CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761066Orig1s000

CLINICAL REVIEW(S)

Medical Officer's Review of BLA 761066
Division of Dermatology and Dental Products

Type: Biosimilar 351(k)
Serial Amendment: 000
Supporting Document Number: 001
Correspondence date: 25-MAY-2017
CDER Stamp date: 25-MAY-2017
Review Date: 19-MAR-2018

Applicant: Samsung Bioepis Co., Ltd.
107 Cheomdan-daero, Yeonsu-gu
Incheon, Republic of Korea 21987

Drug: SB4, a proposed biosimilar to U.S.-licensed Enbrel (etanercept)
Route of Administration: Subcutaneous
Dosage Form: Single-use pre-filled syringes: 50 mg/1.0 mL (50 mg/mL); 25 mg/0.5 mL (50 mg/mL)
Pharmacologic Category: 1-235-tumor necrosis factor receptor (human) fusion protein with 236-467-immunoglobulin Gi (human γ1-chain Fc fragment), dimer
Proposed Indications:

1) Rheumatoid Arthritis (RA) in combination with methotrexate:
    - Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active disease.
2) Polyarticular Juvenile Idiopathic Arthritis
    - Reducing signs and symptoms of moderately to severe active polyarticular juvenile idiopathic arthritis (JIA) in patients 2 years and older and weigh 63 kg (138 pounds) or more.
3) Ankylosing Spondylitis (AS):
    - Reducing signs and symptoms in patients with active disease
4) Psoriatic Arthritis (PsA):
    - Reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function.
5) Plaque Psoriasis (PsO):
    - Treatment of patients 4 years and older with chronic moderate or severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

Project Manager: Barbara Gould
Team Leader: David Kettl, MD
Medical Officer: Gary Chiang, MD, MPH.

Executive Summary:

The Division of Dermatology and Dental Products has concluded that the Applicant has provided sufficient clinical scientific evidence under section 351(k) of the Public Health Service Act (PHS Act) to demonstrate that the proposed drug product SB4, a proposed

biosimilar to US-licensed Enbrel (etanercept) (proposed biosimilar product) is highly similar to the reference product notwithstanding minor differences in inactive components, and that there are no clinically meaningful differences between the proposed biosimilar product and U.S.-licensed Enbrel in terms of safety, purity and potency.

Although the applicant did not conduct a clinical study in plaque psoriasis patients, the Applicant has provided adequate scientific justification for the use of extrapolation of the data and information submitted, to support licensure under section 351(k) of SB4 as a biosimilar for non-studied indications, including plaque psoriasis.

Etanercept has been widely used in clinical practice for about 18 years. Originally licensed for use in moderately to severely active RA, additional therapeutic indications were approved subsequently for U.S.-licensed Enbrel: treatment of patients with polyarticular JIA in patients aged 2 years or older, PsA, AS, PsO in patients 4 years or older. The Applicant is seeking licensure for the same therapeutic indications for SB4 as those granted for U.S.-licensed Enbrel. The proposed presentations of 25 mg per 0.5 mL and 50 mg per mL limits the biosimilar product for patients who weigh 63 kg (138 pounds) or more (i.e. pediatric PsO in patients aged 17 years or older and weigh 63 kg [138 pounds] or more; JIA in patients aged 2 years or older and weigh 63 kg [138 pounds] or more). The proposed adult dosing and the recommended posology of SB4 correspond with the indications approved for U.S.-licensed Enbrel.

For additional information on the clinical data submitted to support the indications evaluated in this application, please refer to the clinical review from DPARP or the Cross-Discipline Team Leader (CDTL) review for details of the submitted application.

It is the Division's conclusion that sufficient scientific evidence is presented for use of SB4 in "the treatment for patients with chronic moderate to severe plaque psoriasis (PsO) who are candidates for systemic therapy or phototherapy."

Introduction:

Samsung Bioepis Co., Ltd is developing SB4 as a proposed biosimilar to US-licensed Enbrel (etanercept). Enbrel was licensed in the United States (US) in 1998. Enbrel is also licensed in many countries worldwide, including the European Union (EU) via the Centralized Procedure and in South Korea, Australia, and Canada.

Etanercept is a recombinant human tumor necrosis factor receptor p75Fc fusion protein. It interferes with soluble TNF-α by mimicking the inhibitory effects of naturally occurring soluble TNF receptors that deactivate TNF-α and therefore down-regulate immune responses. Etanercept acts as a decoy receptor for TNF-α, reducing the effects of TNF-α and hence represents a competitive TNF-α inhibitor. Etanercept may also modulate biological responses controlled by molecules further down the inflammatory cascade (e.g., cytokines, adhesion molecules, proteinases etc.) that are induced or regulated by TNF-α.

A total of 51 US-licensed Enbrel lots, 56 EU-approved etanercept lots, and 24 lots of SB4 Drug substance (DS)/Drug product (DP) lots were used in the assessment of quality attributes. The analytical similarity assessment was designed to provide data to support a demonstration that SB4 is highly similar to US-licensed Enbrel. The sponsor also provided analytical data to justify the relevance of comparative data generated using the (EU)-approved etanercept to support a demonstration of biosimilarity of SB4 to US-licensed Enbrel.

- Tier 1 (equivalence test): TNF-α binding FRET assay and TNF-α neutralization reporter gene assay.
- Tier 2 (quality ranges): HMW%s by SEC; peaks 1 -3 by HIC, purity by rCE-SDS, total sialic acid concentration, protein concentration, and LTα3 (TNF-β) binding FRET assay.
- Tier 3 (raw data/graphical comparisons)

For purposes of the bridging exercise, SB4, US-licensed Enbrel, and EU-approved etanercept were similar with respect to Tier 1 TNF-α binding and TNF-α neutralization. With respect to Tier 2 attributes, SB4 has less HMW and HIC peak 3 variants in comparison with US-licensed Enbrel and EU-approved etanercept. The HIC %peak 2 content of SB4 lots (91.0 – 94.8%) was significantly higher than that of US-licensed Enbrel (80.6 – 86.0%) and EU-approved etanercept (81.0 – 87.6%).

As part of the totality of the evidence for a demonstration of biosimilarity, the clinical development program for SB4 is to support a demonstration that no clinically meaningful differences exist between SB4and US-licensed Enbrel in terms of its pharmacokinetics, efficacy, safety, and immunogenicity.

The following two controlled clinical studies provide the primary evidence to support the determination of no clinically meaningful differences between SB4 and US-licensed Enbrel:

- SB4-G11-NHV was a randomized, single-blind, 3-part, 2-period, 2-sequence, single-dose cross-over study in 138 healthy males. The objective was to assess 3-way PK similarity and safety, tolerability, and immunogenicity. The comparison products were SB4, EU-approved etanercept, and US-licensed Enbrel.

- SB4-G31-RA was a randomized, double-blind, parallel-group, multi-center clinical study in 596 patients with moderate to severe RA despite MTX therapy. Subjects were randomized either to SB4 or EU-approved etanercept (1:1 randomization) at 50 mg S.C. weekly. The primary endpoint was ACR20 at Week-24.

Additional long-term safety and immunogenicity data was collected in the 52 week extension in patients who completed SB4-G31-RA. The extension period consisted of 48 weeks of active treatment and 4 weeks of safety follow-up to evaluate the long-term

safety, tolerability, immunogenicity and efficacy of SB4 in patients with RA treated previously with SB4 or EU-approved etanercept.

Extrapolation for the Plaque Psoriasis indication:

Samsung Bioepis Co., Ltd. is seeking licensure for the indications studied in the clinical program, RA, as well as for the following additional indications: ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, and polyarticular juvenile idiopathic arthritis, indications that the applicant did not specifically study. Samsung has provided adequate scientific justification for the extrapolation, from the data and information submitted by the applicant, to support licensure under section 351(k) for those additional indications.

If a biological product meets the statutory requirements for licensure as a biosimilar biological product under section 351(k) of the PHS Act based on, among other things, data derived from a clinical study or studies sufficient to demonstrate safety, purity and potency in an appropriate condition of use, the applicant may seek licensure for one or more additional conditions of use for which the reference product is licensed.[1] However, the applicant would need to provide sufficient scientific justification for extrapolating data and information to support a determination of biosimilarity for each non-studied condition of use for which licensure is sought.

Such scientific justification for extrapolation should address, for example, the following issues for the studied and extrapolated conditions of use:

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

The Agency has determined that differences between conditions of use with respect to the factors described above do not necessarily preclude extrapolation. A scientific justification should address these differences in the context of the totality of the evidence supporting a demonstration of biosimilarity.

Consistent with the principles outlined in the above FDA guidance, the Applicant has provided sufficient scientific justification to support licensure of SB4 as biosimilar to U.S.-licensed Enbrel for the non-studied indications through the use of extrapolation. Considerations specific to plaque psoriasis include:

[1] Guidance for Industry "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009", April 2015
http://www fda.gov/downloads/Drugs/Guidances/UCM273001.pdf

- The primary mechanism of action (MOA) of etanercept is direct binding and blocking of TNF receptor-mediated biological activities. Etanercept binds to both soluble (s) and transmembrane (tm) TNF, thus blocking TNF binding to its receptors TNFR1 and TNFR2 and the resulting downstream pro-inflammatory cascade of events. The scientific literature indicates that this MOA is the primary MOA in RA, AS, PsA, PsO and polyarticular juvenile idiopathic arthritis. The data provided by Samsung showed similar TNF binding and potency to neutralize TNFα, supporting that U.S.-licensed Enbrel and SB4 have the same MOA, which supports the use of extrapolation to support licensure for the non-studied plaque psoriasis indication.

- Because similar PK was demonstrated between SB4 and US-licensed Enbrel, a similar PK profile would be expected for SB4 in patients with chronic moderate to severe plaque psoriasis.

- No differences in expected toxicities that are relevant to the plaque psoriasis population were noted between the SB4 product and the EU-approved etanercept arms in the clinical studies.

- Based on the above considerations, the Division concludes that the applicant has provided adequate scientific justification for the extrapolation, from the data and information submitted by the applicant, to support licensure under section 351(k) for the proposed plaque psoriasis indication.

Overall Conclusion:

The biosimilar licensure pathway under section 351(k) of the Public Health Service Act (PHS Act) requires a demonstration that the proposed biosimilar 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 proposed biosimilar product and the reference product in terms of the safety, purity and potency of the product.

DDDP has determined that the applicant has provided proper justification to support extrapolation for the use of SB4 for the treatment of moderate to severe plaque psoriasis in patients who are candidates for systemic or phototherapy. However, deficiencies in the validation of bioanalytical assay used to determine study drug concentrations in human serum, among other deficiencies, do not support licensure of SB4 as a biosimilar to US-licensed Enbrel.

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/s/

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03/19/2018

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03/19/2018

CLINICAL REVIEW

Application Type	351(k) BLA
Application Number(s)	761066
Priority or Standard	Standard
Submit Date(s)	05/25/2017
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Division / Office	DPARP/ODE2/OND
Reviewer Name(s)	Rachel L. Glaser, M.D.
Review Completion Date	2/16/2018
Established Name	SB4 (etanercept-xxxx)
(Proposed) Trade Name	
Therapeutic Class	TNF inhibitor
Applicant	Samsung Bioepis Co, Ltd
Formulation(s)	Subcutaneous Injection
Dosing Regimen	RA, AS, PsA: 50 mg once weekly PsO: 50 mg twice a week for 3 months, then once weekly PJIA: 0.8 mg/kg once weekly, no more than 50 mg once weekly
Indication(s)	RA, AS, PsA, PsO, PJIA
Intended Population(s)	• 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 RA • Juvenile Idiopathic Arthritis (JIA): Reducing signs and symptoms of moderately to severely active polyarticular JIA in patients ages 2 and older

- Psoriatic Arthritis (PsA): Reducing signs and symptoms, inhibiting the progression of structural damage of active arthritis, and improving physical function in adult patients with active PsA.
- Ankylosing Spondylitis (AS): Reducing signs and symptoms in patients with active AS
- Plaque Psoriasis (PsO): The treatment of patients 4 years or older with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This biologic licensing application (BLA 761066) submitted by Samsung Bioepis seeks approval of the product SB4 (proposed trade name: (b) (4) which is a proposed biosimilar to US-licensed Enbrel (etanercept, a TNF inhibitor). The Biologics Price Competition and Innovation Act is a pathway under section 351(k) of the Public Health Service (PHS) 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, with the foundation being an extensive structural and functional characterization to support a demonstration that the products are highly similar.

