10% of total subjects total included clobetasol propionate (topical), methotrexate, belosalic (topical), dithranol (topical), and daivobet (topical), and these were used by similar proportions of patients in each treatment group. In addition, clobetasol propionate (used by 23.9% of patients in the GP2015 group and 19.1% of patients in the EU-approved Enbrel group) and methotrexate (used by 14.4 % of patients in the GP2015 group and 13.1% of patients in the EU-approved Enbrel group) were the most frequently used psoriasis specific prior medications. The most frequently used prior medications were in the 'all other therapeutic products' term and were used by 27.7% and 25.8% of patients in the GP2015 and EU-approved Enbrel groups, respectively. The use of other psoriasis medications was similar between the groups.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Compliance with study drug administration during TP1 was similar between the treatment groups. The number of missed doses during TP1 was also similar between the two treatment groups, with the majority of patients (86.6%, total) not missing any doses of study drug. During the BDRM it was defined that missing >4 doses of study drug, out of which more than 2 doses were missed consecutively, constituted a major protocol deviation. Overall, 3.6% of patients missed >4 doses of study drug; 2.7% and 4.5% in the GP2015 and EU-Enbrel groups, respectively. During TP2, compliance with study drug administration was similar between the continued GP2015 and continued EU-approved Enbrel groups. The majority of patients (90.9%, total) did not miss any doses of study drug. Similar numbers of patients missed >4 doses of study drug in the continued GP2015 (4.7%) and continued Enbrel (5.3%) groups, as well as the pooled continued (5.0%) and pooled switched treatment groups (4.1%).

Concomitant medications were used by 144 (27.1% total) patients in TP1, balanced between the treatment groups. The most frequently used medications were paracetamol (3.4% GP2015; 2.2% EU-approved Enbrel), and ibuprofen (1.5% GP2015; 3.0% EU-approved Enbrel). In TP2, 135 (27.2% total) patients received concomitant medications, balanced between the 4 treatment groups. The most frequently used concomitant medications were paracetamol and ibuprofen.

Rescue therapy was not provided in this study. Only those patients who achieved a PASI 50 or greater response were re-randomized in TP2.

Efficacy Results – Primary Endpoint

The primary endpoint was the PASI 75 at Week 12. The originally implemented version of the protocol dated 04-FEB-2013, specified that the primary analysis would be analyzed with an exact 90% confidence interval for the difference in response rates between GP2015 and EU-approved Enbrel using the per protocol population (PP), which excluded patients with major protocol deviations. Protocol Amendment 1 (dated 18-SEP-2013) changed the confidence level to 95% citing advice from national European Health Authorities. The similarity margin in each case was ±18%. Supportive analyses were also conducted with the full analysis set (FAS; all randomized patients). Missing data was not imputed for the PP population (except that dropouts due to unsatisfactory therapeutic effect were to be imputed as non-responders, however no subjects dropped out for this reason). In the FAS, missing PASI 75 responses were imputed as non-response.

The results of the Applicant's per protocol analysis and the full analysis set analysis are similar, and the 90% and 95% confidence intervals based on both the per protocol set and the full analysis set were within the pre-specified margin of ±18% (Table 7).

Table 7: PASI 75 Response Rates (Primary Endpoint) Week 12, Study 302

	GP2015	EU-etanercept
Per Protocol Population	N=239	N=241
Adjusted response rate	73.3%	75.8%
Difference (GP2015-etanercept)	-2.5%	
90% Confidence interval	(-8.8%, 3.9%)	
95% Confidence interval	(-10.0%, 5.1%)	
Full Analysis Set	N=264	N=267
Adjusted response rate	70.3%	71.7%
Difference (GP2015-etanercept)	-1.4%	
90% Confidence interval	(-7.7%, 5.0%)	
95% Confidence interval	(-9.0%, 6.3%)	

Note: Confidence intervals computed using a logistic regression model with terms for treatment group, 'actual' body weight stratum, and 'actual' prior systemic therapy classification
Source: Applicant's 351(k) submission; Study 302, Week 12 Clinical Study Report and Statistical Overview

As per the protocol, the strata for prior systemic therapy was to be assigned as "no prior systemic therapy", "any prior systemic therapy including biologic immunomodulating agents but no prior treatment with a tumor necrosis factor (TNF) antagonist," and "prior treatment with a TNF antagonist." In the Statistical Analysis Plan (SAP), a logistic regression model with terms for treatment group, body weight category, and prior systemic therapy category was proposed. The blinded data review of the 12-week database identified that many patients'

stratification values for prior therapies and weight did not match the data recorded on the CRF; therefore, the SAP stated that 'actual' values in the clinical database for both stratification variables would be used in the logistic regression model rather than the classification entered into the IRT at randomization. Due to the few patients with previous use of other TNF-α inhibitors, the SAP stated that these patients would be grouped with the subjects who had previously received other prior therapies.

The Applicant proposed two different versions of the 'actual' prior therapy classification: one in Week 12 report and one in the Week 30 report amendment. For the Week 12 report, subjects who received UVA or UVB phototherapy, but no systemic treatments for psoriasis were considered to have had prior systemic therapy. At the Week 30 database lock, the Applicant classified patients who had received UVA or UVB phototherapy, but no systemic treatments in the 'No prior therapy' category. Other subjects were also reclassified as vitamins, analgesics, and antihistamines were no longer considered systemic therapies for psoriasis. Based on this re-categorization, 57 patients were re-stratified: 54 patients from "prior systemic treatment" to "no prior systemic treatment" and 3 patients from "no prior systemic treatment" to "prior systemic treatment." Analysis by the Agency Biostatistician of the logistic regression analysis using the Week 12 report 'actual' prior therapy and weight classifications, the Week 30 amendment 'actual' prior therapy and weight classifications , and the 'randomization' prior therapy and weight classifications used in the randomization showed small differences in point estimates with 90% confidence intervals within the range of ±9%. While the results of the analyses using the various definitions of the prior therapy classification lead to similar results (Table 10), 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) as displayed in Table 8.

Table 8: Exact Confidence Intervals for the Risk Difference of PASI 75 Response Rates

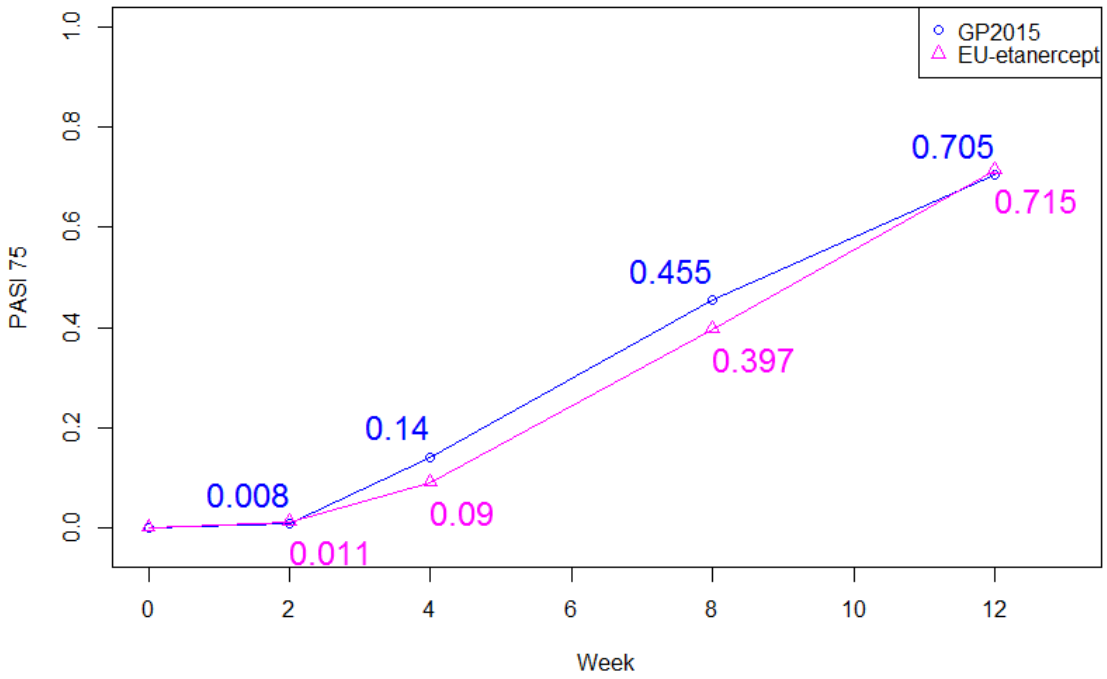
Population	GP2015 N=264	EU-etanercept N=267	Difference	90% Conf. Int.
FAS	186/264 70.5%	191/267 71.5%	-1.1%	(-8.3%, 6.0%)
PPS	176/239 73.6%	182/241 75.5%	-1.9%	(-9.4%, 5.6%)

FAS = full analysis set, PPS = per protocol set
Source: FDA Biostatistics reviewer analysis of data from Sandoz's 351(k) BLA submission

Sensitivity analyses conducted by the Agency biostatistical review team under varying assumptions regarding missing data were supportive of the conclusion of similarity.

In TP1, PASI 75 response was evaluated at Week 2, 4, 8, and 12. The response rates over time were similar for subjects treated with GP2015 and EU-approved Enbrel as displayed in Figure 5.

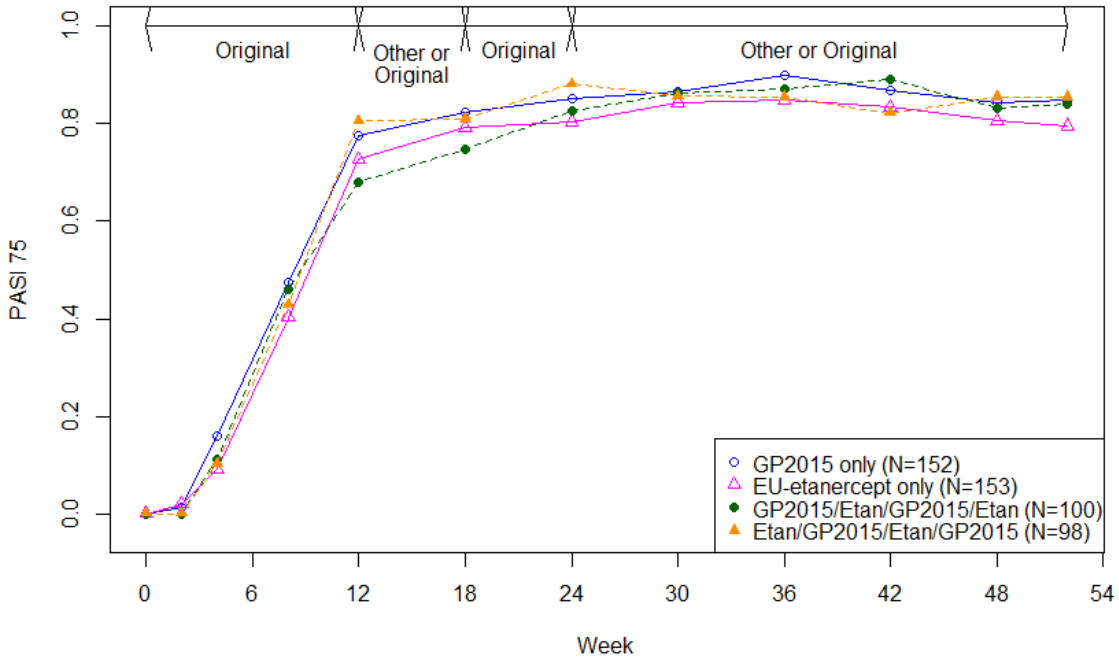
Figure 5: PASI 75 Response Rates in Treatment Period 1 (FAS, Missing as Failure)



Source: FDA Biostatistics reviewer analysis of data from Sandoz's 351(k) BLA submission

At Week 12, subjects with at least a PASI 50 response were randomized to either remain on the original treatment through the end of the study or to switch between treatments (Figure 2). Subjects randomized to the switching arms switched from the treatment received in TP1 to the alternate treatment between Weeks 12 and 18, the original treatment between Weeks 18 and 24, and the alternate treatment between Weeks 24 and 52. The PASI 75 response rates were similar in TP2 and the Extension Period across all four arms (continued GP2015, continued EU-approved Enbrel, switched GP2015, and switched EU-approved Enbrel) as shown in Figure 6. Note that the data available from the extension period was limited.