The product quality review by the Office of Biotechnology Products (OBP) team, is currently ongoing, including the review of responses to recent information requests. However, based on the currently available information on structural and functional characterization, the OBP team has assessed that SB4 is highly similar to US-licensed Enbrel notwithstanding minor differences in clinically inactive components. Pending resolution of the outstanding information requests, from a clinical standpoint, the data submitted to the 351(k) BLA from the clinical development program of SB4 support a demonstration of no clinically meaningful differences between SB4 and US-licensed Enbrel in pharmacokinetic (PK) parameters and in the efficacy, safety, and immunogenicity assessments of the comparative clinical study conducted in rheumatoid arthritis (RA). A demonstration that SB4 is highly similar to US-licensed Enbrel, notwithstanding minor differences in clinically inactive components together with the clinical data discussed in this review, support licensure of SB4 as a biosimilar to US-licensed Enbrel under section 351(k) of the PHS Act. The Applicant, Samsung Bioepis, has also provided adequate scientific justification to allow for extrapolation of data to support biosimilarity in all indications for which US-licensed Enbrel is licensed. Therefore, I recommend approval of BLA 761066, for SB4 as a biosimilar to US-licensed Enbrel, pending resolution of the outstanding information requests.

1.2 Risk Benefit Assessment

Brief Overview of the Clinical Program

The following two controlled studies provide the primary evidence to support the determination of no clinically meaningful differences between SB4 and US-licensed Enbrel:

- Study SB4-G11-NHV, was a single-dose, 3-way PK study to assess the similarity in PK between SB4 and US-licensed Enbrel. It also supports the PK bridge between US-licensed Enbrel and EU-approved Enbrel, and provides the PK component of the scientific justification for the relevance of data generated using EU-approved Enbrel to the demonstration of biosimilarity of SB4 to US-licensed Enbrel. Study SB4-G11-NHV also provides safety and immunogenicity data for SB4 and US-licensed Enbrel following single dose administration.

- Study SB4-G31-RA was a comparative clinical study that provides efficacy, safety, and immunogenicity data in RA for SB4 in comparison with EU-approved Enbrel. It was designed as a randomized, double-blind, parallel-group study to compare efficacy, safety and immunogenicity between the two products for 52 weeks. Following the randomized controlled period, an open label extension was conducted at sites in Poland and the Czech Republic to provide additional long-term safety and immunogenicity data from Week 52 to Week 100 in subjects who continued on SB4 or who underwent a single transition at Week 52 from EU-approved Enbrel to SB4.

Clinical Efficacy Overview

Study SB4-G11-NHV compared the PK, safety, tolerability, and immunogenicity of single 50 mg subcutaneous administration of either SB4, US-licensed Enbrel, or EU-approved Enbrel in healthy subjects. The pairwise comparisons of SB4, US-licensed Enbrel, and EU-approved Enbrel met the pre-specified acceptance criteria for PK similarity (90% Confidence Interval (CI) for the ratios of geometric mean of AUCinf, AUClast, and Cmax, within the interval of 80% to 125%), thus establishing the PK similarity and providing the PK bridging data that, together with the analytical bridging data, justifies the relevance of the comparative clinical data generated using EU-approved Enbrel. Supportive PK assessment demonstrated similar trough concentrations for SB4 and EU-approved Enbrel in patients with RA in Study SB4-G31-RA. Overall, pending resolution of the outstanding information requests, the clinical pharmacology review team concluded that the clinical pharmacology studies support the demonstration of PK similarity between SB4 and US-licensed Enbrel and did not raise any new uncertainties in the assessment of biosimilarity of SB4 to US-licensed Enbrel.

Study SB4-G31-RA, the comparative clinical study in RA patients, met its primary objective of demonstrating that the proportion of patients achieving an ACR20 response at Week 24 was similar between the SB4 and EU-approved Enbrel treatment groups. Approximately 74% of subjects randomized to SB4 and 72% of subjects randomized to EU-approved Enbrel were ACR20 responders, with an adjusted difference of 1.66% (90% CI: -4.4%, +7.7%). The 90% CI for the adjusted treatment difference fell within the protocol-specified equivalence margin, as well as within the equivalence margin recommended by FDA to have a lower bound no greater in magnitude than -12%. ACR20, ACR50, and ACR70 responses over time, in addition to mean changes from baseline in the components of the ACR composite endpoint, and the disease activity score (DAS28-CRP), were also similar between the treatment arms. These data, together with the analytical and PK bridging data, support similar efficacy between SB4 and US-licensed Enbrel in patients with RA.

Clinical Safety Overview

The safety evaluation plan of SB4 was based on the known safety profile of US-licensed Enbrel as described in the USPI and other published data. The submitted safety and immunogenicity data from SB4-G31-RA, supported by the data from the single-dose PK similarity study SB4-G11-NHV, are adequate to support the demonstration of no clinically meaningful differences in safety and immunogenicity between SB4 and US-licensed Enbrel. The safety database submitted for SB4 is adequate to provide a reliable descriptive comparison between the two products. The safety risks identified are consistent with the known adverse event profile of US-licensed Enbrel. There were no notable differences

between SB4 and EU-approved Enbrel in treatment-emergency adverse events (TEAEs), serious adverse events (SAEs), deaths, or adverse events leading to discontinuation between the treatment groups. No cases of drug-induced liver injury meeting Hy's law criteria were reported in the SB4 clinical program. In addition, a single transition of non-treatment naïve patients to the proposed biosimilar, i.e., patients previously treated with EU-approved Enbrel to SB4, did not result in an increase in immunogenicity or clinically significant adverse reactions.

Clinical Efficacy and Safety Overview Conclusions

Overall, the safety and efficacy data from clinical studies SB4-G11-NHV and SB4-G31-RA support a demonstration that there are no clinically meaningful differences between SB4 and US-licensed Enbrel, pending resolution of the outstanding information requests.

Extrapolation to Non-Studied Indications

Samsung Bioepis is seeking licensure for the indication studied in the clinical program, rheumatoid arthritis, as well as other approved indications for the reference product, including psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, and plaque psoriasis, which have not been directly studied in the SB4 clinical program. To support the use of SB4 for these indications, Samsung Bioepis has provided adequate scientific justification relying on extrapolation of biosimilarity to these indications. The justification addresses issues for the testing and extrapolating conditions of use outlined in Guidance for Industry: "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009." First, Samsung Bioepis' extensive analytical characterization data support a demonstration that SB4 is highly similar to US-licensed Enbrel notwithstanding minor differences in clinically inactive components, and the data support a demonstration that there are no clinically meaningful differences between SB4 and US-licensed Enbrel in terms of safety, purity, and potency, based on similar clinical PK, and similar efficacy, safety, and immunogenicity in RA.

The primary mechanism of action (MOA) of etanercept across indications is direct binding and blocking of TNF receptor-mediated biological activities. Etanercept binds to both soluble (s) and transmembrane (tm) TNF, thus blocking TNF binding to its receptors TNFR1 and TNFR2 and the resulting downstream pro-inflammatory cascade of events. The scientific literature indicates that this MOA is the primary MOA in RA, AS, PsA, PsO and polyarticular juvenile idiopathic arthritis. The Applicant has demonstrated similarity in TNFα neutralization and TNFα binding between SB4 and US-licensed Enbrel, supporting the demonstration that SB4 and US-licensed Enbrel utilize the same MOAs. Based on the demonstration of similar PK, efficacy, and safety between SB4 and US-licensed Enbrel as discussed above, together with the demonstration that SB4 is highly similar to US-licensed Enbrel, as assessed by the OBP review team, a similar PK profile, and similar efficacy and safety, would be expected for SB4 and US-licensed Enbrel in patients across the indications being sought for licensure.

Therefore, based on the above considerations, it is scientifically justified to conclude that SB4 is biosimilar to US-licensed Enbrel in the indications being sought for licensure but not directly studied, i.e. PsA, AS, JIA, and PsO. In aggregate, extrapolation of data to the additional indications for which Samsung Bioepis is seeking licensure is scientifically justified and support licensure of SB4 for these indications.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

SB4 is a proposed biosimilar to US-licensed Enbrel. There were no new safety signals identified in the comparative clinical study and PK study. The safety profile is anticipated to be the same as that of 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 SB4 labeling, is appropriate, should SB4 be approved as a biosimilar.

1.4 Recommendations for Postmarket Requirements and Commitments

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 the clinical perspective.

2 Introduction and Regulatory Background

2.1 Product Information

Samsung Bioepis submitted a biologics license application (BLA) under section 351(k) of the PHS Act for SB4, a proposed biosimilar biological product to US-licensed Enbrel (etanercept). Etanercept is a recombinant human tumor necrosis factor receptor Fc (TNFR:Fc), consisting of a dimer of two molecules of the extracellular ligand binding domain of the 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. Etanercept competitively inhibits TNF-α binding to cell surface TNFR, preventing TNF-mediated cellular responses by rendering TNF-α biologically inactive.

SB4 is a clear to opalescent, colorless to pale yellow, sterile and preservative-free solution for subcutaneous (SC) administration, presented in single-use pre-filled syringes containing etanercept 50 mg/mL and etanercept 25 mg/0.5 mL. SB4 is a homodimer, consisting of 934 amino acids, and has a molecular weight of approximately 130 kDa. Each single chain contains 29 Cys residues that are linked by multiple intra-chain and inter-chain disulfide bonds. The same formulation of SB4 was used throughout the clinical development program.

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently approved non-biologic and biologic systemic therapies for RA, PsA, AS, PJIA, and PsO are listed in Table 1 and Table 2. Available therapies may be approved for treatment of more than one condition, as discussed below and indicated in the tables.

Rheumatoid Arthritis (RA)
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.

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 an IL-12/IL-23 inhibitor, ustekinumab, an IL-17 inhibitor, secukinumab, and abatacept, are approved biologic therapies, while the small molecule phosphodiesterase 4 inhibitor, apremilast, and Jak inhibitor, tofacitinib, are also approved for treatment of active psoriatic arthritis. Currently approved therapies for treatment of adult patients with PsA 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. Currently approved therapies for treatment of adult patients with AS are listed in Table 1 and Table 2.

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

Plaque Psoriasis (PsO)
The available approved systemic treatments for moderate to severe PsO in candidates for systemic therapy or phototherapy are presented in Table 1and 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 and carries an increased risk of squamous cell carcinoma of the skin.

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	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[1]	
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		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	CD
Tocilizumab (ACTEMRA) [Genentech/Roche] {2010}	Humanized IgG1 k mAb *IL-6 receptor inhibitor*	X			X		SJIA, GCA
Golimumab (SIMPONI ARIA) [Janssen Biotech] {2013}	Humanized IgG1 mAb *TNF inhibitor*	X	X	X			
Secukinumab (Cosentyx) [Novartis] {2015}	Humanized IgG1 mAb *IL-17 inhibitor*		X	X		X	
Sarilumab (KEVZARA) [Sanofi and Regeneron] {2017}	Humanized IgG1 mAb *IL-6 receptor inhibitor*	X					
Ixekizumab (TALTZ) [Eli Lily] {2016}	Humanized IgG4 mAb *IL-17A inhibitor*		X			X	
Brodalumab (SILIQ) [Valeant} {2017}	Humanized IgG2 mAb *IL-17 receptor A inhibitor*					X	
Guselkumab (TREMFYA) [Janssen Biotech] {2017}	Humanized IgG1 mAb *IL-23 inhibitor*					X	
*Year = Year of first approval	mAb=mononclonal antibody, 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, GCA= Giant Cell Arteritis						

[1] Approved for psoriasis in patients ages 4 years and older

Recently, biosimilars to Enbrel (Erelzi,/etanercept-szzs), Humira (Amjevita/ adalimumab-atto, Cyltezo/adalimumab-adbm), and Remicade (Inflectra/infliximab-dyyb, Renflexis/infliximab-abda, Ixifi/infliximab-qbtx) have been approved for the same indications as the reference products.

2.3 Availability of Proposed Active Ingredient in the United States

SB4 is not currently marketed in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

The US-licensed Enbrel label contains a 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.
- Enbrel should be discontinued if a patient develops a serious infection or sepsis during treatment.
- Perform test for latent TB; if positive, start treatment for TB prior to starting Enbrel.
- Monitor all patients for active TB during treatment, even if initial latent TB test is negative.

MALIGNANCIES

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

In addition to the boxed warning on the label, the WARNINGS AND PRECAUTIONS section of the label includes warnings regarding serious infections, neurologic reactions, malignancies, postmarketing reports of heart failure, hematologic reactions, hepatitis B reactivation, allergic reactions, interference with immunizations, autoimmunity and the formation of autoantibodies, and immunosuppression.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The development of SB4 was conducted outside the US with minimal regulatory input from the FDA. A PIND meeting was held on 13-Feb-2012, at which time discussion focused on the analytical similarity assessment. Clinical discussion centered on the Agency recommendation for a comparative dose-response study, the Applicant's proposed modeling and simulation to inform the clinical development program, and the need for a scientific bridge to justify the relevance of comparative data obtained with EU-approved Enbrel. Additionally, the Agency provided comments on extrapolation to non-studied indications.

A pre-BLA meeting was held on 23-June-2016. In addition to discussion of the format of the submission, clinical discussion focused on a recommended similarity margin with a lower bound no greater in magnitude than -12%, that the primary analysis should be conducted on all randomized patients, and the recommendation that tipping point analyses be conducted. As the RA extension study did not include a comparator group that continued on EU-approved Enbrel, the Applicant was advised to provide a comparison of demographic and disease characteristics

that could impact immunogenicity prior to the time of the transition, as well as a comparison of safety and immunogenicity. The Applicant was further advised to include justification of the observed differences in immunogenicity in both clinical studies in the BLA. The requirement for development of an age-appropriate formulation and presentation to address PREA was discussed. A pediatric study plan was subsequently agreed upon on 01-Sept-2016.