Figure 6: PASI 75 Response Rates in TP2 (Subjects re-randomized in TP2, Observed Cases)



Source: FDA Biostatistics reviewer analysis of data from Sandoz's 351(k) BLA submission

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) in the covariate analyses lead to similar results as the exact confidence interval. All fall within the pre-specified margin of 18%, supporting a demonstration of no clinically meaningful differences in PASI 75 response in plaque PsO between GP2015 and EU-approved Enbrel.

Efficacy Results – Secondary and other relevant endpoints

The key secondary endpoint was the percent change in PASI from baseline up to Week 12. The protocol proposed two analyses in order to calculate 2 sided 95% CIs for the difference between treatment groups. A mixed-effect model repeated measures (MMRM) analysis was conducted using factors for treatment group, visit, weight classification, and prior systemic therapy classification, and a covariate for baseline PASI score. A 95% confidence interval for the difference in adjusted means was calculated. A second analysis calculated the average treatment effect (ATE) of percent PASI change between Week 2 and Week 12 for each patient. The ATE analysis used an ANCOVA model, with terms for treatment group, body weight classification, prior systemic therapy classification, and baseline PASI as a covariate.

Both the repeated measures analysis and the analysis of the average treatment effect yielded similar results for the average percent change in PASI across Weeks 2, 4, 8, and 12. Point estimates for the two analyses in both the FAS and PPS populations for both treatments ranged from 50 to 56% with treatment differences ranging from -0.57% to 2.05%. All confidence intervals were within the pre-specified margin of 15% (Table 9).

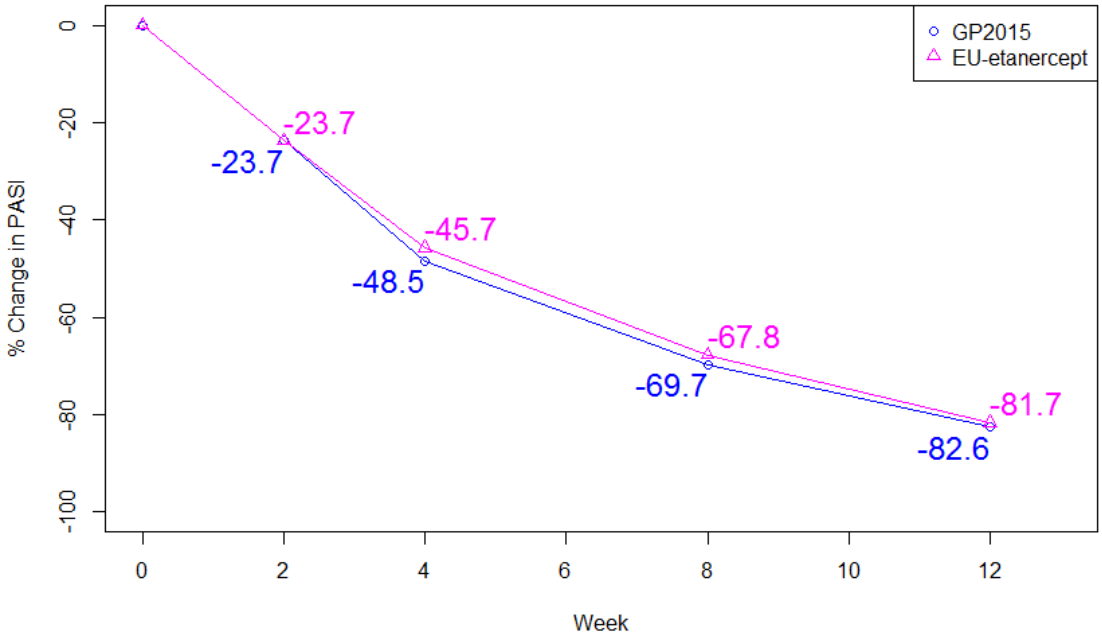
Table 9: Average Percent Change in PASI During Treatment Period 1

	GP2015	EU-Enbrel	Difference	95% Conf. Int.
PPS	N=239	N=241		
MMRM	-55.89	-55.32	-0.57	(-3.41, 2,26)
ATE	-52.84	-52.05	-0.78	(-3.51, 1.94)
FAS	N=264	N=266		
MMRM	-55.84	-54.29	-1.55	(-4.32, 1.22)
ATE	-52.18	-50.12	-2.05	(-4.88, 0.77)

PPS = Per protocol set; FAS = Full analysis set; MMRM = mixed-effect model repeated measurement; ATE = average treatment effect
Source: FDA Biostatistics reviewer analysis of data from Sandoz's 351(k) BLA submission

Although the key secondary endpoint assessed the average treatment effect across Treatment Period 1, the supportive endpoint of percent change in PASI at Week 12, which is related to the primary endpoint of PASI 75, is also of interest. The Applicant did not specify an analysis method for percent change in PASI at individual time points, except to present point estimates. The Agency Biostatistician computed 90% confidence intervals to be consistent with the primary analysis. As no method of handling missing data was specified, both observed cases and results for relatively extreme differential imputation were considered (imputing missing values as 0% improvement on one arm and 100% improvement on the other). Confidence intervals were computed using an ANOVA model with baseline PASI score as a covariate. The estimated treatment difference for the observed cases analysis (FAS) is -0.93%. The results in the per protocol population are similar. While these differential imputations shift the point estimates for the treatment differences by 3 to 4%, the 90% confidence intervals remain relatively narrow—within ±8%. Thus the analyses of percent change in PASI outcomes for GP2015 and EU-approved Enbrel are similar for the MMRM, ATE, and Week 12 analyses, and support the findings of the primary analysis. The mean percent change in PASI values by visit (FAS, observed cases) are presented in Figure 7.

Figure 7: Percent Change in PASI by Visit during TP1 (FAS, Observed Cases)



Source: FDA Biostatistics reviewer analysis of data from Sandoz's 351(k) BLA submission

Additional secondary endpoints included PASI 50, PASI 75, and PASI 90 response rates over time, observed PASI scores at each visit (Weeks 2, 4, 8, and 12), IGA response (0 or 1), DLQI, EQ-5D, and HAQ-DI. Response rates in these secondary endpoints were similar between treatment groups and supportive of the demonstration of no clinically meaningful differences between GP2015 and EU-approved Enbrel.

Additional Analyses Conducted on the Individual Trial

The randomization was stratified by weight and prior systemic therapy. As noted above, during the blinded review of the data after the Week 12 database lock, the Applicant discovered inconsistences in the data for prior psoriasis medications between the data selected by the investigator during randomization and that recorded in the CRF. For prior therapy classification, the Agency biostatistics review team evaluated three classifications provided by the Applicant, and found that in all three cases, the treatment differences were similar.

Table 10: Week 12 PASI 75 Response Rate by Prior Therapy Classification

	GP2015 N=264	EU-Enbrel N=267	Difference	90% Conf. Int.
Randomization Stratum				
Any	83/121 68.6%	88/122 72.1%	-3.5%	(13.8%, 7.3%)
No	103/143 72.0%	103/145 71.0%	1.0%	(-8.7%, 10.7%)
Actual (Week 12 Report)				
Any	84/111 75.7%	80/105 76.2%	-0.5%	(-11.7%, 10.8%)
No	102/153 66.7%	111/162 68.5%	-1.9%	(-11.2%, 7.5%)
Actual (Week 30 Report)				
Any	61/82 74.4%	64/83 77.1%	-2.7%	(-15.1%, 10.4%)
No	125/182 68.7%	127/184 69.0%	-0.3%	(-8.9%, 8.3%)

Source: FDA biostatistics reviewer analysis of data from Sandoz's 351(k) BLA submission

Changing the prior therapy classification twice, including after the initial study report was finalized, raises concerns about post-hoc changes to the database. Thus the clinical team concurs with the recommendation of the FDA Biostatistics reviewer to use the analysis for the primary endpoint most consistent with the original protocol, i.e. exact confidence intervals that do not use the stratification factors. Irrespective of the various approaches to stratification by prior therapy, the treatment responses were very similar between GP2015 and EU-approved Enbrel treatment arms and supportive of the primary analysis.

The Applicant also stratified the randomization by weight (<90 kg, ≥90 kg) and defined an 'actual' weight classification for subjects were the weight stratum classification did not agree with the recorded weight at baseline (11 subjects). The Agency Biostatistician analyzed two classifications by weight.

Table 11: Week 12 PASI 75 Response Rates by Weight Classification

	GP2015 N=264	EU-Enbrel N=267	Difference	90% Conf. Int.
Randomization Stratum				
<90 kg	122/162 75.3%	127/164 77.4%	-2.1%	(-11.2%, 7.0%)
≥ 90 kg	64/102 62.8%	64/103 62.1%	0.6%	(-10.6%, 12.4%)
Actual				
<90 kg	120/160 75.0%	126/161 78.3%	-3.3%	(-12.3%, 6.1%)
≥ 90 kg	66/104 63.5%	65/106 61.3%	2.1%	(-9.0%, 13.7%)

Source: FDA biostatistics reviewer analysis of data from Sandoz's 351(k) BLA submission

The subjects in the lighter stratum had higher response rates than those in the heavier stratum; however, the subgroup results were similar between the treatment groups.

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

Not applicable. This is a biosimilar development program with a single comparative clinical study that evaluates efficacy. The comparative clinical study, Study 302, is discussed in section 6.

8 Review of Safety

8.1. Safety Review Approach

The clinical safety program for GP2015 consists of the five controlled clinical studies listed in Table 3. Of these studies, four PK studies were conducted to determine the PK similarity of GP2015 to EU-approved Enbrel, or to US-licensed Enbrel. A single comparative clinical study in plaque psoriasis was conducted. The primary endpoint was the PASI 75 response at Week 12. Following assessment of the primary endpoint, patients were re-randomized to continue their

original treatment or transition to the other treatment group and undergo switching between the groups. The continued treatment and the transition groups provide further assessment of safety and immunogenicity. The Applicant provided data up to Week 30 in a supplemental safety report. The safety population includes 216 healthy subjects from the PK studies and 346 patients from Study 302 who received at least one dose of GP2015 until the data cut-off of 29-OCT-2014.

The majority of the safety data comes from studies comparing GP2015 and EU-approved Enbrel. US-licensed Enbrel was used only in Study 102. As discussed in section 4.5 above, a PK bridge was established between GP2015, EU-approved Enbrel, and US-licensed Enbrel that, in addition to the analytical bridge between the three products, supports the applicability of the data generated using EU-approved Enbrel for the demonstration of biosimilarity between GP2015 and US-licensed Enbrel. This bridge justifies the use of safety and efficacy data from Study 302, comparing GP2015 and EU-approved Enbrel, in this biosimilar application to support a demonstration of biosimilarity to US-licensed Enbrel.

The potential safety issues are referenced in the current label for US-licensed Enbrel as described in Section 3.1 above.

Of note, Study 103 will not be included in the integrated tables of the safety events in the healthy subject studies. In Study 103, subjects received a single dose of GP2015 via PFS and a single dose of GP2015 via AI. Inclusion of this study in the integrated tables would distort the denominator, and therefore the assessment, as all safety events occurred with GP2015 as the only study drug in this study. Notable findings from Study 103 will be included in the text.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

In Study 302, subjects were exposed to either GP2015 or EU-approved Enbrel in the two treatment arms during TP1, of this comparative clinical study. The median duration of exposure was 81 days and >96% of subjects were exposed for at least 8 weeks; the mean duration of exposure to study drug was similar between the two groups.