2.6 Other Relevant Background Information

SB4 has received marketing authorization/approval in Korea, Australia, and the EU for treatment of RA, PsA, axial spondyloarthritis (non-radiographic axial spondyloarthritis and ankylosing spondylitis), and psoriasis in adult patients (age 18 years and older). It received regulatory approval in Canada for treatment of RA and AS.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

In general, the data quality and integrity of the studies were good. The amount of missing data was small and did not impact the overall conclusions on safety and efficacy. The BLA submission was in electronic common technical document (eCTD) format and was adequately organized.

OSI Inspection

The Office of Scientific Investigations (OSI) was consulted to conduct routine applicant/monitor inspections for two clinical sites (site SB41018 in Poland and site SB40703 in Lithuania) that contributed to the data for Study SB4-G31-RA. Both sites were selected based on high enrollment; additionally, SB41018 was a participating site in the OLE. Inspection of site SB41018 found that 5 subjects had altered ESR values to meet eligibility criteria and 1 subject did not meet eligibility criteria based on ESR and CRP at re-screening. These protocol violations were initially noted on routine monitoring and led to quality control audits and a corrective action plan at the site. The six subjects were excluded from the efficacy analysis. Except for the noted protocol violations at SB41018, the inspections showed the clinical sites to be in compliance with Good Clinical Practices. The OSI investigators concluded that the data submitted were considered reliable to support the current BLA. The Division of New Drug Bioequivalence Evaluation (DNDBE) did not recommend on-site inspections of the clinical site for Study SB4-G11-NHV based on the outcomes of the recent inspections at the sites.

3.2 Compliance with Good Clinical Practices

All studies were conducted in accordance with Good Clinical Practice as described in International Conference on Harmonization (ICH) Guideline E6 and applicable local regulatory requirements and laws, and in accordance with the ethical principles outlined in the Declaration of Helsinki. Informed consent was obtained from each subject before any study related procedures were

performed. Consent documents were reviewed and approved by the appropriate Institutional Review Board/Independent Ethics Committee.

3.3 Financial Disclosures

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.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

To support a determination that SB4 is highly similar to US-licensed Enbrel, Samsung Bioepis submitted an extensive analytical similarity package consisting of multiple orthogonal physiochemical and biological assays. The assessment also included assays that addressed each potential mechanism of action, either directly or indirectly. The amino acid sequences of SB4 and US-licensed Enbrel are identical. TNF-α binding and neutralization activities, reflecting the primary mechanism of action of US-licensed Enbrel, are similar between SB4 and US-licensed Enbrel.

The Product Quality review has not been finalized at the time of this review. The working assessment of the Product Quality review team is that the sponsor provided a sufficiently robust analysis for the purposes of establishing the analytical component of the scientific bridge among SB4, US-licensed Enbrel, and EU-approved Enbrel, and justify the relevance of comparative data generated from clinical studies that used EU-approved Enbrel. The evidence submitted supports a demonstration that SB4 is highly similar to US-licensed Enbrel.

For a detailed review and analysis of the CMC data, refer to the review by the Product Quality review team.

4.2 Clinical Microbiology

No issues have been identified by the OBP review team regarding clinical microbiology at the time of this review.

4.3 Preclinical Pharmacology/Toxicology

Three nonclinical studies of SB4 were submitted in support of the BLA: an efficacy study in BALB/c mice comparing SB4 vs. EU-approved Enbrel vs. US-licensed Enbrel, a single dose PK study in SD rats comparing SB4 vs. EU-approved Enbrel, and a repeat dose toxicity study in cynomolgus monkeys comparing SB4 vs. EU-approved Enbrel vs. US-licensed Enbrel. The results of the three studies were considered comparable to that of US-licensed Enbrel and there was no evidence to indicate potential clinical safety concerns associated with SB4 administration.

Overall, the pharmacology and pharmacokinetic data submitted in BLA 761066 support the demonstration of biosimilarity between SB4 and US-licensed Enbrel. There were no outstanding issues from the nonclinical Pharmacology and Toxicology perspective and the results of these animal studies can be taken together with the data from the analytical bridging studies to support a demonstration that SB4 is biosimilar to US-licensed Enbrel. No residual uncertainties have been identified by this discipline. For a detailed review and analysis of the nonclinical data, refer to the pharmacology/toxicology review by Dr. Ijeoma Uzoma, PhD.

4.4 Clinical Pharmacology

Refer to the clinical pharmacology review by Bhawana Saluja, PhD, for a detailed analysis of the pharmacokinetic aspects related to this application.

The objectives of the clinical pharmacology program were to evaluate the pharmacokinetic similarity between SB4 and US-licensed Enbrel, and to support the scientific bridge between SB4, US-licensed Enbrel, and EU-approved Enbrel in order to justify the relevance of comparative data generated using EU-approved Enbrel to support a demonstration of the biosimilarity of SB4 to US-licensed Enbrel. The Applicant submitted PK data from two studies. The pivotal PK similarity study, Study SB4-G11-NHV, was conducted in healthy male subjects comparing SB4, US-licensed Enbrel, and EU-approved Enbrel. Similarities in PK between SB4 and EU-approved Enbrel were supported by the PK assessment in the comparative clinical study, SB4-G31-RA.

Study SB4-G11-NHV was a randomized 3 part, 2 period, cross-over study in 138 healthy male subjects. See 5.3 Discussion of Individual Studies/Clinical Trials for details of the study design. 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.

4.4.1 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.

4.4.2 Pharmacodynamics

Not applicable for this application.

4.4.3 Pharmacokinetics

Analysis of the results of Study SB4-G11-NHV, showed that the 90% confidence intervals (CIs) for the geometric mean ratios (GMR) of SB4 to EU-approved Enbrel, SB4 to US-licensed Enbrel, and EU-approved Enbrel to US-licensed Enbrel for the tested PK parameters (AUCinf, AUCt, and Cmax) were all within the PK similarity acceptance interval of 80-125% as shown in Table 3, demonstrating PK similarity between the 3 products and establishing a PK bridge to support the relevance of the data generated using EU-approved Enbrel in the comparative clinical efficacy trial, Study SB4-G31-RA.

Table 3: PK Results, Study SB4-G11-NHV

Summary Statistics: % Ratio of Geometric Means (90% CI)					
	Parameter	Ratio	90% CI		Met margins
Part A					
SB4/EU-Enbrel	Cmax (µg/mL)	1.037	0.985	1.092	Yes
SB4/EU-Enbrel	AUCt (µg•h/mL)	0.986	0.942	1.033	Yes
SB4/EU-Enbrel	AUCinf (µg•h/mL)	0.990	0.947	1.036	Yes
Part B					
SB4/US-Enbrel	Cmax (µg/mL)	1.044	0.977	1.114	Yes
SB4/US-Enbrel	AUCt (µg•h/mL)	1.010	0.954	1.069	Yes
SB4/US-Enbrel	AUCinf (µg•h/mL)	1.011	0.958	1.067	Yes
Part C					
EU-Enbrel/US-Enbrel	Cmax (µg/mL)	1.033	0.947	1.127	Yes
EU-Enbrel/US-Enbrel	AUCt (µg•h/mL)	1.013	0.923	1.111	Yes
EU-Enbrel/US-Enbrel	AUCinf (µg•h/mL)	1.005	0.915	1.104	Yes

Source: Adapted from Summary of Clinical Pharmacology Studies Table 4 page 18, Table 6 page 20, and Table 8 page 22

ADA were observed in 7 subjects following administration of EU-approved Enbrel, 10 subjects following administration of US-licensed Enbrel, and no subjects following administration of SB4. Three of the 14 subjects (17.6%) with injection site reactions were ADA positive, while 11 subjects (78.6%) were ADA negative. The presence of ADA did not impact the PK profile or safety events, however this assessment is limited by the lack of ADA observed in subjects receiving SB4.

Overall, the clinical pharmacology review team has determined that PK similarity has been established between SB4 and US-licensed Enbrel, and the PK results support a demonstration of no clinically meaningful differences between SB4 and US-licensed Enbrel, pending resolution

of issues identified by OSIS during inspection of the bioanalytical site utilized for Study SB4-G11-NHV.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Key design features of the SB4 clinical studies are summarized in Clinical Development: Controlled Studies Table 4.

Table 4: Clinical Development: Controlled Studies

Study	Design	Objectives	Subjects	Treatments	Endpoints
SB4-G11-NHV	R, SB, 3 part, 2 period, single dose cross-over	PK, safety, immunogenicity	Healthy male subjects (N=138)	Single 50 mg SC dose etanercept Part A: SB4 vs. EU-Enbrel (N=46, 23/arm) Part B: SB4 vs. US-Enbrel (N=46, 23/arm) Part C: EU-Enbrel vs. US-Enbrel (N=46, 23/arm)	Cmax, AUCt and AUCinf
SB4-G31-RA	52 wk R, DB, PG	Efficacy, safety, immunogenicity, PK	RA patients with MTX-IR N=596	50 mg SC etanercept weekly with: • SB4 (N=299) • EU-Enbrel (N=297)	ACR20 at Wk 24
	52 wk open-label extension	Safety, immunogenicity, PK	RA patients previously treated with SB4 or EU-Enbrel N=245	SB4 50 mg SC weekly	Safety, immunogenicity

DB=Double-blind, MTX-IR=Methotrexate incomplete responders, PG=Parallel group, PK=Pharmacokinetics, R=Randomized, RA=Rheumatoid arthritis, SB=Single blind, SC=Subcutaneous
Source: Adapted from Clinical Overview Table 2, page 14

5.2 Review Strategy

The clinical development program for SB4 consists of two controlled clinical studies, listed in Table 4. The following studies provide the primary evidence to support the demonstration of no clinically meaningful differences between SB4 and US-licensed Enbrel:

- SB4-G11-NHV was a single-dose, cross-over study in healthy male subjects providing PK and safety data to directly compare SB4, US-licensed Enbrel, and EU-approved Enbrel

- Study SB4-G31-RA was the comparative clinical study that provides the comparative clinical efficacy and safety data for SB4 as compared to EU-approved Enbrel in patients with rheumatoid arthritis
- The open-label extension portion of SB4-G31-RA provides additional long-term safety and immunogenicity data for subjects who transitioned from EU-approved Enbrel to SB4 or continued to receive SB4

Pending resolution of the outstanding information requests, Study SB4-G11-NHV supports the PK component of the scientific bridge between SB4, EU-approved Enbrel, and US-licensed Enbrel, and justifies the relevance of the comparative data generated using EU-approved Enbrel in Study SB4-G31-RA to support a demonstration of no clinically meaningful differences between SB4 and US-licensed Enbrel. The PK results are presented in Section 4.4.3 Pharmacokinetics above. Detailed review of the pharmacokinetic analyses of Study SB4-G11-NHV can be found in the review by the clinical pharmacology reviewer Dr. Bhawana Saluja.

Evaluation of the single comparative clinical study, SB4-G31-RA, in rheumatoid arthritis provides evidence to further support a demonstration of no clinically meaningful differences between SB4 and EU-approved Enbrel, and based on the analytical and PK similarity data, also SB4 and US-licensed Enbrel. The following efficacy analysis sets were defined:

- The Full Analysis Set (FAS) consists of all subjects who were randomized at the Randomization Visit, analyzed based on intent-to-treat. Subjects who did not qualify for randomization, but were inadvertently randomized and did not receive investigational product (IP) during that study phase, were not included in the full analysis set
- The Randomized Set includes all subjects who received a randomization number at the Randomization Visit
- The Per-protocol set 1 (PPS1) includes all FAS subjects who completed the Week 24 visit and had an adherence (through Week 24) within the range 80-120% of both the expected number of IP injections and the expected sum of MTX doses without any major protocol deviations that affect the efficacy assessment
- The Per-protocol set 2 (PPS2) includes all FAS subjects who completed the Week 52 visit and had an adherence (through Week 52) within the range 80-120% of both the expected number of IP injections and the expected sum of MTX doses without any major protocol deviations that affect the efficacy assessment
- The PK population includes all subjects in the safety population who had at least one post-dose PK sample collected
- The Extended Population (Ex-POP) includes all enrolled subjects who received at least one dose of IP in the OLE

Protocol deviations (PDs) did not lead to subject withdrawal unless they indicated a significant risk to the subject's safety. Major protocol deviations that led to exclusion from the PPS1 were pre-specified prior to unblinding the treatment codes for analysis. In addition, subjects were excluded from analysis sets due to non-protocol deviations as listed in Table 5.

Table 5: Analysis Set Exclusions Due to Non-Protocol Deviations

Non-Protocol Deviation	Excluded from Analysis Set:
Subject without a randomization number	Randomized Set, Full Analysis Set

Subject mis-randomized	Full Analysis Set
Subjects not receiving any dose of double-blind study medication	Safety
Subject withdrew before Week 24	PPS1
Subject withdrew after Week 24 and before Week 52	PPS2

PPS1=Per Protocol Set 1, PPS2=Per Protocol Set 2

The primary endpoint was the ACR20 response at Week 24. The protocol-specified primary analysis was carried out on the per-protocol population (PPS1) using a 95% CI and a similarity margin of ± 15%, however, based on discussion at the pre-BLA meeting, the Applicant has also presented analysis for the full analysis set using a 90% CI and a similarity margin of ± 12%. All endpoints used are validated endpoints used in the approval of other drugs in RA and represent clinically meaningful endpoints.

The primary safety data were derived from Study SB4-G31-RA. The safety set (SAF) consisted of all subjects who received at least one dose of double-blind IP during the study phase. Subjects were analyzed according to the treatment received. The safety data from Weeks 52-100 includes an assessment of safety and immunogenicity in subjects who transitioned from EU-approved Enbrel to SB4 (EU-Enbrel/SB4), as compared to subjects who remained on SB4 (SB4/SB4), as well as providing longer term safety data. Study SB4-G11-NHV provides additional comparative safety and immunogenicity data and contributes towards the safety database. AEs were analyzed according to the treatment received prior to the event.

In general, the overall clinical program is adequate to provide the evidence to support the demonstration of no clinically meaningful differences in the studied indication of RA.

5.3 Discussion of Individual Studies/Clinical Trials

SB4-G11-NHV

Protocol: SB4-G11-NHV

Title: A randomized, single-blind, three-part, two-period, two-sequence, single-dose, cross-over study to compare the pharmacokinetics, safety, tolerability and immunogenicity of three formulations of etanercept (SB4, EU-approved Enbrel and US-licensed Enbrel) in Healthy Male Subjects

Dates Conducted: May 3, 2013-July 12, 2013

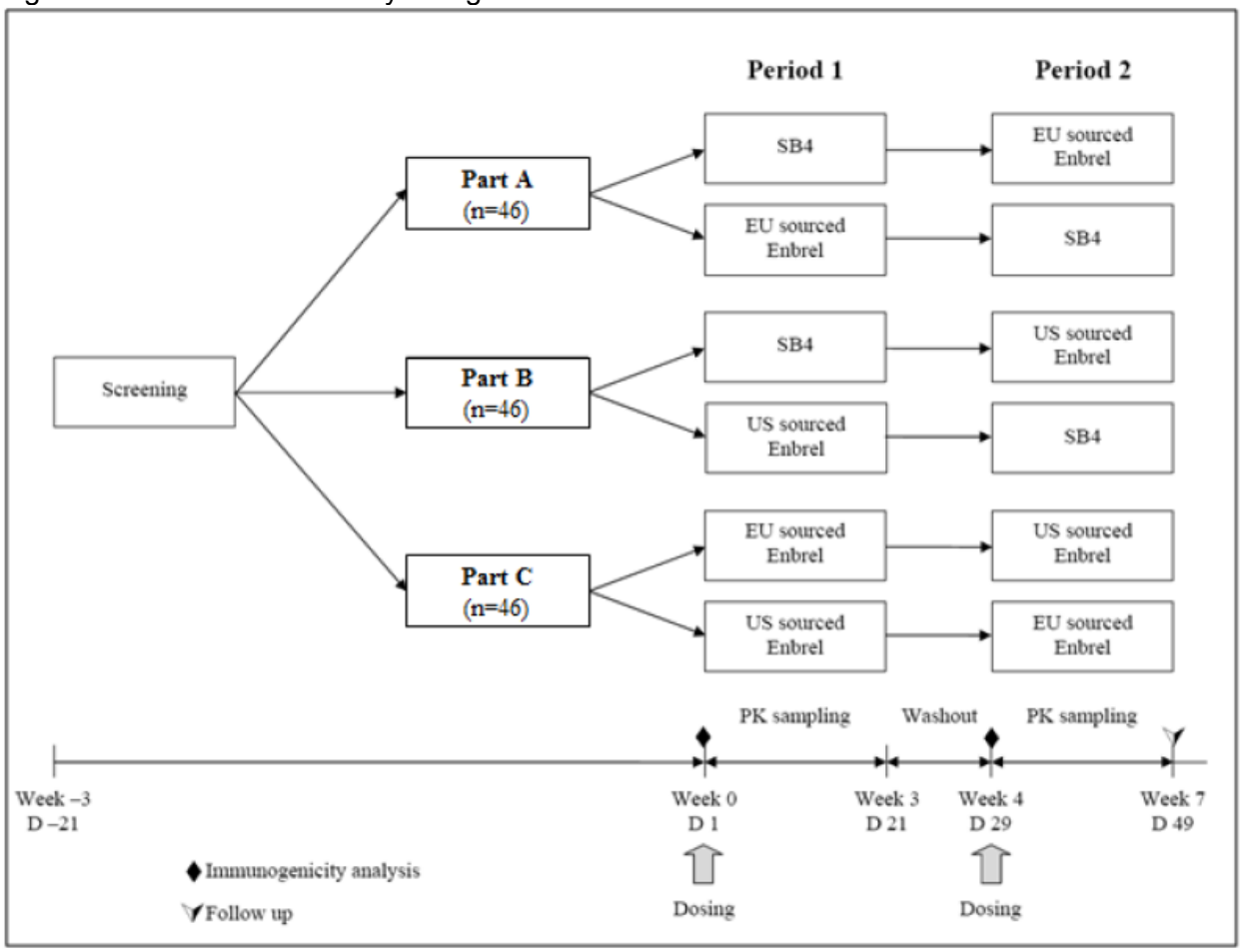
Objectives:
Primary Objective: To investigate and compare the PK profiles between SB4 and EU-approved Enbrel (Part A), between SB4 and US-licensed Enbrel (Part B), and between EU-approved Enbrel and US-licensed Enbrel (Part C) in healthy males

Secondary Objective: To investigate the safety, tolerability and immunogenicity of SB4 and EU-approved Enbrel (Part A), SB4 and US-licensed Enbrel (Part B), and EU-approved Enbrel and US-licensed Enbrel (Part C) in healthy male subjects

Overall Design:
SB4-G11-NHV was a single-blind, three-part, two-period, single-dose, cross-over study in 138 healthy male subjects (Figure 1). In Part A, subjects were randomized to receive a single dose of SB4 or EU-approved Enbrel in Period 1 followed by the cross-over treatment in Period 2, and in Parts B and C, subjects received treatments with SB4 and US-licensed Enbrel, and EU-approved Enbrel and US-licensed Enbrel, respectively. Forty-six subjects were enrolled in each study part and randomized 1:1 to one of two sequences by a computer-generated randomization code. PK and safety and tolerability assessments were conducted over 21 days following treatment. Treatment periods were separated by 7 days, resulting in a 28 day washout between the doses.

On the first day of Period 1 in Part A, 4 subjects received doses with a one hour or longer dosing interval between dosing of subjects. If there were no serious or unexplained safety issues as determined by the Investigator or Sponsor, on Day 2, 12 subjects in Part C received EU-approved Enbrel or US-licensed Enbrel. On Day 3, an additional 4 subjects in Part A were dosed with a dosing interval of 1 hour or longer between subjects. If there were no serious or unexplained safety issues, on Day 4, 12 subjects in Part C received EU-approved Enbrel or US-licensed Enbrel. From Day 5, the remainder of the subjects received SB4, EU-approved Enbrel, or US-licensed Enbrel in a non-sequential manner.

Figure 1: SB4-G11-NHV Study Design



Source: SB4-G11-NHV CSR Figure 9-1, page 26

Injections were administered in the left or right upper quadrant of the abdomen, and a different side was used for each injection. Subjects wore a blindfold during administration to maintain single-blind conditions. Subjects were permitted to take acetaminophen at single doses up to 1 g and at maximum daily doses of up to 4 g. Other concomitant medication required approval from the Investigator and/or Sponsor, except in emergency situations.

Safety assessments included AEs, standard laboratory assessments (chemistry, hematology, serology, and urinalysis), physical examination, vital signs, injection site assessment, ECG, and immunogenicity.

Subjects were discontinued from study treatment in the event of:

- Subject wished to discontinue participation
- In the Investigator's opinion, the subject's safety or well-being could have been compromised by further participation in the study
- Withdrawal of a subject upon request of the Sponsor, for reasons that might include but was not limited to: suspicion of fraud, subject enrolling in multiple clinical studies, lack of compliance, etc

- Subject had increase of liver function test values (ALT or AST > 3x upper limit of normal (ULN) or bilirubin > 2x ULN) which had been confirmed by a repeat test
- Clinically relevant allergic/hypersensitivity reaction, which in the opinion of the Investigator was related to the IP
- Subject needed to undergo surgery
- Subject experienced any severe or serious reaction known for etanercept such as (opportunistic) infections, anemia/pancytopenia, anaphylaxis, vasculitis, demyelinating diseases of the central nervous system or toxic epidermal necrolysis/Stevens-Johnson syndrome
- Subject experienced an unacceptable AE or other medically important condition such as:
    - Any new clinically significant infection, including opportunistic infections, occurring during study participation
    - Any new signs and symptoms suggestive of TB infection
    - Any clinically significant hematological reactions, e.g., aplastic anemia, pancytopenia, signs of increased bleeding, etc
    - Any new reported clinically significant neurologic symptoms, e.g. symptoms of demyelinating disease
    - Signs and symptoms indicating heart failure of New York Heart Assocation class II or above
    - A QT interval corrected according to Bazett's formula or QTcF values >5 00 msec or change from Baseline of > 60 msec

Subjects who withdrew from the study were requested to return to the study site for a withdrawal visit, as per the assessments for Day 49.

Eligibility:

Inclusion Criteria:

1. Healthy male subjects aged 18-55 years, inclusive
2. All screening results (vital signs, physical examination, clinical laboratory tests, 12-lead ECG) within the normal range or outside the normal range but assessed as clinically non-significant by the Investigator
3. Body weight 60.0-94.9 kg and body mass index 20.0-29.9 kg/m^2, inclusive
4. Systolic blood pressure of ≤ 145 and ≥ 90 mmHg, diastolic blood pressure of ≤ 95 and ≥ 50 mmHg, and heart rate of ≥ 45 and ≤ 95 beats per minute
5. Subjects who did not smoke or smoked less than 10 cigarettes, 2 cigars or 2 pipes per day (and who agreed to abstain from smoking while resident in the clinical study site)
6. Willing to abstain from sexual intercourse or willing to use a condom in addition to having their female partner use another form of contraception unless their partners were infertile from time of first administration of IP until completion of study procedures
7. Willing and able to comply with study procedures
8. Subjects who had provided written informed consent

Exclusion Criteria:

1. Subjects with a history and/or current presence of clinical significant atopic allergy, hypersensitivity or allergic reactions (either spontaneous or following drug administration), also including known or suspected clinically relevant drug hypersensitivity to any components of the test and reference IP formulation or comparable drugs
2. Subjects with active or latent TB or who had history of TB
3. Subjects with history of invasive systemic fungal infections or other opportunistic infections judged relevant by the Investigator, including local fungal infections or history of herpes zoster
4. Subjects with any systemic or local infection, known risk for developing sepsis and/or known active inflammatory process within six months prior to first administration of IP. Subjects with C-

reactive protein > 1.5 times the ULN at screening or baseline were not enrolled in order to exclude those subjects with chronic inflammatory processes

5. Subjects who had a serious infection (associated with hospitalization and/or which required intravenous antibiotics) within 6 months prior to the first administration of IP
6. Subjects who had previously been treated with etanercept
7. Subjects with a history of and/or current cardiac disease defined as one of the following:
    a. Personal or family history of prolonged QT interval syndrome
    b. Personal or family history of Torsade de Pointes
    c. QT interval corrected according to Fridericia's formula > 430 msec
    d. Signs and symptoms of any history suggestive for heart failure
8. Subjects with a history of and/or current gastrointestinal, renal, hepatic, cardiovascular, hematological (including pancytopenia, aplastic anemia or blood dyscrasia), metabolic (including known diabetes mellitus), or pulmonary disease classed as significant by the Investigator
9. Subjects with a history of cancer including lymphoma, leukemia and skin cancer
10. Impaired liver function as determined by one of the following:
    a. Serum alanine transaminase (ALT) and/or aspartate transaminase (AST) ≥ 1.5 times ULN at baseline
    b. Gallbladder or bile duct disease
    c. Acute or chronic pancreatitis
    d. A positive hepatitis C antibody test or hepatitis B surface antigen test
    e. Hepatic disease (e.g., cirrhosis) classed as clinically significant by the Investigator
11. Subjects with a history of immunodeficiency including subjects with a positive test for human immunodeficiency virus
12. Subjects who had an illness within 4 weeks prior to Screening that was classed as clinically significant by the Investigator
13. Subjects with a mental disease classed as serious by the Investigator
14. Subjects who had received live vaccine(s) within 30 days prior to Screening or who required live vaccine(s) between Screening and the final study visit
15. Subjects who had an alcoholic beverage intake of more than 28 units per week
16. Subjects for whom there was reasonable evidence (in the opinion of the Investigator) of drug abuse as indicated by a positive urinary drug screening at Screening and/or Baseline
17. Subjects who took medication with a half-life >24 h within 1 month or 10 half-lives of the medication prior to the first administration of IP
18. Subjects who donated > 100 mL blood within 4 weeks prior to the first administration of IP
19. Subjects who participated in another study with an investigational drug within 1 month by local regulation prior to first treatment. Subjects who received treatment with a biological or immunosuppressive agent within 3 months of Screening were also to be excluded
20. Subjects who, in the opinion of the Investigator, were not likely to complete the study for whatever reason
21. Subject who was the Investigator or any sub-investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the clinical study
22. Vulnerable subjects (e.g., persons kept in detention)

Endpoints:
Primary PK endpoints: AUCinf and Cmax
Secondary PK endpoints: AUClast, Tmax, Tz/F, Terminal rate constant, Terminal half-life, CL/F, %AUCextrap
Safety: AEs, laboratory evaluations, vital signs, injection site assessments, 12 lead ECG, immunogenicity

Statistics: A sample size of 46 subjects per study part was determined to provide 90% power to detect a 20% difference in PK between test and reference IP, based on assumption of a 5%

difference in true geometric means and an anticipated 15% dropout rate. The PK population included all randomized subjects who received at least one of the treatments, with evaluable primary PK parameters and without any major protocol deviation. Equivalence for the primary endpoints was to be concluded if the 90% CIs for the ratio of the geometric means of the IPs were within the interval 0.8 to 1.25. The safety population included all subjects who received at least one dose of IP. Interim analysis was performed by an unblinded statistical team of the preliminary safety profiles after 102 subjects received a single dose of study drug in Period 1.