Table 12: Summary of Exposure to Study Drug, TP1, Study 302

Drug administration	GP2015 N=264 n (%)	EU-ENBREL N=267 n (%)
Any Exposure n (%)	264 (100)	267 (100)
≥2 weeks	263 (99.6)	263 (98.5)
≥4 weeks	262 (99.2)	258 (96.6)
≥8 weeks	257 (97.3)	257 (96.3)
Duration of exposure (days)		
Mean	80.6	79.2
SD	9.7	11.6
Median	81.0	81.0
Patient exposure (years)	58.3	57.9

Source: Applicant's 351(k) submission; Study 302, Week 30 Clinical Study Report

Overall, the duration and number of subjects exposed to study drug was sufficient to demonstrate safety in this Phase 3 clinical study. The average patient-years of exposure was 58.3 for GP2015 and 57.9 for EU-approved Enbrel.

Similarly, evaluation of the exposure from Weeks 12 to Weeks 30 was sufficient to demonstrate safety in the second phase of the clinical study. As discussed above under Protocol Amendments & Study Conduct, the re-randomization ratio for Treatment Period 2 was modified in amendments to the protocol during the course of the study. Approximately 60% of subjects were randomized to maintain the original treatment and 40% of subjects were randomized to switch treatments, an actual randomization ratio of approximately 3:2.

Table 13: Summary of exposure to Study Drug, TP2, Study 302

Drug administration	Continued GP2015 N=150 n (%)	Continued EU-ENBREL N=151 n (%)	Pooled continued treatment N=301 n (%)	Pooled switched treatment N=196 n (%)
Exposure				
Patients exposed for ≥ Week 18	147 (98.0)	148 (98.0)	295 (98.0)	192 (98.0)
Patients exposed for ≥ Week 24	143 (95.3)	146 (96.7)	289 (96.0)	189 (96.4)
Duration of exposure (days)				
Mean	117.0	117.2	117.1	117.5
SD	15.67	15.13	15.38	15.04
Median	120.0	120.0	120.0	120.0
Range	8.0-134.0	1.0-134.0	1.0-134.0	8-169.0
Patient exposure (years)	48.1	48.4	96.5	63.0

Source: Applicant's 351(k) submission; Study 302, Week 30 Clinical Study Report

Accounting for the overall randomization scheme, an imbalance in exposure is not seen in the study.

In the studies in healthy subjects, 216 subjects received a single 50 mg dose of GP2015, 54 received a single dose of US-licensed Enbrel, and 111 subjects received a single dose of EU-approved Enbrel.

8.2.2. Relevant characteristics of the safety population:

The patient population in Study 302 consists of adult male and female patients at least 18 years of age with active, but clinically stable chronic plaque-type psoriasis involving at least 10 percent of the body surface area (BSA), having a minimal PASI of 10 (indicating moderate-to-severe psoriasis) and Investigator's Global Assessment ≥3, and who previously received at least once phototherapy or systemic therapy for psoriasis or are candidates to receive such therapy. Studies 101 and 102 enrolled healthy adult male and female subjects, while Studies 103 and 104 enrolled healthy adult males.

8.2.3. Adequacy of the safety database:

Overall, the safety database for the comparative clinical study, supported by the safety data from the healthy subject PK studies, is sufficient to determine there are no clinically meaningful

differences between the proposed biosimilar, GP2015, and the comparator product, EU-approved Enbrel.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

Please see section 4.1 Office of Scientific Investigations and study efficacy section 6 for details regarding data integrity. Briefly, stratification inconsistencies were observed across many sites in Study 302. As discussed in section 4.1, the Applicant submitted an amendment to the BLA dated 14-JAN-2016, noting that some members of the clinical team misunderstood the protocol's provision to list concomitant treatments within 6 months prior to baseline, while all treatments for psoriasis without time restriction were to be entered in the CRF. This led to erroneous requests by the CRO asking sites to remove concomitant medication/therapy stopped before 6 months prior to baseline, without specifying that this would not apply for psoriasis treatments.

There were 110 randomization stratification deviations, 99 of which were related to prior therapy only, 7 related to weight stratum only, and 4 patients with deviations related to both stratum variables. The strata allocation deviations in TP1 occurred similarly across the two treatment group; 51 patients (19.3%) had at least one deviation related to strata allocation in the GP2015 group and 59 patients (22.1%) had at least one deviation in the EU-approved Enbrel group. In this review, attention was not paid to whether they were classified as major or minor deviations, but most were classified as minor in the listings. The Applicant used the 'actual' strata in the analysis, rather than the value used to stratify the randomization. Across the study, while only 19% of patients were flagged as protocol violations for misclassification in the prior therapy stratum, 36% of patients had this variable reclassified for the analysis.

In an amendment to the Week 30 clinical study report, submitted to the BLA 09-NOV-2015, the Applicant unlocked the database and defined a revised version of the 'actual' prior therapy stratum which was used in the efficacy analyses. In this report, 49 patients who received phototherapy but not systemic therapy were reclassified in the 'no systemic therapy' stratum, and 8 other patients were reclassified for other reasons. The rationale provided for the reclassification in the amendment was that "it was identified that some patients were incorrectly classified regarding the stratification variable 'prior systemic therapy', which might affect the efficacy analyses already presented in the CSR".

The information on which prior therapies were taken wasn't captured on the CRF but instead in an 'external stratification file' which the Applicant did not include with the datasets. The reader is referred to the biostatistics review for additional discussion of the sensitivity analyses performed to assess the potential impact of the various stratification variables on the overall results. Analysis of the PASI 75 response conducted by Dr. Kathleen Fritsch comparing each

stratification definition (SAP, Week 12, and Week 30), as well as analysis based on the exact confidence intervals without covariate adjustments, demonstrate similar findings in which the difference for each analysis falls within the similarity margin. For the safety population, stratification issues seen in efficacy did not affect the relevant characteristics of the safety set. Safety assessments were performed on the safety set which included all patients who took at least 1 dose of study treatment during the treatment period. Patients were analyzed according to treatment received. The safety analysis was summarized descriptively and no statistical testing was done. Stratification was not included in the safety analyses.

8.3.2. Categorization of Adverse Events

Safety was assessed in patients with chronic plaque-type psoriasis who received at least one dose of drug product (i.e. GP2015 or EU-approved Enbrel) in Study 302 until the data cut-off date of 29-OCT-2014. The safety population was used to evaluate the following:

- The rate, type, severity and assessment of investigational medical product (IMP) relationship of adverse events (AEs) in each study and the pooled safety population
- The rate of deaths, serious adverse events (SAEs) and adverse events of special interest (AESI)
- The rate and type of AEs in sub-groups (including demographic and disease baseline characteristics)
- Changes over time in laboratory variables, electrocardiograms (ECGs), vital signs and physical examination and when relevant reported as treatment treatment-emergent adverse event (TEAEs)
- Immunogenicity

Additionally, safety was assessed in healthy subjects in Studies 101, 102, 103, and 104. AEs were classified using Medical Dictionary for Regulatory Activities (MedDRA version 14.1 for Studies 101, 102; version 17 for Studies 103, 104, 302) and arranged by body system. Safety data were summarized descriptively and no statistical tests were used.

8.3.3. Routine Clinical Tests

Hematology, clinical chemistry, and urinalysis were collected in Study 302 and the PK studies in healthy subjects. In Study 302, safety labs were collected at screening, baseline, Week 2, 4, 8, 12, 18, 24, 42, 52 (End of Study (EOS)), and at follow-up. High sensitivity C-reactive protein was checked at baseline, week 4, and week 12. ADA testing was performed at each visit following the screening visit. ECGs were collected at screening, week 12, and EOS. Additional labs included screening assessments for TB, Hepatitis B and C, and HIV. PK testing was performed during TP1 at selected centers.

In Study 101 and 102, safety labs were collected at screening, visit 2, 4, 6, 7, 10, as well as 12, 14, 16, 17, 20, and follow-up visit, while in Study 103 and 104, safety labs were collected at screening, visit 2, 4, 6, 8, 9, 12, 14, 16, 18, 20, 21, 24, and follow-up. ECGs were performed at screening and at day -1 of period 2. PK assessments were performed throughout both treatment periods. ADA were assessed prior to dosing at the start of each period, and at follow-up on day 28. Additional labs included screening assessments for TB, Hepatitis B and C, and HIV.

The clinical tests performed and the timing of the assessments are appropriate to assess for clinically meaningful differences between GP2015 and US-licensed Enbrel.

8.4. Safety Results

8.4.1. Deaths

A single death occurred in Study 302 in the EU-approved Enbrel treatment group during TP1. This 58 year old Caucasian male patient with concomitant conditions including diabetes and elevated systolic blood pressure, died of cardiopulmonary failure not suspected to be related to the study drug. The patient's death was reviewed and determined unlikely to be related to the study drug. There were no other deaths in the GP2015 clinical program.

8.4.2. Serious Adverse Events

There were no SAEs reported in Studies 101, 102, 103, and 104. The serious adverse events observed in Study 302 are described in Table 14. One patient that experienced cardiopulmonary failure and died was discussed in the section describing deaths above. The proportion of patients who experienced at least one SAE was similar between the two treatment groups, GP2015 and EU-approved Enbrel. In TP1, in the GP2015 treatment group, there was one event of malignant melanoma in situ that was excised prior to start of study treatment with GP2015, however the pathological results were available only after initiation of study drug. There were no other SAEs in the Neoplasms benign, malignant, and unspecified SOC in TP1 or TP2. One patient in the EU-approved Enbrel treatment group experienced drug-induced liver injury in TP1; study drug was withdrawn and the event subsequently resolved.

The incidence of SAEs was slightly lower in those patients who continued on EU-approved Enbrel as compared to those who underwent a transition from EU-approved Enbrel to GP2015 (1.3% vs. 3.1%), as well as those in those that continued on GP2015 as compared to those that transitioned from GP2015 to EU-approved Enbrel (0.7% vs. 3.0%) in TP2. None of the SAEs were reported in more than one patient. Overall, SAEs were rare (1.3% of overall population in TP1, 1.6% in TP2) and did not identify any new safety concerns related to etanercept treatment.