Protocol Amendments & Study Conduct:
There were 3 amendments to the original protocol (dated 02Oct2012). All amendments were made prior to enrollment of first subject. Key changes in each amendment are summarized below:

Amendment 1 (07Jan2013):
- Modification of time points for questioning of AEs and concomitant medications
- Clarification of definition of AE, when hospitalization considered serious, expectedness of AE, and analysis of safety data (AEs and TEAEs)

Amendment 2 (11Jan2013):
- Blood volume to be collected during study was updated
- Management of subjects with QTcF prolongation clarified
- Assessment of injection site reactions clarified

Amendment 3 (06Feb2013):
- Changes in sample size
- Changes made to ensure safety according to IEC's recommendation
- Change in final composition of IP excipient

In addition, the normal ranges for hsCRP were updated on 03June2013 due to changes in the laboratory. The protocol amendments and other protocol changes do not impact the comparative PK, safety, and immunogenicity assessments of Study SB4-G11-NHV.

A total of 138 subjects were enrolled and randomized in SB4-G11-NHV, and 132 subjects completed the study and were included in the PK population. Six subjects discontinued the study during Period 1 or the washout period; no subjects discontinued during Period 2. Reasons for discontinuation from the study included 4 subjects discontinued for adverse events, 1 with pathological lab value (ALT increased), and 1 subject discontinued for other reasons (increased ethanol level).

There were a total of 46 protocol deviations across the 3 parts. Five protocol deviations were considered to be major and included failure to complete both periods in 6 subjects and history of dental abscess in 1 of the subjects who did not complete both periods. These subjects were not included in the PK population. The most frequent minor protocol deviation was PK blood study procedure related to PK sample adequacy and timing of centrifugation. These protocol deviations were generally balanced between the treatment groups by study part and are not expected to impact the analysis and interpretation of the results of SB4-G11-NHV.

Overall, the baseline demographics were similar between treatment arms. All subjects were males, most were White (97.8%) and non-Hispanic (100%), and the mean age was 40 years. While there were small differences in height and weight, BMI was comparable between sequences in each study part.

SB4-G31-RA

Protocol: SB4-G31-RA

Title: A randomized, double-blind, parallel group, multicenter clinical study to evaluate the efficacy, safety, pharmacokinetics, and immunogenicity of SB4 compared to Enbrel in subjects with moderate to severe rheumatoid arthritis despite methotrexate therapy

Dates Conducted: The first subject signed informed consent on 11June2013. The last subject, last visit at Week 56 was 28Nov2014. The open label extension was conducted from 09July2014 through 02Nov2015.

Objectives:
Primary Objective:
To demonstrate equivalence of SB4 to EU-approved Enbrel at Week 24, in terms of ACR20 response rate in subjects with moderate to severe rheumatoid arthritis despite MTX therapy

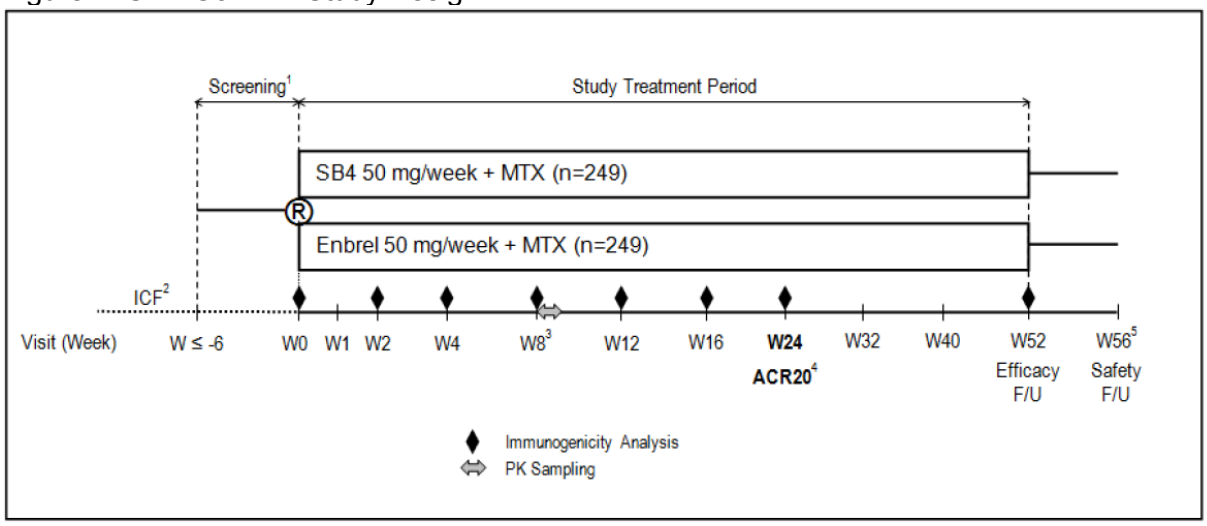
Secondary Objectives:
- To evaluate the efficacy of SB4 compared to EU-approved Enbrel using relevant efficacy endpoints other than ACR20 at Week 24 in subjects with moderate to severe RA despite MTX therapy
- To evaluate the safety and tolerability of SB4 compared to EU-approved Enbrel in subjects with moderate to severe RA despite MTX therapy
- To evaluate the PK of SB4 compared to EU-approved Enbrel in subjects with moderate to severe RA despite MTX therapy
- To evaluate the immunogenicity of SB4 compared to EU-approved Enbrel in subjects with moderate to severe RA despite MTX therapy

Overall Design:
Study SB4-G31-RA was a 56 week multicenter (73 sites in 10 countries), randomized, double-blind, parallel-group study with a planned enrollment of 498 subjects with moderate to severe RA despite MTX therapy. Subjects were randomized 1:1 to receive one of the following treatment regimens:
- SB4 50 mg weekly by SC injection
- EU-approved Enbrel 50 mg weekly by SC injection

Subjects were assigned a unique subject number at Screening, which was used to register the subject using the interactive web response system or the interactive voice response system. Subjects were then randomized at the site level by a computer-generated randomization scheme. All subjects received oral or parenteral MTX at a stable dose of 10-25 mg/week from 4 weeks prior to Screening until the End-of-Treatment Visit (Week 52) and concomitant folic acid 5-10 mg/week while taking MTX during the study period. Following a screening period of up to

6 weeks, subjects were treated with self-administered IP for 52 weeks, followed by a 4 week safety follow-up period (Figure 2).

Figure 2: SB4-G31-RA Study Design



ACR20=American College of Rheumatology 20% response criteria; F/U=Follow-up; ICF=Informed consent form; MTX=methotrexate; R=Randomisation; W=Week.
1 Screening had to be done within 6 weeks prior to Randomisation.
2 Informed consent had to be obtained prior to any study related procedures.
3 Blood sampling at 24, 48, 72, 96 and 168 h after injection at Week 8 in the subgroup undergoing PK assessment. C_{trough} was assessed in the PK population at Weeks 0, 2, 4, 8, 12, 16 and 24.
4 The primary endpoint (ACR20 response) was assessed at Week 24.
5 A telephone interview for the safety follow-up was scheduled for Week 56.
Source: SB4-G31-RA 52 wk CSR Figure 9-1, page 24

There were 13 scheduled visits including the Screening Visit and a safety follow-up telephone interview as presented in Appendix 1: SB4-G31-RA Schedule of Events. At each in-person visit, efficacy evaluations included subject global assessment, physician global assessment, pain visual analogue scale (VAS), and subject-completed Health Assessment Questionnaire – Disability Index (HAQ-DI). A trained independent joint count assessor without access to other study related outcomes performed tender and swollen joint counts. The same joint count assessor was to perform all joint counts at an Investigator site when possible. X-rays of the hands and feet were performed at the End-of-Treatment or Early Termination Visit. A subset of 60 subjects (30/arm) had blood samples taken for PK analysis.

Study treatment was supplied by the Sponsor to the Investigator site as pre-packaged and labelled pre-filled syringes, identical in appearance, packaging, and labeling. The labels contained the protocol number, unique identifier, Sponsor company name, expiry date, storage details and all other details required by local regulations and Good Manufacturing Practice. When the visits were greater than 1 week apart, the appropriate number of syringes was dispensed to the subject who would return all used and unused syringes at each visit.

Subjects, Investigators, joint accessors, and other study personnel were blinded throughout the entire treatment period. After the last subject completed the Week 24 visit, or after the last

subject discontinued from the study prior to the Week 24 visit, a limited number of prospectively identified individuals were unblinded and analysis of the primary efficacy data was performed.

Safety assessments performed at each visit included AEs, standard laboratory assessments (clinical chemistry, hematology, inflammatory markers, serology, and urinalysis), physical examination, vital signs, and immunogenicity and were performed as presented in Appendix 1: SB4-G31-RA Schedule of Events. Adverse events of special interest were identified as tuberculosis and serious infections. Safety laboratory results determined to be clinically significant by the Investigator, were considered an AE/SAE. Vital sign and physical examination abnormalities that were determined to be clinically significant were also reported as an AE. The Sponsor, medical monitor, and pharmacovigilance team conducted ongoing blinded review of AEs including laboratory data.

An independent data safety monitoring board (DSMB) reviewed the safety and tolerability data at pre-specified intervals. Subjects were considered for permanent discontinuation of study treatment in the event of:

- Serious infection including active tuberculosis (TB) or opportunistic infection
- Malignancy
- Pregnancy or pregnancy planned within the study period or within 2 months after the last dose of IP
- Congestive heart failure (NYHA Class III/IV)
- Demyelinating disease
- Serious injection site reactions related to IP
- Any other adverse events (AEs) which, in the opinion of the Investigator or the Sponsor, could compromise the subject's safety or well-being if they continued to participate in the study
- The initiation of protocol-prohibited medication
- The subject was in severe non-compliance with the protocol, as determined by the Investigator in discussion with the Sponsor

Subjects could be withdrawn from the study at any time for any reason, including withdrawal of informed consent, lost to follow-up, and death. Subjects who discontinued study treatment and subjects who withdrew consent were requested to return to the study site for an Early Termination visit and to participate in a telephone follow-up interview.