Table 14: Serious Adverse Events in Treatment Periods 1 and 2 Through Week 30, Study 302

	Treatment Period 1		Treatment Period 2			
System organ class Preferred term	**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 (%)**
Number of patients with SAEs	**4 (1.5)**	**3 (1.1)**	**1 (0.7)**	**2 (1.3)**	**3 (3.1)**	**3 (3.0)**
Cardiac disorders	**0**	**1 (0.4)**				
Cardiopulmonary failure	0	1 (0.4)				
Eye disorders	**0**	**1 (0.4)**				
Retinal detachment	0	1 (0.4)				
Gastrointestinal disorders			**0**	**0**	**0**	**1 (1.0)**
Umbilical hernia			0	0	0	1 (1.0)
Hepatobiliary disorders	**0**	**1 (0.4)**	**0**	**0**	**0**	**1 (1.0)**
Cholelithiasis			0	0	0	1 (1.0)
Drug-induced liver injury	0	1 (0.4)				
Immune system disorders	**1 (0.4)**	**0**				
Milk allergy	1 (0.4)	0				
Infections and infestations	**1 (0.4)**	**0**	**0**	**1 (0.7)**	**2 (2.1)**	**0**
Appendicitis	1 (0.4)	0				
Diverticulitis			0	0	1 (1.0)	0
Pneumonia			0	1 (0.7)	0	0
Tonsillitis			0	0	1 (1.0)	0
Injury, poisoning, and procedural complications	**1 (0.4)**	**0**	**1 (0.7)**	**1 (0.7)**	**0**	**0**
Lower limb fracture	1 (0.4)	0				
Meniscus injury			1 (0.7)	0	0	0
Upper limb fracture			0	1 (0.7)	0	0
Musculoskeletal and connective tissue disorders			**0**	**0**	**0**	**1 (1.0)**
Psoriatic arthropathy			0	0	0	1 (1.0)
Neoplasms benign, malignant, and unspecified	**1 (0.4)**	**0**				
Malignant melanoma in situ	1 (0.4)	0				
Respiratory, thoracic, and mediastinal disorders			**0**	**0**	**1 (1.0)**	**0**
Pulmonary sarcoidosis			0	0	1 (1.0)	0
Skin and subcutaneous tissue disorders			**0**	**0**	**0**	**1 (1.0)**
Psoriasis			0	0	0	1 (1.0)

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 within the same SOC and PT are counted once under those categories and total row
Source: FDA analysis of data from Sandoz's 351(k) BLA submission

In summary, the reported SAEs were rare and similar between treatment groups. No new safety signals were identified. These findings support the similar safety profiles between EU-approved Enbrel and GP2015.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Adverse events leading to discontinuation were rare overall and did not cluster within any specific system organ class (SOC). The number of patients in the psoriasis clinical study 302 who reported AEs leading to discontinuation in TP 1 was low in both the GP2015 and the EU-approved Enbrel treatment groups (5 patients, 1.9% vs. 4 patients, 1.5%). The number of patients who reported AEs leading to discontinuation in TP 2 was also low in all groups, although it was slightly higher in those that transitioned from EU-approved Enbrel to GP2015 (5 patients, 5.2%) as compared to the switched GP2015 (1 patient, 1.0%), or the continued treatment groups (continued GP2015 1 patient, 0.7%; continued EU-approved Enbrel 2 patients, 1.3%), as detailed in Table 15. Reasons for discontinuation in the switched EU-approved Enbrel group included pustular psoriasis (1), lymphadenopathy mediastinal (1), drug abuse (1), panic attack (1), and hepatic steatosis (1). Overall, the discontinuations in TP1 and TP2 appear to be single occurrences without observed clustering in any particular SOC.

Reference ID: 3964787

Table 15: TEAEs Leading to Study Drug Discontinuation in Treatment Periods 1 and 2 through Week 30, Study 302

	Treatment Period 1		Treatment Period 2			
System organ class Preferred term	**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 (%)**
Number of patients with TEAEs	**5 (1.9)**	**4 (1.5)**	**1 (0.7)**	**2 (1.3)**	**5 (5.2)**	**1 (1.0)**
Blood and lymphatic system			**1 (0.7)**	**0**	**1 (1.0)**	**0**
Lymphadenopathy mediast			0	0	1 (1.0)	0
Thrombocytopenia			1 (0.7)	0		
Gastrointestinal disorders	**1 (0.4)**	**1 (0.4)**				
Abdominal distention	1 (0.4)	0				
Colitis ulcerative	0	1 (0.4)				
Immune system disorders			**0**	**1 (0.7)**	**0**	**0**
Hypersensitivity			0	1 (0.7)	0	0
Investigations	**2 (0.8)**	**1 (0.4)**				
Alanine aminotransferase	0	1 (0.4)				
Transaminases increased	1 (0.4)	0				
White blood cell decreased	1 (0.4)	0				
Cardiac disorders	**0**	**1 (0.4)**				
Cardiopulmonary failure[1]	0	1 (0.4)				
Hepatobiliary disorders	**0**	**1 (0.4)**				
Drug-induced liver injury[2]	0	1 (0.4)				
Hepatic steatosis			0	0	1 (1.0)	0
Neoplasms	**1 (0.4)**	**0**				
Malignant melanoma in situ[3]	1 (0.4)	0				
Psychiatric disorders			**0**	**0**	**2 (2.1)**	**0**
Drug abuse			0	0	1 (1.0)	0
Panic attack			0	0	1 (1.0)	0
Skin and subc. tissues	**1 (0.4)**	**0**	**0**	**1 (0.7)**	**1 (1.0)**	**1 (1.0)**
Dermatitis psoriasiform			0	0	0	1 (1.0)
Psoriasis			0	1 (0.7)	0	0
Pustular psoriasis	1 (0.4)	0	0	0	1 (1.0)	0

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
TEAE= treatment emergent adverse event; SAE= serious adverse event
[1] SAE leading to death
[2] SAE suspected to be related to drug
[3] SAE not suspected to be related to drug
Source: FDA analysis of data from Sandoz's 351(k) BLA submission

Two events leading to discontinuation were considered to be SAEs. There was an event of drug-induced liver injury in the EU-approved Enbrel treatment group, which was suspected to be treatment-related, and an event of malignant melanoma in situ in the GP2015 treatment group (described in section 8.4.2), which was not suspected to be treatment-related.

Study drug was interrupted in TP 1 in 3 patients in the GP2015 group and 6 patients in the EU-approved Enbrel group. The interruptions were mostly due to infections (2 pyelonephritis, 2 urinary tract infection, 1 gastroenteritis, 1 nasopharyngitis, 1 otitis media, 1 pharyngitis, and an upper respiratory tract infection).

For TP2, study drug was interrupted in 6 patients (4.0%) in each of the continued GP2015 and continued EU-approved Enbrel treatment groups, and 2 patients each (2.0 and 2.1%) in the switched GP2015 and switched EU-approved Enbrel groups. The majority of the TEAEs leading to study drug interruption were in the infections and infestations SOC (3 patients (2.0%) in continued GP2015, 2 patients (1.3%) in continued EU-approved Enbrel, and 1 patient (1.0%) in each of the switched groups). Types of infections leading to study drug interruption in TP2 included pharyngitis, bacterial infection, bronchitis, respiratory tract infection viral, and viral diarrhea. With the exception of pharyngitis which was reported by 2 patients (continued EU-approved Enbrel and switched GP2015), the other events occurred in only one patient each.

There were few AEs leading to drug discontinuation in the healthy subject studies. In Study 101, two subjects were withdrawn due to AEs of neutropenia and body tinea, in patients who received GP2015 and EU-approved Enbrel, respectively. In 102, one subject who received GP2015 was withdrawn due to an AE of rash. In Study 103, one subject who received GP2015 was withdrawn due to an AE of an animal bite. No AEs leading to discontinuation were reported in Study 104. The observed AEs leading to drug discontinuation were single events.

Overall, the incidence of AEs leading to drug discontinuation was low throughout the GP2015 development program and similar across treatment groups.

8.4.4. Significant Adverse Events

The Applicant identified potential AESI as defined by MeDRA SOC, HLGT, HLT, and PT as listed in Table 16. Consideration of an AE as an AESI was determined by the medical advisor. AESI were not defined for the healthy subject studies.

Table 16: List of TEAEs of Special Interest

System Organ Class (SOC)	High level group term (HLGT)/High level term (HLT)/Preferred term (PT)
Infections and infestations	Tuberculous infections (HLT) Atypical mycobacterial infections (HLT) Hepatitis B (PT) Acute hepatitis B (PT) Chronic hepatitis (PT) Hepatitis C (PT) Acute hepatitis C (PT) Chronic hepatitis C (PT) Sepsis, bactermia, viremia and fungemia NEC (HLT) Listeriosis (PT) Legionella infection (PT) Pneumonia legionella (PT) Fungal infectious disorders (HLGT) Pneumocystis infections (HLT) Aspergillus infections (HLT) Herpes viral infections (HLT)
Neoplasms benign, malignant, and unspecified (incl. cysts and polyps)	All PTs
Allergic/anaphylactic reactions	Angioedema and urticarial (HLGT) Hypersensitivity (PT) Drug hypersensitivity (PT) Bronchospasm (PT) Rubber sensitivity (PT) Rashes, eruptions and exanthemas NEC (HLT)
Immune system disorders/Autoimmune events	Acute and chronic sarcoidosis (HLT) Autoimmune pancytopenia (PT) Autoimmune hepatitis (PT) Lupus-like syndrome (PT) Vasculitides (HLT) Vasculitides NEC (HLT)
Neurological events Hematological events	Demyelinating disorders (HLGT) Pancytopenia (PT) Thrombocytopenia (PT) Anemia (PT) Aplastic anemia (PT) Leukopenia (PT) Neutropenia (PT) White blood cell count decreased (PT)
Congestive Heart Failure	Cardiac failure congestive (PT) Interstitial lung disease (PT)

Source: Applicant's 351(k) submission; Summary of Clinical Safety

Table 17 lists the observed treatment emergent AESI in treatment periods 1 and 2 by system organ class and preferred term. A similar proportion of patients in both treatment groups reported AESI; 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 TP 1. A higher proportion of patients in the GP2015 treatment group (5 patients (1.9%)) experienced AESI in the neoplasms benign, malignant, and unspecified (incl cysts and polyps) SOC 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. The single malignant event was a malignant melanoma in situ that was resected prior to initiation of study treatment. In the infections and infestations SOC, the groups were generally similar with regard to incidence of TEAEs at the PT level.

In TP 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 in the neoplasms benign, malignant, and unspecified (incl cysts and polyps) SOC; this was the only reported AESI in this SOC in TP2. As in TP1, in the infections and infestations SOC, the groups were generally similar with regard to incidence of TEAEs at the PT level.

There were 2 reports of urticaria, one event in the continued EU-approved Enbrel group and one in the switched GP2015 group in TP2, and, in addition, there was one case of facial swelling in the Enbrel group in TP1. There were no reports of anaphylaxis. An SMQ analysis of "hypersensitivity and anaphylactic reactions" was conducted at the suggestion of FDA on the un-pooled groups in treatment period 2 after the first transition (Week 12 to 18). The analysis identified a single patient who reported Type I hypersensitivity in the continued GP2015 group. A review of the CRF did not identify a relationship to the investigational drug product. Analysis of the safety data of patients who underwent a transition from EU-approved Enbrel to GP2015, as compared to those who continued treatment with EU-approved Enbrel did not reveal any increase in adverse events. Comparison of GP2015 and EU-approved Enbrel demonstrated no notable differences between the treatment groups with respect to AESI.

Table 17: Adverse Events of Special Interest in Treatment Periods 1 and 2 Through Week 30, Study 302

	Treatment Period 1		Treatment Period 2			
System organ class Preferred term	**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 (%)**
Number of patients with at least one AESI	**9 (3.4)**	**5 (1.9)**	**7 (4.7)**	**3 (2.0)**	**2 (2.1)**	**3 (3.0)**
Neoplasms	**5 (1.9)**	**1 (0.4)**	**1 (0.7)**	**0**	**0**	**0**
Skin papilloma	1 (0.4)	1 (0.4)				
Colon neoplasm[1]	1 (0.4)	0				
Lipoma	1 (0.4)	0				
Melanoma in situ[2]	1 (0.4)	0				
Melanocytic nevus	1 (0.4)	0	1 (0.7)	0	0	0
Infections and infest	**3 (1.1)**	**3 (1.1)**	**4 (2.7)**	**0**	**2 (2.1)**	**1 (1.0)**
Blastomycosis			1 (0.7)	0	0	0
Oral candidiasis			1 (0.7)	0	0	0
Oral herpes	1 (0.4)	2 (0.7)				
Herpes simplex	1 (0.4)	1 (0.4)	1 (0.7)	0	0	1 (1.0)
Herpes zoster			0	0	1 (1.0)	0
Tinea infection	1 (0.4)	0	1 (0.7)	0	0	0
Tinea versicolour			0	0	1 (1.0)	0
Skin and subcut. tissue	**0**	**1 (0.4)**	**0**	**2 (1.3)**	**0**	**2 (2.0)**
Rash			0	1 (0.7)	0	0
Rash generalized			0	0	0	1 (1.0)
Swelling face	0	1 (0.4)				
Urticaria			0	1 (0.7)	0	1 (1.0)
Blood and lymphatic system disorders			**2 (1.3)**	**0**	**0**	**0**
Neutropenia			1 (0.7)	0		
Thrombocytopenia			1 (0.7)	0		
Immune system disorders	**1 (0.4)**	**0**	**0**	**1 (0.7)**	**0**	**0**
Hypersensitivity	1 (0.4)	0	0	1 (0.7)	0	0
Investigations	**1 (0.4)**	**0**				
White blood cell decr	1 (0.4)	0				

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
[1] tubular-villous adenoma with low grade dysplasia
[2] severe unrelated SAE the histological results were communicated after start of drug, but the diagnostic melanocytic nevus excision was done during screening, which resulted in study discontinuation.
Source: FDA analysis of data from Sandoz's 351(k) BLA submission

There was a single case of hypersensitivity in the continued EU-approved Enbrel group and two reports of urticaria, one in the continued EU-approved Enbrel group and one in the switched GP2015 group in TP2. There was one report of facial swelling in the EU-approved Enbrel group of TP1; this event was qualified as slight facial swelling in the patient narrative. There were no reports of anaphylaxis. The Applicant performed a retrospective assessment of events using Sampson's criteria for anaphylaxis. They identified a single case of a patient randomized into the continued EU-approved Enbrel group who developed moderate allergic dermatitis (PT dermatitis allergic) leading to study drug interruption on 17-Feb-2014, approximately 1 week after the last dose of study drug. On 07-Mar-2014, the patient had an exacerbation of bronchial asthma (PT asthma) and a severe general allergic reaction with blisters (PT hypersensitivity). These events led to study discontinuation. The events of asthma and hypersensitivity were nearly one month after the last dose of study medication, making it unlikely that this was an episode of anaphylaxis.