Eligibility:
Inclusion Criteria:

1. Males or Females ages 18-75 years at time of signing the consent form
2. Diagnosed with RA according to revised 1987 ACR criteria for at least 6 months but not exceeding 15 years prior to Screening
3. Moderate to severe active disease despite MTX therapy defined as:
    a. ≥ 6 swollen joints and ≥ 6 tender joints (from the 66/68 joint count system) at Screening and Randomization
    b. Either ESR ≥ 28 mm/h or serum CRP ≥ 1.0 mg/dL at Screening
4. Treated with MTX ≥ 6 months prior to Randomization and on stable dose of MTX 10-25 mg/week given orally or parenterally for at least 4 weeks prior to Screening
5. If using NSAIDs or other analgesics for RA, must be on stable dose for ≥ 4 weeks prior to Randomization. If taking oral glucocorticoids, must be on stable dose equivalent to ≤ 10 mg prednisolone for ≥ 4 weeks prior to Randomization. Low potency topical, otic, and ophthalmic glucocorticoid preparations are permitted

6. Female subjects who are not pregnant or nursing at Screening and who are not planning to become pregnant from Screening until 2 months after the last dose of IP
7. Subjects of child-bearing potential (female or male) who agree to use at least 2 forms of appropriate contraception (e.g., established use of oral, injected or implanted hormonal contraceptive, placement of an intrauterine device or intrauterine system, physical barrier, male sterilization or true abstinence) from Screening until 2 months after the last dose of IP
8. Must be able to, in the opinion of the Investigator, understand the implications of taking part in the study and be willing to follow the study requirements
9. Must be able to provide informed consent, which must be obtained prior to any study related procedures

Exclusion Criteria:

1. Previously treated with any biological agents including any TNF inhibitor
2. Known hypersensitivity to human immunoglobulin proteins or other components of Enbrel or SB4
3. Have been taking any of the following concomitant medications, within the timeframe specified:
    a. Corticosteroids above levels equivalent to 10 mg prednisolone daily within 4 weeks prior to Randomization
    b. Any DMARDs, systemic immunosuppressive agents, other than MTX, including hydroxychloroquine, chloroquine, sulfasalazine, azathioprine, cyclosporine, or mycophenolate mofetil within 4 weeks prior to Randomization
    c. Leflunomide within 12 weeks prior to randomization or within 4 weeks prior to randomization if the subject had washout with 8 g of cholestyramine three times daily for at least 11 days
    d. Alkylating agents within 12 months prior to Randomization
    e. Live/life-attenuated vaccine within 8 weeks prior to Randomization
    f. Injectable corticosteroids within 4 weeks prior to Randomization
    g. Investigational product from another study within 5 half-lives of that product prior to Randomization or use of an investigational device at Screening
4. Abnormal renal or hepatic function at Screening defined as the following:
    a. Serum creatinine ≥ 2x ULN
    b. Serum alanine transaminase or aspartate transaminase ≥ 2x ULN
5. Abnormal hematological parameters at Screening defined as the following:
    a. Hemoglobin < 8.0 g/dL
    b. White blood cell count < 3.5 x 10^3 cells/μL
    c. Neutrophil count < 1.5 x 10^3 cells/μL
    d. Platelet count < 100 x 10^3 cells/μL
    e. Lymphocyte count < 800 cells/μL
6. Positive serological test for hepatitis B or hepatitis C or have a known history of infection with human immunodeficiency virus
7. Current diagnosis of active tuberculosis (TB)
8. Recent exposure to person with active TB, considered to have latent TB from screening tests (QuantiFERON Gold test and chest X-ray). If such subjects complete at least 30 days of isoniazid prophylaxis or other anti-TB therapy according to country-specific guidelines and are willing to complete the entire course of recommended anti-TB therapy they may be enrolled into the study following re-screening
9. Serious infection (such as sepsis, abscess, opportunistic infections, or invasive fungal infection including histoplasmosis) or have been treated with intravenous antibiotics for an infection within 8 weeks or oral antibiotics within 2 weeks prior to Randomization. Non-significant infections do not need to be considered exclusionary at the discretion of the Investigator
10. History of infected joint prosthesis which has not been removed or replaced
11. Any of the following conditions:
    a. Bone marrow hypoplasia which, in the opinion of the Investigator, will put the subject at risk if they are enrolled

b. Significant systemic RA involvement (e.g., vasculitis, pulmonary fibrosis, etc) which in the opinion of the Investigator, will put the subject at risk if they are enrolled
c. Other inflammatory or rheumatic disease, including but not limited to PsA, AS, systemic lupus erythematosus, Lyme disease, or fibromyalgia, which may confound the evaluation of the effect of IP
d. History of any malignancy within the previous 5 years prior to Screening except completely excised and cured squamous carcinoma of the uterine cervix, cutaneous basal cell carcinoma, or cutaneous squamous cell carcinoma
e. History of lymphoproliferative disease including lymphoma
f. History of congestive heart failure (New York Heart Association Class III/IV) or unstable angina
g. Uncontrolled diabetes mellitus or uncontrolled hypertension
h. History of organ transplantation
i. Physical incapacitation (ACR function Class IV or wheelchair-/bed-bound)
j. History of demyelinating disorders (such as multiple sclerosis or Guillain-Barré syndrome)
k. Any conditions significantly affecting the nervous system (e.g., neuropathic conditions or nervous system damage) which may interfere with the Investigator's assessment on disease activity scores including joint counts
l. Any other disease or disorder which, in the opinion of the Investigator, will put the subject at risk if they are enrolled

12. Have or have had a substance abuse (alcohol or drug) problem within the previous 3 years prior to Screening

Concomitant Medications:
All subjects received concomitant MTX and folic acid as discussed above. If a subject required change in dose of MTX during the study, this would be discussed with the Sponsor medical monitor prior to the dose change. Stable doses of NSAIDs and oral glucocorticoids were permitted as well, as specified in Table 6. In addition, paracetamol up to 4 g/day was permitted. After Week 24, doses and types of NSAIDs could be adjusted. Up to two intra-articular injections were permitted after Week 24, however the injected joint(s) would be considered swollen and tender from the time of first intra-articular injection onward. Low potency topical, otic, and ophthalmic glucocorticoid preparations were permitted, and subjects could be treated with short courses of oral, IV, intramuscular or inhaled corticosteroids for prevention or treatment of asthma, chronic obstructive pulmonary disease, allergic conditions, or any condition other than RA, if needed.

Table 6: Permitted Concomitant Medications

Medication	Dose
Paracetamol	Subjects may take paracetamol at doses of up to 4 g/day.
Oral glucocorticoids	Subjects may take oral glucocorticoids at doses equivalent to ≤ 10 mg prednisolone daily. Doses must be stable for at least 4 weeks prior to Randomisation.
Ibuprofen	Subjects may take ibuprofen at doses of up to 1200 mg/day. Doses must be stable for at least 4 weeks prior to Randomisation and during the first 24 weeks of the study if taken regularly although it may be used on an 'as required basis' for mild pain relief for AEs (e.g., headaches etc).
Other NSAIDs	Subjects may take other NSAIDs according to the prescription instructions. Doses must be stable for at least 4 weeks prior to Randomisation and during the first 24 weeks of the study.

Source: SB4-G31-RA Protocol Amendment 3. March 12, 2014

Prohibited medications included oral glucocorticoids at a prednisolone equivalent > 10 mg daily, DMARDs/systemic immunosuppressive agents excluding methotrexate, leflunomide with chelation with 8 g cholestyramine three times daily for 11 days, and injections of corticosteroids (washout period 4 weeks), leflunomide without chelation (washout period 12 weeks), investigational product from another study (washout period 5 half-lives of that investigational product), and alkylating agents (washout period 12 months). Treatment with other biological agents was also prohibited.

Endpoints:
Primary endpoint: ACR20 response at Week 24
Secondary efficacy endpoints:

- ACR20 response at Week 52
- ACR50 and ACR70 response at Week 24 and Week 52
- The numeric index of the ACR response (ACR-N) at Week 24 and Week 52
- The area under the curve (AUC) of ACR-N up to Week 24
- DAS28 score at Week 24 and Week 52
- EULAR response at Week 24 and Week 52
- AUC of the change in DAS28 from baseline to Week 24
- Major clinical response (ACR70 response for 6 consecutive months) at Week 52
- Change from baseline in modified Total Sharp Score (mTSS) at Week 52

Safety endpoints:

- Incidence of adverse events (AEs) and serious adverse events (SAEs)
- Incidence of clinical laboratory abnormalities
- Vital sign abnormalities

PK endpoints:

- Serum concentration of etanercept at baseline and prior to dosing at Weeks 2, 4, 8, 12, 16, and 24 (Ctrough)
- Area under the concentration-time curve during the dosing interval(AUC_T) at Week 8
- Maximum concentration (Cmax) at Week 8
- Minimum concentration (Cmin) at Week 8
- Peak-trough concentration ratio at Week 8
- Average serum concentration (Cav) during the dosing interval at Week 8
- Swing during the dosing interval at Week 8
- Time to reach Cmax (Tmax) at Week 8
- Apparent total body clearance (CL/F) at Week 8
- Terminal half-life (t1/2) at Week 8

Immunogenicity endpoints:

- Incidence of anti-drug antibodies
- Incidence of neutralizing antibodies

Statistics:
A sample size of 249 subjects per arm was selected to provide approximately 80% power for the primary analysis at Week 24, accounting for a 12% drop out rate. As specified in the protocol, equivalence between the two treatment groups would be declared if the two sided 95% CI of the difference of the two proportions of subjects achieving an ACR20 response based on the per protocol set is entirely contained within the equivalence margin of [-15%, 15%]. The similarity margin was selected by the Applicant to preserve 50% of the effect of Enbrel over and

above placebo based on historical studies with Enbrel. Sensitivity analyses were conducted using the full analysis set. For subjects who dropped out prematurely, a missing at random approach was applied. Similar analyses were conducted for the ACR20 response at Week 52 and ACR50 and 70 responses at Week 24 and Week 52. Continuous efficacy variables were summarized descriptively by treatment group and visit. Continuous ACR-N and AUC of ACR-N were analyzed using an ANOVA with treatment group and study site as factors. Change from baseline in DAS28 and AUC of change from baseline in DAS28 were analyzed using ANCOVA with treatment group and study site as factors, and baseline DAS28 as covariate. Change in mTSS was summarized by treatment group at Week 52 and analyzed using ANCOVA with treatment group and center as factors, and baseline values as a covariate for subjects who completed the Week 52 visit.

PK analysis was performed on the PK population. PK parameters were summarized descriptively by treatment group and visit. The safety analysis was summarized descriptively by treatment group. AEs were coded using Medical Dictionary for Regulatory Activities version 16.0. The incidence of ADA and NAb were also summarized descriptively.

SB4-G31-RA Open-Label Extension

Dates Conducted: The first subject signed informed consent for the extension period on 09July2014. The last subject, last visit at Week 104 was 02Nov2015. The study was conducted in 24 centers (Czech Republic 10, Poland 14).

Objectives:
Primary Objective:
Primary objective of SB4-G31-RA discussed above.

Secondary Objectives for the open-label extension period:

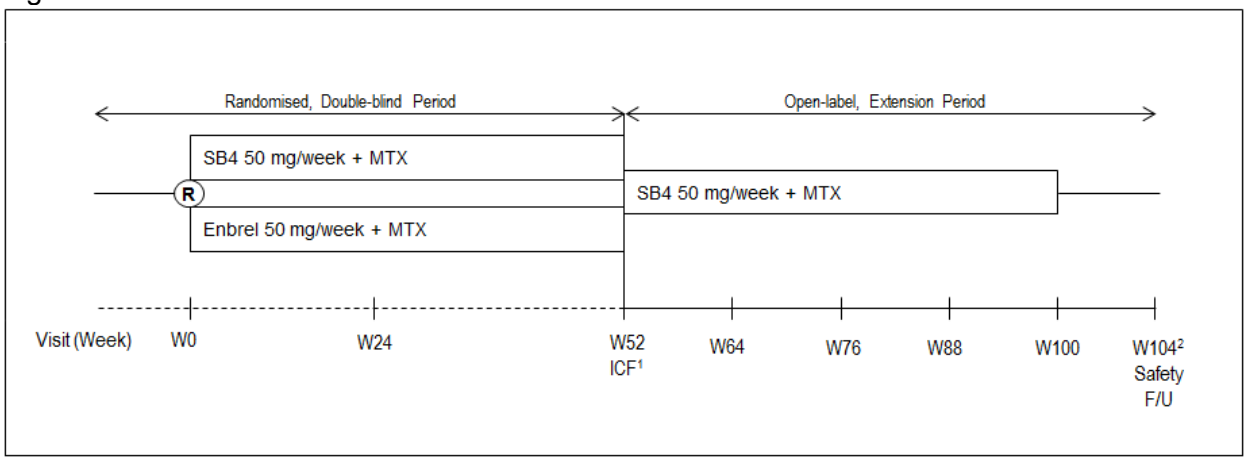
- To evaluate the long-term safety and tolerability of SB4 in subjects with RA treated previously with SB4 or Enbrel
- To evaluate long-term immunogenicity of SB4 in subjects with RA treated previously with SB4 or Enbrel
- To evaluate long-term efficacy of SB4 in subjects with RA treated previously with SB4 or Enbrel

Overall Design:
The open-label, extension period (OLE) of Study SB4-G31-RA was a 52 week open-label, single-arm, multicenter (24 sites in 2 countries) study to evaluate long-term safety, tolerability, immunogenicity, and efficacy of SB4 in subjects with RA previously treated with SB4 or EU-approved Enbrel. Subjects who completed the scheduled Week 52 visit of the randomized, double-blind period and were willing to participate, were enrolled in the OLE conducted in the Czech Republic and Poland. After the last dose of IP in the randomized, double-blind period, subjects who enrolled in the OLE did not have a safety follow-up telephone interview and instead followed the schedule of events for the OLE (Appendix 2). Subjects, Investigators, joint assessors and other study personnel remained blinded up to Week 52.

During the OLE, subjects received treatment with SB4 50 mg by self-administered subcutaneous injection weekly for 48 weeks, followed by 4 weeks of safety follow-up (Figure 3).

Subjects continued a stable dose of oral or parenteral MTX (10-25 mg/week from 4 weeks before Screening of the double-blind period until the end-of-treatment visit of the OLE (Week 100). Subjects were required to take folic acid 5-10 mg/week while taking MTX.

Figure 3: SB4-G31-RA Double-blind and OLE Periods



F/U = Follow-up; ICF = Informed consent form; MTX = methotrexate; R = Randomisation; W = Week.
[1] Informed consent had to be obtained prior to the first administration of investigational product for the open-label, extension period.
[2] A telephone interview for the safety follow up was scheduled for Week 104.
Source: SB4-G31-RA 100 Week CSR, Figure 9-1, page 20

There were 5 scheduled visits including the Screening Visit and a safety follow-up telephone interview as presented in Figure 3 and Appendix 2. Efficacy evaluations, including subject global assessment, physician global assessment, pain visual analogue scale (VAS), subject-completed HAQ-DI, and tender and swollen joint counts were performed at Weeks 52, 76, and 100. X-rays of the hands and feet were performed at Week 52 and the End-of-Treatment or Early Termination Visit. Safety assessments were performed at Weeks 52, 64, 76, 88, and 100. In addition, assessment of AEs, concomitant medications, and a TB evaluation was performed in the follow-up telephone interview. Individual stopping rules were the same as those for the double-blind portion of the study.

Eligibility:
Inclusion Criteria:
1. Completed scheduled Week 52 visit of the randomized, double-blind period of SB4-G31-RA study, may have benefited from SB4 treatment at the discretion of the Investigator, and were willing to participate in the OLE
2. Able to provide informed consent for the OLE, which had to be obtained prior to the first administration of IP for the OLE

Exclusion Criteria:
1. Withdrawn from SB4-G31-RA Study for any reason
2. Significant medical conditions, such as occurrence of a SAE or intolerance of SB4 or Enbrel during the 52 week randomized, double-blind period, which may have rendered the subjects undesirable to participate in the study, at the discretion of the Investigator
3. Were taking, or planning to take, any of the following medications during the OLE:
    a. Corticosteroids above levels equivalent to 10 mg prednisolone daily

   b. Any DMARDs/systemic immunosuppressive agents, other than MTX, including hydroxychloroquine, chloroquine, sulfasalazine, azathioprine, cyclosporine, mycophenolate mofetil, or leflunomide
   c. Alkylating agents
   d. Live or live-attenuated vaccine
4. Taking any biological agents, except SB4 and Enbrel or planned to take any biological agents except SB4 during the open-label, extension period

Concomitant Medication:
Permitted and prohibited concomitant medications were unchanged during the OLE period. Intra-articular injections were limited to 4 during the OLE, and joints in which intra-articular injection was performed were considered swollen and tender from the time of first injection onward.

Endpoints:
Efficacy:
- ACR20, ACR50, and ACR70 response at Week 76 and Week 100
- ACR-N at Week 76 and Week 100
- Change in DAS28 from Week 0 at Week 76 and Week 100
- EULAR response at Week 76 and Week 100
- Change from Week 0 in mTSS at Week 100

Safety:
- Incidence of AEs and SAEs
- Incidence of clinical laboratory abnormalities
- Vital signs abnormalities

Immunogenicity:
- Incidence of ADA
- Incidence of nAb

Statistics:
Continuous and categorical efficacy variables were summarized descriptively by treatment group and visit based on the Ex-POP. All AEs were coded using MedDRA version 16.0. Safety events were summarized by frequency and percentage of subjects experiencing events by SOC, PT, and treatment group. Changes in vital signs, clinical laboratory measurements, and immunogenicity were also summarized by treatment group and visit.

Protocol Amendments & Study Conduct:
There were 3 global amendments and 4 country-specific amendments to the original protocol (dated 08Nov2012). Amendments 1, 1.1, 2, and 2.1 were made prior to the date the first subject signed the informed consent form on 11June2013, while amendments 3 and 3.1 were made after initiation of study enrollment. Key changes in the protocol amendments include:

Amendment 1 (26Dec2012):
- Increase in screening period to 6 weeks
- Removal of washout period as not all subjects require washout
- Limit of 2 permitted intra-articular injections
- Use of corticosteroid for prevention or treatment of condition other than RA allowed

- Clarifications as to expectedness of an AE, condition when hospitalization considered SAE (ie staying in the emergency room or other floor for more than 24 h)

Amendment 1.1 (23April2013) *Poland only*:

- Updated period of contraception (from 2 months to 6 months) after last dose of MTX in subjects of child-bearing potential

Amendment 2 (15March2013):

- Duration of morning stiffness removed from listing of continuous variables
- Sample size re-estimations removed

Amendment 2.1 (29May2013) *Poland only*:

- Changes to reflect the changes made in Amendment 2 to the previous version released in Poland

Amendment 3 (12March2014):

- Coordinating Investigator for the study was designated

Amendment 3.1 (12March2014) *Czech Republic and Poland only*:

- Protocol was amended to include a 52 week extension study in the Czech Republic and Poland

Amendment 3.2 (17March2015) *Czech Republic and Poland only*:

- Change to study staff

On 03July2013, the laboratory parameter changed from high sensitivity CRP to CRP for assessment of eligibility criteria and efficacy endpoints.

All subjects who had a high sensitivity CRP rather than a CRP measured at Screening, also had an ESR ≥ 28 mm/hr and would have laboratory evidence of active disease to meet inclusion criterion #3. Protocol amendments 1-2.1 were instituted prior to the screening of the first subject in the study, while amendments 3-3.2 were primarily administrative. Therefore, these changes, as well as the change in the CRP assessment, did not have an unbalanced impact on safety and efficacy analyses.

6 Review of Efficacy

Efficacy Summary

Two controlled studies provide the primary evidence to support the determination of no clinically meaningful differences between SB4 and US-licensed Enbrel:

- SB4-G11-NHV: a single-dose pharmacokinetic (PK) study providing a 3-way comparison of SB4, US-licensed Enbrel, and EU-approved Enbrel intended to (i) support PK similarity of SB4 and US-licensed Enbrel and (ii) provide a PK bridge to support the relevance of the comparative data generated using EU-approved Enbrel to support a demonstration of the biosimilarity of SB4 to US-licensed Enbrel.

- SB4-G31-RA: a comparative clinical study between SB4 and EU-approved Enbrel in patients with rheumatoid arthritis to support a demonstration of no clinically meaningful differences in terms of safety, purity, and potency. This was a 56 week, randomized, double-blind, parallel group study conducted in 596 subjects with moderate to severe active RA on background MTX, who were randomized 1:1 to SB4 or EU-approved Enbrel at a dose of 50 mg weekly by subcutaneous injection. In the open-label extension, participating subjects originally randomized to EU-approved Enbrel underwent a single transition to treatment with SB4, while subjects originally randomized to SB4 continued treatment with SB4 through Week 100 to provide a descriptive comparative assessment of safety and immunogenicity between subjects remaining on the originally assigned treatment and those who underwent a single transition to the proposed biosimilar.

Study SB4-G11-NHV compared the PK, safety, tolerability, and immunogenicity of a single 50 mg subcutaneous dose of either SB4, US-licensed Enbrel, or EU-approved Enbrel in healthy subjects. The pairwise comparisons of SB4, US-licensed Enbrel, and EU-approved Enbrel met the pre-specified acceptance criteria for PK similarity (90% CIs for the ratios of geometric mean of AUCinf, AUClast, and Cmax, within the interval of 80% to 125%), thus establishing the PK similarity and providing the PK bridging data that, in addition to the analytical bridging data, justifies the relevance of the comparative data generated using EU-approved Enbrel. Additionally, PK data was collected from a subset of subjects with RA in Study SB4-G31-RA, and was found to be generally comparable between SB4 and EU-approved Enbrel. Overall, pending resolution of the outstanding issues identified by OSIS during inspection of the bioanalytical site utilized for Study SB4-G11-NHV, the clinical pharmacology studies support the demonstration of PK similarity between SB4 and US-licensed Enbrel and did not raise any new uncertainties in the assessment of biosimilarity of SB4 to US-licensed Enbrel.

Study SB4-G31-RA enrolled 596 subjects, 299 randomized to SB4 and 297 randomized to EU-approved Enbrel (also referred to as EU-Enbrel below). The primary endpoint was the proportion of subjects who achieved an ACR20 response at Week 24. Approximately 74% of subjects randomized to SB4 and 72% of subjects randomized to EU-Enbrel were ACR20 responders, with an adjusted difference of 1.66% (90% CI: -4.4%, +7.7%). The 90% CI for the adjusted treatment difference fell within the protocol-specified equivalence margin, as well as within the equivalence margin recommended by FDA to have a lower bound no greater in magnitude than -12%. ACR20, ACR50, and ACR70 responses over time, in addition to mean changes from baseline in the components of the ACR composite endpoint, and the disease activity score (DAS28-CRP), were also similar between the treatment arms. These data support the absence of clinically meaningful differences between SB4 and EU-approved Enbrel in patients with RA.

6.1 Indications

The proposed indications for SB4 are the following:

Rheumatoid Arthritis (RA):
SB4 is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with

moderately to severely active RA. SB4 can be initiated in combination with methotrexate or used alone.

Juvenile Idiopathic Arthritis (JIA):
SB4 is indicated for reducing signs and symptoms of moderately to severely active polyarticular JIA in patients ages 2 and older

Psoriatic Arthritis (PsA):
SB4 is indicated for reducing signs and symptoms, inhibiting the progression of structural damage of active arthritis, and improving physical function in patients with active PsA. SB4 can be used with or without methotrexate

Ankylosing Spondylitis (AS):
SB4 is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis

Plaque Psoriasis (PsO):
SB4 is indicated for the treatment of patients 4 years or older with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy

6.1.1 Methods

In the context of a biosimilar development program, the objective of the clinical development program of a proposed biosimilar is to help resolve any residual uncertainties that arise after a robust analytical similarity is established between the proposed biosimilar and the reference product. To demonstrate therapeutic similarity between SB4 and US-licensed Enbrel, the Applicant conducted the pivotal comparative clinical study in RA patients as RA has been well-studied among the indications for etanercept. Further, use of etanercept in the RA population has been well-characterized with regard to PK profile, safety, and efficacy. The Agency agrees with the Applicant's rationale that the study population is a sensitive population to use in the assessment of no clinically meaningful differences in the context of a proposed biosimilar development.

The primary analysis for SB4-G31-RA was carried out on a per-protocol population using a 95% CI and a similarity margin of ± 15%, however, based on discussion at the pre-BLA meeting, the Applicant has also presented analysis for the full analysis set using a 90% CI and a similarity margin of ± 12%.

6.1.2 Demographics

In Study SB4-G31-RA, baseline demographic characteristics were similar between subjects randomized to treatment with SB4 and those randomized to treatment with EU-Enbrel as presented in Table 7. Subjects were predominantly female (84.2%), White (92.6%), and of non-Hispanic or Latino background (93.8%). The mean age was 51.8 years, with a greater proportion of subjects ≥ 65 years in the SB4 group (15.4%) as compared to the EU-Enbrel group (11.8%). Study SB4-G31-RA was conducted outside of the United States. The regions in which the study was conducted include Poland 1 (124 subjects), Poland 2 (93 subjects), Ukraine (121 subjects), Bulgaria+Hungary+UK+Lithuania (114 subjects), Czech Republic (92 subjects), Columbia+Mexico (29 subjects), and Korea (23 subjects). Similar proportions of

subjects from each region were randomized to each treatment group. The Applicant divided Poland into 2 regions and combined other regions to keep a balanced number of subjects between regions.

Table 7: Demographic Characteristics, Randomized Subjects SB4-G31-RA

	SB4 N = 299 n (%)	EU-Enbrel N = 297 n (%)	Total N=596 n (%)
Age, years			
Mean (SD)	52.1 (11.7)	51.6 (11.6)	51.8 (11.7)
Median	53	53	53
Age Group			
< 65 years	253 (84.6)	262 (88.2)	515 (86.4)
≥ 65 years	46 (15.4)	35 (11.8)	81 (13.6)
Sex			
Female	249 (83.3)	253 (85.2)	502 (84.2)
Male	50 (16.7)	44 (14.8)	94 (15.8)
Race			
American Indian or Alaska Native	5 (1.7)	7 (2.4)	12 (2.0)
Asian	11 (3.7)	13 (4.4)	24 (4.0)
Other	4 (1.3)	4 (1.3)	8 (1.3)
White	279 (93.3)	273 (91.9)	552 (92.6)
Ethnicity			
Hispanic or Latino	18 (6.0)	19 (6.4)	37 (5.2)
Other	281 (94.0)	278 (93.6)	559 (84.2)
Weight, kg			
Mean (SD)	72.5 (15.9)	71.0 (14.6)	71.7 (15.3)
Median	71	68.5	70
Height, cm			
Mean (SD)	164.4 (8.8)	164.4 (8.6)	164.4 (8.7)
Median	164	164.1	164
BMI, kg/m^2			
Mean (SD)	26.8 (5.5)	26.3 (5.3)	26.6 (5.4)
Median	26.1	25.8	25.9

Source: Adapted from SB4-G31-RA 52 Week CSR, Table 11-2, page 67
Reviewer JMP analysis, ADSL dataset using variables RANFL, AGE, AGEGR, SEX, RACE, ETHNIC, WTBL, HTBL, BMIBL, ARM

Two hundred and forty-five subjects from Poland and the Czech Republic continued in the open-label extension period of the study. Subjects were female (84.4%), White (99.6%), and of non-Hispanic or Latino background (97.1%). The mean age was 51.0 years, with a greater mean age in the group that transitioned from EU-Enbrel to SB4 (52.1 years), as compared to the group that continued on SB4 (49.9 years). Mean weight at baseline and extended baseline (Week 52) was greater in subjects who continued on SB4 (72.8 kg and 74.1 kg, respectively), as compared to subjects who transitioned from EU-Enbrel to SB4 (70.4 kg and 71.5 kg, respectively). Overall, the population of subjects participating in the open-label extension was similar to the overall population with regard to baseline demographic characteristics, and extended baseline demographic characteristics other than region of origin.