The full safety data set up to Week 30 identifies no specific new safety concerns with regard to AESI. Infections and infestations were seen in similar numbers in the GP2015 and EU-approved Enbrel groups, and in the groups who continued on their originally assigned treatment as well as the groups who transitioned to the alternative treatment.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Adverse events in the Infections and Infestations SOC were the most common adverse events in the Study 302 with event rates similar between GP2015 and the comparator products (Table 18 and Table 20). The most frequently reported infections were nasopharyngitis and pharyngitis.

Table 18: TEAEs (≥2% incidence) in Treatment Period 1, Study 302

System organ class Preferred term	**GP2015** **N=264** **n (%)**	**EU-Enbrel** **N=267** **n (%)**
Number of patients with TEAEs	**99 (37.5)**	**95 (35.6)**
Infections and infestations	**49 (18.6)**	**45 (16.9)**
Nasopharyngitis	17 (6.4)	13 (4.9)
Pharyngitis	3 (1.1)	7 (2.6)
Skin and subcut. tissue disorders	**17 (6.4)**	**11 (4.1)**
Gastrointestinal disorders	**10 (3.8)**	**17 (6.4)**
Musculoskeletal and connective tissue disorders	11 (4.2)	15 (5.6)
Arthralgia	1 (0.4)	7 (2.6)
Investigations	**15 (5.7)**	**7 (2.6)**
Nervous system disorders	11 (4.2)	9 (3.4)
Respiratory, thoracic and mediastinal disorders	**8 (3.0)**	**6 (2.2)**
Metabolism and nutrition disorders	**7 (2.7)**	**6 (2.2)**
Vascular disorders	**4 (1.5)**	**6 (2.2)**

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

The common adverse event profile remained consistent during treatment period 2. The period following the first transition (Week 12 to Week 18) was analyzed to compare the safety of continuing on treatment as compared to the safety of switching to the alternative treatment (Table 19). In this initial transition, there was no major imbalance between the continued EU-approved Enbrel and switched EU-approved Enbrel treatment groups for any of the SOCs. The most frequently reported TEAEs were in the SOCs of infections and infestations (primarily pharyngitis), followed by musculoskeletal and connective tissue disorders (primarily back pain), and nervous system disorders (primarily headache). The proportion of patients with TEAEs was similar between pooled continued treatment and pooled switch groups as well (15.6% vs. 18.4%) in the first transition period.

Table 19: TEAEs by PT, Wk 12-18, Study 302

Preferred term	Cont'd GP2015 N=150 n (%)	Cont'd EU-Enbrel N=151 n (%)	Switched EU-Enbrel N=96 n (%)	Switched GP2015 N=100 n (%)
Number of patients with at least one TEAE	**24 (16.0)**	**23 (15.2)**	**18 (18.8)**	**18 (18.0)**
Pharyngitis	4 (2.7)	4 (2.6)	2 (2.1)	2 (2.0)
Nasopharyngitis	3 (2.0)	2 (1.3)	1 (1.0	0
Hypertension	3 (2.0)	1 (0.7)	1 (1.0)	1 (1.0)
Viral upper respiratory tract infection	2 (1.3)	0	1 (1.0)	0
Cough	2 (1.3)	1 (0.7)	0	0
Arthralgia	1 (0.7)	2 (1.3)	0	0
Influenza	0	2 (1.3)	0	0
Backpain	0	1 (0.7)	2 (2.1)	1 (1.0)
Headache	0	1 (0.7)	3 (3.1)	2 (2.0)

Source: Applicant's 351(k) submission; Summary of Clinical Safety

In the overall assessment of treatment period 2 (Week 12-30), the proportion of patients with TEAEs was similar between groups (31.3% vs. 34.4% vs. 36.5% vs. 32.0%, for the continued GP2015, continued EU-approved Enbrel groups, switched EU-approved Enbrel, and switched GP2015, respectively (Table 20). The most frequently reported TEAEs were in the SOCs of infections and infestations (primarily pharyngitis and nasopharyngitis), musculoskeletal and connective tissue disorders (including back pain and arthralgia) and skin and subcutaneous tissue disorders (psoriasis, i.e. exacerbation of psoriasis). There was no major imbalance between the treatment groups for any of the SOCs. Differences between the treatment groups on the SOC level were below 4% except for the SOC musculoskeletal and connective tissue disorders, which was reported in more patients in the continued EU-approved Enbrel and switched EU-approved Enbrel, than in the continued GP2015 and switched GP2015 (6.6% and 8.3% vs. 4.0% and 4.0%), and in the skin and subcutaneous tissue disorders, which was reported in a lower proportion of patients in the continued GP2015 than in the continued EU-approved Enbrel treatment group (2.0% vs. 7.3%), while the proportion of patients in the switched groups was similar (4.2% vs. 5.0% for switched EU-approved Enbrel and switched GP2015, respectively).

Table 20: TEAEs (≥2% incidence) in Treatment Period 2, Study 302

System organ class Preferred term	**Cont'd GP2015 N=150 n (%)**	**Cont'd EU-Enbrel N=151 n (%)**	**Switched EU-Enbrel N=96 n (%)**	**Switched GP2015 N=100 n (%)**
Number of patients with at least one TEAE	**47 (31.3)**	**52 (34.4)**	**35 (36.5)**	**32 (32.0)**
Infections and infestations	**23 (15.3)**	**24 (15.9)**	**14 (14.6)**	**13 (13.0)**
Pharyngitis	5 (3.3)	5 (3.3)	2 (2.1)	3 (3.0)
Nasopharyngitis	4 (2.7)	4 (2.6)	2 (2.1)	2 (2.0)
Viral upper respiratory tract infection	2 (1.3)	2 (1.3)	3 (3.1)	2 (2.0)
Respiratory tract infection viral	3 (2.0)	1 (0.7)	0	1 (1.0)
Rhinitis	1 (0.7)	3 (2.0)	1 (1.0)	0
Tonsillitis	2 (1.3)	0	2 (2.1)	1 (1.0)
Musculoskeletal and connective tissue disorders	**6 (4.0)**	**10 (6.6)**	**8 (8.3)**	**4 (4.0)**
Arthralgia	2 (1.3)	3 (2.0)	3 (3.1)	0
Back pain	3 (2.0)	1 (0.7)	2 (2.1)	2 (2.0)
Skin and subcut. tissue disorders	**3 (2.0)**	**11 (7.3)**	**4 (4.2)**	**5 (5.0)**
Psoriasis	0	4 (2.6)	1 (1.0)	3 (3.0)
Nervous system disorders	**2 (1.3)**	**5 (3.3)**	**4 (4.2)**	**2 (2.0)**
Headache	0	5 (3.3)	3 (3.1)	2 (2.0)
Respiratory, thoracic and mediastinal disorders	4 (2.7)	4 (2.6)	1 (1.0)	4 (4.0)
Cough	2 (1.3)	1 (0.7)	0	2 (2.0)
Gastrointestinal disorders	**2 (1.3)**	**3 (2.0)**	**3 (3.1)**	**3 (3.0)**
Injury, poisoning and procedural complications	**4 (2.7)**	**4 (2.6)**	**1 (1.0)**	**2 (2.0)**
Investigations	**3 (2.0)**	**3 (2.0)**	**0**	**4 (4.0)**
General disorders and administration site conditions	**2 (1.3)**	**3 (2.0)**	**1 (1.0)**	**2 (2.0)**
Pyrexia	0	1 (0.7)	1 (1.0)	2 (2.0)
Psychiatric disorders	**2 (1.3)**	**3 (2.0)**	**2 (2.1)**	**1 (1.0)**
Vascular disorders	**3 (2.0)**	**3 (2.0)**	**1 (1.0)**	**1 (1.0)**
Hypertension	3 (2.0)	1 (0.7)	1 (1.0)	1 (1.0)
Blood and lymphatic system disorders	**3 (2.0)**	**0**	**2 (2.1)**	**1 (1.0)**
Hepatobiliary disorders	**0**	**1 (0.7)**	**2 (2.1)**	**2 (2.0)**

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

In the pooled safety analysis of the healthy subject studies, 102, 101, and 104, the numbers of subjects who experienced treatment emergent adverse events (TEAEs) were similar between GP2015 and US-licensed Enbrel, and between GP2015 and EU-approved Enbrel as displayed in Table 21. Most TEAEs were mild or moderate; there was a single severe TEAE of vasovagal syncope in Study 101 assessed as unrelated to study drug. The most frequently reported TEAEs were in the infections and infestations, nervous system disorders, and respiratory, thoracic and mediastinal disorder SOCs. The most common PTs included neutropenia, oropharyngeal pain, headache, and nasopharyngitis. Overall, these were observed with similar frequency in the GP2015 treatment groups as in the comparator treatment groups.

In Study 103, 32 subjects experienced at least one TEAE. The most frequently reported TEAEs by PT were headache and neutropenia. This is consistent with the safety profile observed in the other healthy subject studies.

Table 21: TEAEs (≥2% incidence) in Pooled Healthy Subject Studies 101, 102, 104

System organ class Preferred term	**GP2015** **N =162** **n (%)**	**EU-Enbrel** **N= 107** **n (%)**	**US-Enbrel** **N=56** **n (%)**
Number of patients with at least one TEAE	**87 (53.7)**	**55 (51.4)**	**28 (50.0)**
Infections and Infestations	**24 (14.8)**	**18 (16.8)**	**7 (12.5)**
Nasopharyngitis	15 (9.3)	10 (9.3)	4 (7.1)
Upper respiratory tract infection	4 (2.5)	1 (0.9)	0
Nervous system disorders	**20 (12.3)**	**17 (15.9)**	**8 (14.3)**
Headache	15 (9.3)	11 (10.3)	5 (8.9)
Dizziness	6 (3.7)	2 (1.9)	2 (3.6)
Respiratory, Thoracic and mediastinal disorders	**19 (11.7)**	**11 (10.3)**	**10 (17.9)**
Oropharyngeal pain	8 (4.9)	8 (7.5)	6 (10.7)
Nasal congestion	7 (4.3)	2 (1.9)	3 (5.4)
Cough	6 (3.7)	1 (0.9)	1 (1.8)
General disorders and administration site conditions	**13 (8.0)**	**12 (11.2)**	**6 (10.7)**
Injection site reaction	11 (6.8)	5 (4.7)	3 (5.4)
Feeling hot	0	3 (2.8)	
Blood and Lymphatic Disorders	**13 (8.0)**	**12 (11.2)**	**3 (5.4)**
Neutropenia	13 (8.0)	12 (11.2)	3 (5.4)
Gastrointestinal Disorder	**17 (10.5)**	**6 (5.6)**	**5 (8.9)**
Diarrhea	5 (3.1)	1 (0.9)	0
Musculoskeletal and connective tissue disorders	**8 (4.9)**	**10 (9.3)**	**1 (1.8)**
Back pain	4 (2.5)	4 (3.7)	
Pain in extremity	1 (0.6)	3 (2.8)	
Skin and subcutaneous disorders	**5 (3.1)**	**6 (5.6)**	**4 (7.1)**
Injury, Poisoning and procedural complications	**9 (5.6)**	**4 (3.7)**	**1 (1.8)**

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

The incidence and types of common adverse events in the healthy subject studies were similar between GP2015 the comparator products, were consistent with the known safety profile of etanercept, and no new safety signals have been identified supporting the conclusion that there are no clinically meaningful differences between GP2015 and US-licensed Enbrel.

In summary, treatment emergent adverse events (TEAEs) were similar in the GP2015 and EU-

approved Enbrel treatment arms in Study 302. TEAEs were also similar in subjects who underwent a single transition from EU-approved Enbrel to GP2015 and those who continued on EU-approved Enbrel. Furthermore, analysis of the overall safety data of patients who underwent a transition between EU-approved Enbrel and GP2015 or GP2015 and EU-approved Enbrel, as compared to those who continued treatment without a switch did not reveal any increase in adverse events related to the switching of the products. This is supported by the findings of the healthy subject studies in which TEAEs were similar between GP2015 and EU-approved Enbrel and GP2015 and US-licensed Enbrel. No new safety signals were identified in these studies. The results contribute to a demonstration of no clinically meaningful differences in safety between GP2015 and the comparator product.

8.4.6. Laboratory Findings

Hematology
In Study 302, no meaningful changes over time or differences between treatment groups (i.e. GP2015 vs. EU-approved Enbrel in TP1, and continued GP2015 vs. continued EU-approved Enbrel, and pooled continued vs. pooled switched treatment groups in TP2) were observed for mean basophils (% and absolute), eosinophils (% and absolute), erythrocytes, hematocrit, hemoglobin, leukocytes, lymphocytes (% and absolute), monocytes (% and absolute), neutrophils (% and absolute), and platelets. Shifts from baseline values were observed infrequently and occurred similarly in all treatment groups and in small numbers of patients. There were also no notable differences between the groups with respect to the maximum increase and maximum decrease from baseline in hematology parameters. No patterns were evident that would suggest a relation to treatment or a potential safety concern in any group.

In Study 101, 1 subject experienced clinically significant neutropenia following administration of GP2015 and was ultimately withdrawn from the study due to neutropenia. Neutropenia not felt to be clinically significant was observed in Studies 102, 103, and 104, and occurred with similar incidence between GP2015 and comparator product in Studies 102 and 104.

Consistent with the known safety profile of Enbrel, neutropenia was observed in healthy subjects and plaque psoriasis patients in similar numbers in the proposed biosimilar and the comparator product treatment groups. Most laboratory changes of neutropenia were not felt to be clinically significant.

Chemistry
In Study 302, no meaningful changes over time or differences between treatment groups (i.e. GP2015 vs. EU-approved Enbrel in TP1, and continued GP2015 vs. continued EU-approved Enbrel, and pooled continued vs. pooled switched treatment groups in TP2) were observed for mean ALT, albumin, alkaline phosphatase, AST, bilirubin, calcium, creatinine, GGT, glucose, phosphate, potassium, protein, sodium, and urate. Although some shifts from baseline values

were observed, these occurred similarly in the treatment groups and in small numbers of patients. There were also no notable differences between groups with respect to the maximum increase and maximum decrease from baseline in clinical chemistry parameters. No patterns were evident that would suggest a relation to treatment or a potential safety concern.

One subject in Study 102 had clinically significant AST and ALT laboratory values after receiving GP2015 in Period 2, while in Study 101, one subject had an elevation of AST after receiving GP2015 and one subject had elevations in AST and ALT after receiving EU-approved Enbrel.

Urinalysis
No meaningful clinical changes over time or differences between treatment groups were observed for ketones, occult blood, protein, urine glucose, pH, and specific gravity. There were no observed patterns evident to suggest a potential safety concern.

The distribution of laboratory findings was balanced between the GP2015 and the comparator treatment groups. No new or unexpected laboratory findings were reported in the GP2015 clinical program.

8.4.7. Vital Signs

In Study 302, vital signs (including blood pressure and pulse measurements) were assessed at screening, baseline, and at Weeks 2, 4, 8, 12, 18, 24, 30, 36, 42, 48 and 52. No clinically meaningful changes over time or differences between treatment groups were noted for systolic blood pressure, diastolic blood pressure, pulse rate, body temperature, or body weight. Vital signs parameters were all within the normal ranges for all patients at all visits during TP1 and TP2.

In the PK studies in healthy subjects, vital signs were evaluated at screening, on the dosing day, and 1, 2, 3, 7, and 14 days after dosing during each period, and at the follow-up visit. In Study 101, one subject who experienced clinically significant vasovagal syncope 2 minutes after dosing with GP2015 with hypotension and bradycardia. In 102, one subject had a drop in orthostatic systolic blood pressure after receiving GP2015, while another patient had a low supine diastolic blood pressure on day 1 of period 1 (US-licensed Enbrel). There were no other clinically significant findings in vital signs in the healthy subject studies.

8.4.8. Electrocardiograms (ECGs)

A standard 12-lead ECG was taken at Screening, Week 12 and Week 52 in Study 302. Except for 4 subjects at screening, ECG readouts were not considered clinically significant in all other

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subjects showing abnormal readouts and were similar between the two groups: 26.9% and 27.7% in the GP2015 group and the EU-approved Enbrel group, respectively. At Week 12, these proportions had decreased slightly (mainly due to missing data) with abnormal and clinically not significant results in 22.7% and 19.1% in the GP2015 and EU-approved Enbrel groups, respectively. As of the data cut-off, ECG results were very limited for the extension period with missing data reported for the majority of patients.

There were no clinically significant findings in ECG assessments in the single dose healthy subject studies.

The distribution of ECG findings was balanced between the GP2015 and EU-approved Enbrel treatment groups in Study 302 based on the data following TP1. The abnormal readouts post-study drug administration were not considered clinically significant. There are no specific concerns regarding ECG changes based on the studies in the GP2015 development program or the experience with etanercept.

8.4.9. QT

QT intervals were not evaluated in this study.

8.4.10. Immunogenicity

Development of autoantibodies to the TNFα receptor portion or other protein components of the Enbrel drug product has been described in patients with RA, AS, PsA, and PsO. As described in the USPI for Enbrel, the clinical significance of these autoantibodies is unknown. In three of the healthy subject studies, 101, 102, and 103, all samples were negative for binding anti-etanercept antibodies (ADA) at pre-dose of periods 1 and 2, and at the follow-up visit. In Study 104, three subjects who received GP2015 in period 1 and EU-approved Enbrel in period 2, had binding non-neutralizing ADAs at the follow-up visit and a fourth subject had an indeterminate ADA result. The confirmed ADAs were near the lower limit of quantification and none of the ADAs were neutralizing.

In Study 302, immunogenicity data are available for 501 patients who completed treatment period 1 and 485 patients in treatment period 2 at the end of the first transition period at week 18 (Table 22). ADAs were confirmed in 5 patients in the EU-approved Enbrel treatment arm. The ADA were observed within the first 4 weeks of treatment, and subsequently resolved. No neutralizing antibodies were detected. No patients in the GP2015 treatment group developed ADA through week 18, or subsequently through week 30. Additionally, there was no increase in ADA after a transition from EU-approved Enbrel to GP2015.

Table 22: Anti-drug Antibody Response in TP1 and TP2, Study 302

Treatment Period 1	GP2015 N=264			EU-approved Enbrel N=267		
	Positive	Negative	Missing	Positive	Negative	Missing
Baseline	--	260	4	--	259	8
Week 2	--	250	14	1	253	13
Week 4	--	258	6	5	250	12
Week 8	--	251	13	--	248	19
Week 12	--	251	13	--	250	17

Treatment Period 2	Continued Original Treatment						Switched Treatments					
	Cont GP2015 N=150			Cont EU-Enbrel N=151			Switched EU-Enbrel N=96			Switched GP2015 N=100		
	Pos	Neg	Miss	Pos	Neg	Miss	Pos	Neg	Miss	Pos	Neg	Miss
Week 18	--	147	3	--	148	3	--	92	4	--	98	2
Week 30	--	140	10	--	141	10	--	91	5	--	95	5

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
Pos=Positive, Neg = Negative, Miss=Missing
Source: FDA analysis of data from Sandoz's 351(k) BLA submission

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.

8.5. Analysis of Submission-Specific Safety Issues

Local injection site reactions were recorded for the treatment groups in Study 302 and the healthy subject PK studies.

8.5.1. Local Injection Site Reactions

In Study 302, during TP1, a total of 51 patients (9.6%) reported reactions at the injection site with a lower proportion of patients in the GP2015 group than in the EU-approved Enbrel group reporting reactions (5.3% vs. 14.2%). Most injection site reactions (ISRs) were mild, and only 1 subject in the EU-approved Enbrel treatment group reported a severe reaction (itching). No reaction at the injection site was considered to be a SAE. The right abdomen was the main site of ISRs in both groups and the main signs/symptoms were redness and itching; the proportion of subjects who reported swelling was around 5-fold lower in the GP2015 group than the EU-approved Enbrel group (0.8% vs. 4.1%). These numerical differences however, are not likely to represent clinically meaningful differences. Further, the numbers of patients with ISR reactions were comparable across treatment groups in TP2 and in the healthy subject studies. The proportion of patients with ISR in Study 302 was generally lower than reported proportions of 13% (Leonardi et al, 2003) and 18% (Papp et al, 2005), except for the EU-approved Enbrel treatment group in TP1 which had similar proportions to those published.

From Week 12 to Week 30 in TP2, the proportions of patients reporting ISRs were similar between the continued GP2015 and continued EU-approved Enbrel treatment groups (4.0% vs. 4.6%) and between the switched GP2015 and switched EU-approved Enbrel groups (5.0% vs. 4.2%). None of the ISRs were regarded as severe.

In the PK studies, 101, 102, and 104, injection site reactions were reported in 18 subjects following GP2015, 6 subjects following EU-approved Enbrel, and 3 subjects following US-licensed Enbrel. All injection site reactions were mild in intensity. In Study 103, three subjects, 2 following administration via PFS and one following AI administration, experienced mild injection site reactions.

8.6. Safety Analyses by Demographic Subgroups

The subgroup analyses of the safety data for Study 302 were evaluated by the following treatment periods:

- Treatment period 1 (TP1) up to Week 12: GP2015 vs. EU-approved Enbrel
- Treatment period 2 (TP2) from Week 12 to Week 18: Pooled continued vs. pooled switched treatment groups

Data from the first transition period (Week 12 to Week 18) were pooled and analyzed. Given the low proportions of subjects reporting TEAEs, the subgroup comparisons were performed for pooled continued treatment groups (including both GP2015 and EU-approved Enbrel) vs. pooled switch treatment groups (including both switches of GP2015-EU-approved Enbrel and

EU-approved Enbrel-GP2015). TEAEs were evaluated for the following subgroups based on baseline characteristics:

- Gender
- Stratification factors:
  - Body weight (<90 kg/≥90 kg)
  - Prior systemic therapy (no/any)
- Age group (<65 years/≥ 65 years) (TP1 only)
- Baseline PASI score (≤20/>20) (TP1 only)
- Presence of PsA at baseline (present/absent) (TP1 only)

Gender

In TP1, more female patients in the GP2015 treatment group reported TEAEs than those in the EU-approved Enbrel treatment group, while male patients reported TEAEs with similar frequency in both groups, as detailed in Table 23. The numbers of patients with SAEs or severe TEAEs were small and similar between treatment groups by gender. The most common TEAEs in both male and females are in the SOC of infections and infestations (primarily nasopharyngitis). The differences between treatment groups in female patients for gastrointestinal disorders and investigations SOCs were not clustered to any particular PT. ISRs were reported with similar low frequencies between treatment groups by gender. No meaningful changes over time or differences between treatment groups were observed by gender for chemistry or hematology.

Table 23: TEAEs by SOC and gender, TP1, Study 302

System Organ Class (SOC)	Male		Female	
	GP2015 (N=157) n (%)	EU-Enbrel (N=172) n (%)	GP2015 (N=107) n (%)	EU-Enbrel (N=95) n (%)
Number of patients with at least 1 TEAE	**50 (31.8)**	**62 (36.0)**	**49 (45.8)**	**33 (34.7)**
Infections and infestations	22 (14.0)	26 (15.1)	27 (25.2)	19 (20.0)
Musculoskeletal and connective tissue disorders	9 (5.7)	11 (6.4)	2 (1.9)	4 (4.2)
Skin and subcutaneous tissue disorders	8 (5.1)	4 (2.3)	9 (8.4)	7 (7.4)
Investigations	7 (4.5)	3 (1.7)	8 (7.5)	2 (2.1)
Gastrointestinal disorders	5 (3.2)	7 (4.1)	5 (4.7)	10 (10.5)
Nervous system disorders	4 (2.5)	4 (2.3)	6 (5.6)	5 (5.3)

SOCs greater than 5% in a group are only presented and sorted by descending order of proportion of subjects in the first column
Source: Applicant's 351(k) submission; Summary of Clinical Safety

In the first transition period, the proportions of patients with TEAEs between pooled continued and switched treatment groups were similar for both genders (12.0% vs. 14.5% for males, 22.0% vs. 24.1% for females). In male (pooled continued 5.7%, pooled switched 6.0%) and female (pooled continued 11.0%, pooled switched 8.9%), the most reported TEAEs were in the SOC infections and infestations (male: primarily pharyngitis and nasopharyngitis; female: primarily pharyngitis, nasopharyngitis, and upper respiratory tract infection). The numbers of patients with SAEs or AESI were small. No meaningful changes over time or differences between treatment groups were observed by gender for chemistry or hematology.

Body Weight

In TP1, the proportion of patients with TEAEs in subjects <90kg body weight was higher in the GP2015 treatment group than EU-approved Enbrel treatment group (38.1% vs. 30.4%); however, above ≥90 kg more TEAEs were reported in the EU-approved Enbrel treatment group (Table 24).

Table 24: TEAEs by SOC and Body Weight, TP1, Study 302

System Organ Class (SOC)	<90 kg Body Weight		≥90 kg Body Weight	
	GP2015 (N=160) n (%)	EU-Enbrel (N=161) n (%)	GP2015 (N=104) n (%)	EU-Enbrel (N=106) n (%)
Number of patients with at least 1 TEAE	**61 (38.1)**	**49 (30.4)**	**38 (36.5)**	**46 (43.4)**
Infections and infestations	33 (20.6)	26 (16.1)	16 (15.4)	19 (17.9)
Skin and subcutaneous tissue disorders	12 (7.5)	9 (5.6)	5 (4.8)	2 (1.9)
Gastrointestinal disorders	7 (4.4)	13 (8.1)	3 (2.9)	4 (3.8)
Nervous system disorders	7 (4.4)	4 (2.5)	3 (2.9)	5 (4.7)
Respiratory, thoracic, and mediastinal disorders	6 (3.8)	4 (2.5)	2 (1.9)	2 (1.9)
Investigations	6 (3.8)	2 (1.2)	9 (8.7)	3 (2.8)
Neoplasm benign, malignant and unspecified (incl cycts and polyps)	5 (3.1)	0	0	1 (0.9)
Musculoskeletal and connective tissue disorders	4 (2.5)	7 (4.3)	7 (6.7)	8 (7.5)
General disorders and administration site conditions	4 (2.5)	3 (1.9)	1 (1.0)	0
Metabolism and nutritional disorders	3 (1.9)	4 (2.5)	4 (3.8)	2 (1.9)
Vascular disorders	2 (1.3)	3 (1.9)	2 (1.9)	3 (2.8)

SOCs greater than 2% in a group are only presented and sorted by descending order of proportion of subjects in the first column
Source: Applicant's 351(k) submission; Summary of Clinical Safety

In patients <90 kg body weight and patients ≥90 kg body weight categories, the most reported TEAEs were in the SOC infections and infestations (<90 kg, GP2015, 20.6%; EU-approved Enbrel, 16.1%: primarily pharyngitis and nasopharyngitis; ≥90 kg, GP2015, 15.4%; EU-approved Enbrel, 17.9%: primarily nasopharyngitis, upper respiratory tract infection, and pharyngitis). TEAEs by SOC were generally similar between treatment groups.

In the first transition period, the proportions of patients with TEAEs between pooled continued and switched treatment groups were similar for the body weight category ≥90 kg (20.0% vs. 18.5%), while in the <90 kg body weight group fewer patients in the pooled continued groups reported TEAES (12.5% vs. 18.3%). The most reported TEAEs in both body weight categories were in the infections and infestations SOC and similar between groups (<90 kg: 6.8% vs. 7.8% in pooled continued vs. pooled switched; ≥ 90 kg: 8.8% vs. 6.2%). The numbers of patients

reporting TEAEs in other SOCs were small and generally similar across treatment groups within body weight category.

No meaningful changes over time or differences between treatment groups were observed for any body weight groups in clinical chemistry or hematology parameters in either treatment period.

Prior Systemic Therapy

The overall numbers of subjects with TEAEs in TP1 was similar between treatment groups in both subjects with prior systemic therapy and subjects without prior systemic therapy (Table 25), however, more patients with prior systemic therapy reported TEAEs than those with no prior systemic therapy. In patients without and with any prior systemic therapy, most reported TEAEs were in the infections and infestations SOC (no systemic therapy, GP2015, 15.7%; EU-approved Enbrel, 14.2%: primarily nasopharyngitis and pharyngitis; any systemic therapy, GP2015, 22.5%; EU-approved Enbrel, 21.0%: primarily nasopharyngitis, upper respiratory tract infection, and pharyngitis). The numbers of patients reporting TEAEs in other SOCs was small and generally similar across treatment groups within prior systemic therapy category.

Table 25: TEAEs by SOC and prior systemic therapy, TP1, Study 302

System Organ Class (SOC)	No prior systemic therapy		Any prior systemic therapy	
	GP2015 (N=153) n (%)	EU-ENBREL (N=162) n (%)	GP2015 (N=111) n (%)	EU-ENBREL (N=105) n (%)
Number of patients with at least 1 TEAE	**49 (32.0)**	**53 (32.7)**	**50 (45.0)**	**42 (40.0)**
Infections and infestations	24 (15.7)	23 (14.2)	25 (22.5)	22 (21.0)
Gastrointestinal disorders	8 (5.2)	11 (6.8)	2 (1.8)	6 (5.7)
Skin and subcutaneous tissue disorders	8 (5.2)	7 (4.3)	9 (8.1)	4 (3.8)
Investigations	8 (5.2)	3 (1.9)	7 (6.3)	2 (1.9)
Musculoskeletal and connective tissue disorders	6 (3.9)	7 (4.3)	5 (4.5)	8 (7.6)
Respiratory, thoracic, and mediastinal disorders	6 (3.9)	3 (1.9)	2 (1.8)	3 (2.9)
Nervous system disorders	4 (2.6)	8 (4.9)	6 (5.4)	1 (1.0)
Metabolism and nutritional disorders	4 (2.6)	4 (2.5)	3 (2.7)	2 (1.9)
Vascular disorders	4 (2.6)	3 (1.9)	0	3 (2.9)
Neoplasm benign, malignant and unspecified (incl cycts and polyps)	4 (2.6)	0	2 (1.8)	3 (2.9)
General disorders and administration site conditions	1 (0.7)	2 (1.2)	4 (3.6)	1 (1.0)

SOCs greater than 2% in a group are only presented and sorted by descending order of proportion of subjects in the first column
Source: Applicant's 351(k) submission; Summary of Clinical Safety

As detailed in Table 26, from week 12 to 18, the proportion of patients with TEAEs for any systemic therapy category were lower in pooled continued group than pooled switched group (13.0% vs. 20.8%), while for no systemic therapy the TEAEs were similar between treatment groups (17.6% vs. 16.8%). The most reported TEAEs were in the SOC of infections and infestations. The pooled continued treatment group in the no prior systemic therapy category had the most patients reported TEAEs in this SOC (10.0%), while the pooled switched in no prior systemic therapy, and the pooled continued and pooled switched in any prior systemic therapy were similar. The numbers of patients reporting TEAEs in other SOCs was small.

Table 26: TEAEs by SOC and prior systemic therapy, TP2 Week 12-18, Study 302

System Organ Class (SOC)	No prior systemic therapy		Any prior systemic therapy	
	Pooled continued (N=170) n (%)	Pooled switched (N=119) n (%)	Pooled continued (N=131) n (%)	Pooled switched (N=77) n (%)
Number of patients with at least 1 TEAE	**30 (17.6)**	**20 (16.8)**	**17 (13.0)**	**16 (20.8)**
Infections and infestations	17 (10.0)	9 (7.6)	6 (4.6)	5 (6.5)
Musculoskeletal and connective tissue disorders	5 (2.9)	4 (3.4)	3 (2.3)	3 (3.9)
Skin and subcutaneous tissue disorders	4 (2.4)	1 (0.8)	0	2 (2.6)
Nervous system disorders	0	1 (0.8)	3 (2.3)	4 (5.2)

SOCs greater than 2% in a group are only presented and sorted by descending order of proportion of subjects in the first column
Source: Applicant's 351(k) submission; Summary of Clinical Safety

No meaningful changes over time or differences between treatment groups were observed for no or any prior systemic therapy groups in clinical chemistry or hematology parameters in either treatment period.

Age Group (TP1 only)

The number of patients in the ≥65 years of age (28 patients) was significantly smaller than in the <65 years age group (503 patients). In patients <65, a similar proportion of patients reported TEAEs between treatment groups (GP2015, 37.4%; EU-approved Enbrel, 36.5%), while in those ≥65 years, a higher proportion of patients reported TEAEs in the GP2015 treatment group (4 patients, 40.0%), than the EU-approved Enbrel group (4 patients, 22.4%). In patients < 65 years (GP2015, 18.5%; EU-approved Enbrel, 16.9%) and in patients ≥65 years of age (GP2015, 20.0%; EU-approved Enbrel, 16.7%), the most reported TEAEs were in the SOC of infections and infestations (primarily nasopharyngitis). Differences between treatment groups by age category in the other SOCS were generally small and without significant imbalances. No meaningful changes over time or differences between treatment groups were observed for each age group category groups in clinical chemistry or hematology parameters.

Baseline PASI Score (TP1 only)

In TP1, a similar proportion of TEAEs were reported between treatment groups for both baseline categories of PASI score ≤20 (GP2015, 40.6%; EU-approved Enbrel 41.8%) and PASI

score >20 (GP2015, 34.6%; EU-approved Enbrel 29.3%) in both treatment groups. In patients with a baseline PASI score ≤20 (GP2015, 24.2%; EU-approved Enbrel, 21.6%) and in patients with a baseline PASI score >20 (GP2015, 13.2%; EU-approved Enbrel, 12.0%), the most reported TEAEs were in the SOC of infections and infestations (primarily nasopharyngitis). No meaningful changes over time or differences between treatment groups were observed by baseline PASI score category in clinical chemistry or hematology parameters.

Presence of Psoriatic Arthritis (PsA) at baseline

The proportion of patients with TEAEs was higher in patients with PsA at baseline in the GP2015 treatment group than the EU-approved Enbrel group (40.7% vs. 30.2%) and the difference between treatment groups for patients without PsA at baseline was similar. The most reported TEAEs were in the infections and infestations SOC, however patients without PsA at baseline had higher rates (GP2015, 19.5%; EU-approved Enbrel, 18.2%) than those with PsA at baseline (GP2015, 14.8%; EU-approved Enbrel, 11.3%). Rates of TEAEs in the infections and infestations SOC were similar between treatment groups. Overall, there were no patterns of increased TEAEs for either treatment group within or between category of presence of PsA at baseline. No meaningful changes over time or differences between treatment groups were observed by baseline PsA category in clinical chemistry or hematology parameters.

Overall, the subgroup analysis with gender, body weight, and baseline PASI score did not identify significant differences in the adverse event profile between GP2015 and EU-approved Enbrel. Differences between treatment groups in proportion of patients with TEAEs in those with PsA at baseline, as well as in those > 65 years, are likely related to the small numbers of patients in these subgroups. Given the discrepancies regarding definitions of prior systemic therapy, and the restratification of patients described above, meaningful conclusions cannot be drawn from the subgroup analysis on prior systemic therapy.

8.7. Specific Safety Studies/Clinical Trials

There were no other specific safety studies conducted for GP2015.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Malignancies, including lymphoma, have been identified as potential risk with US-licensed Enbrel and other TNF-inhibitors as described in the Warnings and Precautions section of US-licensed Enbrel's USPI. Few malignancies were reported in the GP2015 program; these were balanced between the treatment arms. The incidence and types of these malignancies are expected for the study population and treatment.

8.8.2. **Human Reproduction and Pregnancy**

No clinical experience with GP2015 in pregnant or breast-feeding women is available. To address the requirements of conforming to the Pregnancy and Lactation Labeling Rule, the Applicant conducted a review of the published literature on the use of etanercept during pregnancy or lactation. Based on three case reports, cord blood levels of etanercept have been observed at delivery in infants born to mothers administered etanercept during pregnancy. Limited data from published literature report the presence of low levels of etanercept in human milk. This information will be included in section 8 of the label; the content and format will conform to the Pregnancy and Lactation Labeling Rule.

8.8.3. Pediatrics and Assessment of Effects on Growth

The Applicant submitted an initial pediatric study plan which was agreed upon by the Agency. The Applicant requested a full waiver of the requirement to submit a pediatric assessment for plaque psoriasis in the pediatric population. The justification for this waiver request is that there is evidence strongly suggesting that the biological product would be (b) (4) unsafe in all pediatric age groups with PsO, (b) (4) Concerns have been raised about pediatric malignancies occurring while on TNF inhibitors; and pediatric patients receiving Enbrel have been reported to have a higher rate of lymphoma. Enbrel also carries a boxed warning regarding the potential for life-threatening infections. The Agency has previously expressed concern about the benefit-risk profile of Enbrel for pediatric patients with psoriasis (June 18, 2008 Dermatologic and Ophthalmologic Drugs Advisory Committee Meeting).

Full waivers were also requested for a pediatric assessment for ankylosing spondylitis and psoriatic arthritis in the pediatric population, based on the justification that the necessary studies are impossible or highly impracticable (b) (4) . A partial waiver was requested for the pediatric assessment for polyarticular juvenile idiopathic arthritis in patients younger than 2 years due to the rarity of the condition in this age group making necessary studies impossible or highly impracticable.

Sandoz also requested a deferral of the submission of a pediatric assessment for pediatric subpopulations that would require a dose-adjustable dosage form (<63 kg) for which the development is not yet complete. The development of an age-appropriate formulation will be a post-marketing requirement under the Pediatric Research Equity Act (PREA).

The requested full waiver for pediatric studies is acceptable for plaque psoriasis, ankylosing spondylitis, and psoriatic arthritis. The partial waiver is acceptable for polyarticular juvenile idiopathic arthritis in patients < 2 years of age. The deferral for pediatric subpopulations that would require a dose-adjustable formulation until such formulation is available is reasonable. Agreement on the pediatric study plan was acknowledged on July 16, 2015. The proposed pediatric plan was review at the FDA Pediatric Review Committee (PeRC) on March 09, 2016. PeRC agreed with the plan, as discussed above, and recommended a PREA PMR for the development of an age-appropriate presentation.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The US-licensed Enbrel label does not indicate that there is potential interaction of etanercept with tobacco, alcohol, and food habits. The Applicant has not reported cases of overdose or

intoxication for GP2015. Information on drug abuse and rebound after withdrawal is not provided in the US-licensed Enbrel USPI.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

No post-marketing experience with GP2015 is available.

8.9.2. Expectations on Safety in the Postmarket Setting

Expectations of safety are derived from the clinical study and marketing experience of the reference product, US-licensed Enbrel. Specific safety concerns are described in the labeling of marketed US-licensed Enbrel. Risks of use of US-licensed Enbrel are discussed in section 8.1 of this review.

8.10. Additional Safety Issues From Other Disciplines

Please see the specific sections for details regarding discipline reviews.

8.11. Integrated Assessment of Safety

The Biologics Price Competition and Innovation Act is a pathway under section 351(k) of the Public Health Service Act which requires that the proposed biological product is highly similar to the reference product notwithstanding minor differences between the proposed biosimilar and the reference product in terms of safety, purity, and potency. Both parts of the statutory definition need to be met to demonstrate biosimilarity, but the foundation of the data demonstrating biosimilarity is extensive structural and functional characterization to support a demonstration that the products are highly similar.

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 US-licensed Enbrel. From a clinical standpoint, the data submitted to this 351(k) BLA from the clinical development program of GP2015 support the demonstration of no clinically meaningful safety differences between GP2015 and US-licensed Enbrel in the indication studied, i.e., plaque psoriasis (PsO). No new safety signals were identified. The single transition from EU-approved Enbrel to GP2015 during the second treatment period of Study 302 did not result in a change in 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.

9 Advisory Committee Meeting and Other External Consultations

As the first 351(k) BLA filed for a proposed biosimilar to Enbrel, an Advisory Committee (AC) meeting was deemed necessary to obtain public input on issues related to the analytical similarity assessment, clinical program, and extrapolation to non-studied indications. The Arthritis AC meeting was held on July 13, 2016.[2] The committee was asked to discuss the adequacy of the evidence to demonstrate that (1) GP2015 and US-licensed Enbrel are highly similar, (2) there are no clinically meaningful differences in the studied indication of PsO, and, (3) 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 in the other indications for which US-licensed Enbrel is licensed.

Several panel members noted that while there remained differences in misfolded protein between GP2015 and US-licensed Enbrel, they were reassured by the in vitro assays conducted and the supportive clinical data. Concerns were voiced about the increased treatment effect observed in study 302 as compared to historical studies, but the panel members were confident that the majority of the treatment benefit was maintained, and that furthermore, safety of GP2015 had been demonstrated. With regard to the evidence to support a demonstration of no clinically meaningful differences in the non-studied indications, the panel members were in agreement that given the demonstration that the molecules were highly similar, the similar clinical PK, efficacy, safety, and immunogenicity in the clinical program, and the similar mechanism of action in PsO, RA, PsA, AS, and JIA, that extrapolation to the other indications based on the similarities demonstrated in the studies conducted was scientifically justified.

The voting question posed to the committee was whether 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). The committee voted unanimously in favor (20 “Yes”, 0 “No”, and 0 “Abstain”).

10 Labeling Recommendations

10.1. Prescribing Information

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

Reference ID: 3964787

- Proprietary name
  The initially proposed proprietary names for GP2015 were [redacted] (b) (4) [redacted]. The Division of Medication Error Prevention and Analysis (DMEPA) found the names [redacted] (b) (4) [redacted] unacceptable due to orthographic and phonetic similarities, as well as shared product characteristics with the proprietary name [redacted] (b) (4) [redacted]. The Applicant subsequently proposed the proprietary names Erelzi and Erelzi Sensoready Pen. The Office of Prescription Drug Promotion (OPDP) determined that the proposed names would not misbrand the proposed product. This name has been reviewed by the Division of Medication Error Prevention and Analysis (DMEPA), who concluded the names were acceptable.
- Non-proprietary/Proper name
  FDA has determined that the use of a distinguishing suffix in the nonproprietary name for Sandoz's GP2015 product is necessary to distinguish this proposed product from Enbrel (etanercept). As explained in FDA's draft Guidance for Industry[3], Nonproprietary Naming of Biological Products, 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. This information is still pending at the time of this review.
- Physician Labeling
  At the time of this review, labeling discussions are ongoing.

10.2. Patient Labeling

The Applicant proposed a Patient labeling/Medication guide closely tracking that of US-licensed Enbrel. At the time of this review, labeling discussions are ongoing.

10.3. Nonprescription Labeling

Not applicable.

11 Risk Evaluation and Mitigation Strategies (REMS)

11.1. Safety Issue(s) that Warrant Consideration of a REMS

[3] 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

None.

11.2. Conditions of Use to Address Safety Issue(s)

None.

11.3. Recommendations on REMS

GP2015 is a proposed biosimilar to US-licensed Enbrel. There were no new safety signals identified in the comparative clinical study and PK studies to date. The safety profile is anticipated to be the same as US-licensed Enbrel. In August 2011, FDA released US-licensed Enbrel from its previously approved REMS and determined that maintaining the Medication Guide as part of the approved labeling is adequate to address the serious and significant public health concern and meets the standard in 21CFR208.1. Accordingly, at this time, a Medication Guide for patients, which is included in the proposed GP2015 labeling, is appropriate, should GP2015 be approved as a biosimilar.

12 Postmarketing Requirements and Commitments

As discussed in section 8.8.3. Pediatrics and Assessment of Effects on Growth Act, the development of an age-appropriate formulation will be a post-marketing requirement under the Pediatric Research Equity Act (PREA). No other post-marketing requirements are recommended from clinical perspective.

13 Appendices

13.1. References

1. Leonardi CL, Powers JL, Matheson RT, Goffe BS, Zitnik R, et al. Etanercept as monotherapy in patients with psoriasis. *N Engl J of Med*. 2003; 349:2014-22.
2. Papp KA, Tyring S, Lahfa M, Prinz J, Griffiths CEM, et al. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. *Br J of Dermatol*. 2005; 152:1304-12.
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.
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.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): BLA 761042 Clinical Program

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 288		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Reference ID: 3964787

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

/s/

RACHEL GLASER
07/27/2016

GARY T CHIANG
07/28/2016

DAVID L KETTL
07/28/2016

NIKOLAY P NIKOLOV
07/28/2016
I concur.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 761042 **Applicant: Sandoz** **Stamp Date: 30-JUL-2015**

Drug Name: GP2015 **NDA/BLA Type: 351 (k)** **Biosimilar Application**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?			X	
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: GP15-302 Indication: Plaque Psoriasis	X			A single Active control without placebo in psoriasis clinical trial is included in this application

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

Reference ID: 3818919

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 Indication:			X	
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

Reference ID: 3818919

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?				
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?				
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?				
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?				
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?				
34.	Are all datasets to support the critical safety analyses available and complete?				
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?				
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?				
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?				
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?				
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __YES_____

DDDP comment: The single confirmatory clinical trial was conducted as agreed upon during the biosimilar planning meetings. The primary endpoint for the active comparative trial is based on the PASI 75 response at Week 12.

If the Application is not fillable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

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

Reference ID: 3818919

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

None

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

None

Gary Chiang	19-SEP-2015
Reviewing Medical Officer	Date
David Kettl	19-SEP-2015
Clinical Team Leader	Date

Reference ID: 3818919

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

/s/

GARY T CHIANG
09/14/2015

DAVID L KETTL
09/14/2015