The randomized population was representative of the intended population of moderate-to-severe RA with average baseline swollen and tender joint counts of 15.1 and 23.4, respectively, and the average disease activity score (DAS28-ESR) was 6.5. The treatment groups were generally balanced with regard to duration of RA, seropositive RF status, and dose and duration of MTX use (Table 8). The disease activity at baseline as determined by swollen and tender joint counts, subject and physician global assessments, inflammatory markers, and DAS28-ESR at baseline was similar in the SB4 and EU-Enbrel treatment groups (Table 8).

Table 8: Baseline Disease Characteristics, Randomized Subjects SB4-G31-RA

	SB4 N = 299	EU-Enbrel N = 297	Total N=596
RA duration, years			
Mean (SD)	6.0 (4.2)	6.2 (4.4)	6.1 (4.3)
Min, Max	0.5, 15.3	0.5, 15.7	0.5, 15.7
Rheumatoid factor, n (%)			
Positive	237 (79.3)	231 (77.8)	468 (78.5)
Negative	62 (20.7)	66 (22.2)	128 (21.5)
Duration of MTX use, months			
Mean (SD)	48.2 (39.9)	47.1 (40.7)	47.6 (40.3)
Min, Max	6.0, 212.9	6.2, 173.9	6.0, 212.9
Weekly dose of MTX at baseline, mg			
Mean (SD)	15.6 (4.5)	15.5 (4.6)	15.5 (4.6)
Min, Max	10.0, 25.0	10.0, 25.0	10.0, 25.0
CRP at baseline, mg/L			
Mean (SD)	14.6 (20.0)	12.7 (16.0)	13.7 (18.1)
Min, Max	1, 140	1, 76	1, 140
ESR (mm/h)			
Mean (SD)	46.5 (22.1)	46.4 (22.6)	46.5 (22.3)
Min, Max	6, 140	2, 137	2, 140
Swollen joint count (0-66)			
Mean (SD)	15.3 (7.4)	14.9 (7.3)	15.1 (7.4)
Min, Max	6, 43	6, 48	6, 48
Tender joint count (0-68)			
Mean (SD)	23.4 (11.9)	23.5 (12.6)	23.4 (12.2)
Min, Max	6, 66	6, 68	6, 68
Physician global assessment VAS (0-100)			
Mean (SD)	62.2 (15.1)	63.2 (14.8)	62.7 (14.9)
Min, Max	2, 94	11, 95	2, 95
Subject global assessment VAS (0-100)			
Mean (SD)	61.7 (19.0)	63.0 (17.7)	62.3 (18.3)
Min, Max	1, 97	12, 100	1, 100
DAS28 (ESR)			
Mean (SD)	6.5 (0.9)	6.5 (0.9)	6.5 (0.9)
Min, Max	3.8, 8.7	2.7, 8.4	2.7, 8.7

Source: Adapted from SB4-G31-RA 52 Week CSR Table 11-3, page 68 and 11-4, page 69
Reviewer JMP Analysis, ADSL dataset using variables RANFL, RADUR, METDUR, CRPVALBL, ACTARM
ADEF dataset using variables RANFL, ABLFL, PARAM, AVAL, ACTARM

The baseline disease characteristics for the extended population who continued in the OLE are presented in Table 9. The extended population had a somewhat shorter average duration of disease of 5.7 years, as compared to 6.1 years in the randomized population. The average

duration of MTX use was similarly less (47.6 vs. 44.9 months). The proportions of subjects who were RF positive were similar in the extended population and the randomized population, as well as between the treatment groups within each population. Measures of disease activity were lower at the baseline for the OLE, reflecting the treatment received during the double-blind period. Mean CRP and ESR at the extended baseline were slightly higher in the SB4/SB4 treatment group as compared to the EU-Enbrel/SB4 group, while tender joint count, physician global assessment, and subject global assessment were slightly higher in the EU-Enbrel/SB4 group. Mean swollen joint counts and DAS28 scores were similar between treatment groups in the OLE, consistent with the generally similar disease activity in each treatment group at the start of the OLE.

Table 9: OLE Baseline Disease Characteristics, Extended Population SB4-G31-RA OLE

Open-Label Extension	SB4/SB4 N = 126 n (%)	EU-Enbrel/SB4 N = 119 n (%)	Total N = 245 n (%)
RA duration, years			
Mean (SD)	5.7 (3.9)	5.8 (4.2)	5.7 (4.1)
Min, Max	0.5, 15.3	0.5, 14.7	0.5, 15.3
Rheumatoid factor, n (%)			
Positive	99 (78.6)	89 (74.8)	188 (76.7)
Negative	27 (21.4)	30 (25.2)	57 (23.3)
Duration of MTX use, months			
Mean (SD)	46.0 (35.6)	43.9 (39.8)	44.9 (37.7)
Min, Max	6, 176.8	5.9, 159.7	5.9, 176.8
Weekly dose of MTX at baseline, mg			
Mean (SD)	16.9 (4.9)	16.5 (4.9)	16.7 (4.9)
Min, Max	10, 25	10, 25	10, 25
CRP at Wk 52 baseline, mg/L			
Mean (SD)	6.2 (15.8)	3.8 (5.5)	5.0 (12.0)
Min, Max	1, 161	1, 42	1, 161
ESR at Wk 52, mm/h			
Mean (SD)	24.5 (18.6)	22.2 (16.2)	23.4 (17.5)
Min, Max	2, 128	2, 125	2, 128
Swollen joint count (0-66)			
Mean (SD)	2.9 (4.8)	2.7 (4.3)	2.8 (4.6)
Min, Max	0, 24	0, 28	0, 28
Tender joint count (0-68)			
Mean (SD)	5.0 (7.1)	5.5 (7.9)	5.2 (7.5)
Min, Max	0, 36	0, 60	0, 60
Physician global assessment VAS (0-100)			
Mean (SD)	16.7 (14.4)	18.7 (15.3)	17.7 (14.8)
Min, Max	0, 70	0, 74	0, 74
Subject global assessment VAS (0-100)			
Mean (SD)	24.7 (21.0)	26.8 (19.6)	25.7 (20.3)
Min, Max	0, 91	0, 83	0, 91
DAS28 (ESR)			
Mean (SD)	3.4 (1.2)	3.5 (1.1)	3.4 (1.1)
Min, Max	0.6, 6.5	0.9, 6.9	0.6, 6.9

Source: Adapted from SB4-G31-RA 100 Week CSR Table 11-3, page 52 and 11-4, page 53
Reviewer JMP analysis ADSL dataset using variables RADUR, RAFBL, CRPVA52, ACTARM

ADEF dataset using variables AVISIT, PARAM, AVAL, TRT01A

Concomitant medications
A similar proportion of subjects in the SB4 and EU-Enbrel groups were previously treated with DMARD therapy that was discontinued prior to the study (32.4% and 31.0%, respectively). The most common prior DMARD therapies were sulfasalazine (102 subjects), leflunomide (55 subjects), methotrexate (54 subjects), chloroquine (44 subjects), and hydroxychloroquine (42 subjects). Prior to the study, 17.6% of the subjects received systemically administered (oral, intramuscular, or intravenous) glucocorticoids, based on reviewer analysis. Prior DMARD use and glucocorticoid treatment by type of agent was generally balanced across the treatment groups.

During the DB period, all subjects received concomitant methotrexate as specified in the protocol. The mean weekly dose of MTX was 15.4 mg in the EU-Enbrel group and 15.5 mg in the SB4 treatment group. One subject in the EU-Enbrel treatment group received concomitant hydroxychloroquine and 2 subjects in the EU-Enbrel group received concomitant leflunomide. One subject receiving SB4 experienced an AE leading to discontinuation of breast cancer and was treated with cyclophosphamide and doxorubicin. Three subjects in the SB4 group and 1 subject in the EU-Enbrel group were treated with concomitant etanercept; all 4 subjects initiated etanercept after completing Week 52 and did not participate in the OLE.

More than half of the subjects received systemic glucocorticoids, balanced across the treatment groups (SB4: 53.5%, EU-Enbrel: 53.5%). A greater number of subjects randomized to SB4 received intraarticular steroid injections (8 subjects) as compared to those receiving EU-Enbrel (2 subjects). Three subjects, all receiving SB4, received 2 intraarticular steroid injections into contralateral joints. Additionally, 1 subject randomized to receive SB4 received an intraarticular shoulder injection with a homeopathic preparation, while 1 subject in the EU-Enbrel group received an intraarticular shoulder injection with trimecaine, an anesthetic. A similar proportion of subjects in the SB4 treatment group (66.9%) were treated with NSAIDs and COX-2 inhibitors during the DB period, as compared to the EU-Enbrel group (61.6%). The use of prohibited concomitant medications was similar between treatment groups (SB4: 4.7%, EU-Enbrel: 5.4%); the most frequently used prohibited medications were glucocorticoids, acetic acid derivatives and related substances, and other opioids.

In the OLE, 1 subject in each treatment group received concomitant sulfasalazine and 1 subject in the EU-Enbrel/SB4 group received rituximab. Similar to the overall population, approximately half of the subjects in the OLE received concomitant glucocorticoids. Four subjects in the SB4/SB4 treatment group and 2 subjects in the EU-Enbrel/SB4 group received intraarticular glucocorticoid injections. Prohibited concomitant medications during the OLE include rituximab, oral methylprednisolone, and anti-tetanus immunoglobulin received by 1 subject each.

6.1.3 Subject Disposition

There were 777 subjects screened in Study SB4-G31-RA and of these, 596 subjects were randomized, 297 subjects to EU-Enbrel and 299 subjects to SB4. Of the 181 subjects who were not randomized, the most frequent reasons for screening failures were not meeting exclusion

criteria (62.4%), not meeting inclusion criteria (22.1%), withdrawal of consent (9.9%), other (8.8%), and lost to follow-up (1.7%). Among the reasons listed under other are sponsor decision (4 subjects) and not meeting eligibility criteria (2 subjects).

Of the 596 subjects randomized, 505 (84.7%) subjects completed the double-blind portion of the study at Week 52. A greater proportion of subjects in the EU-Enbrel treatment group withdrew prior to Week 24 and prior to Week 52 (9.8% and 17.2%, respectively) as compared to the SB4 group (5.4% and 13.4%, respectively). The most frequently reported reasons for withdrawal were withdrawal of consent and adverse event which were reported by a greater proportion of subjects in the EU-Enbrel treatment group, while discontinuations due to investigator discretion were more frequently reported by subjects in the SB4 group (Table 10).

Table 10: Subject Disposition, Randomized Population SB4-G31-RA and OLE

	SB4 N = 299 n (%)	EU-Enbrel N = 297 n (%)
Completed Week 24	283 (94.6)	268 (90.2)
Withdrawal before Week 24	16 (5.4)	29 (9.8)
Reason for withdrawal		
Adverse event	8 (2.7)	14 (4.7)
Investigator discretion	2 (0.7)	1 (0.3)
Lack of efficacy	0	3 (1.0)
Protocol deviation	1 (0.3)	0
Subject lost to follow-up	0	0
Withdrew consent	5 (1.7)	11 (3.7)
Completed Week 52	259 (86.6)	246 (82.8)
Withdrawal before Week 52	40 (13.4)	51 (17.2)
Reason for withdrawal		
Adverse event	13 (4.3)	17 (5.7)
Investigator discretion	15 (5.0)	10 (3.4)
Lack of efficacy	1 (0.3)	3 (1.0)
Protocol deviation	1 (0.3)	0
Subject lost to follow-up	1 (0.3)	3 (1.0)
Withdrew consent	9 (3.0)	18 (6.1)
Open-Label Extension	SB4/SB4 N = 126 n (%)	EU-Enbrel/SB4 N = 119 n (%)
Completed Week 100	119 (94.4)	113 (95.0)
Withdrawal before Week 100	7 (5.6)	6 (5.0)
Reason for withdrawal		
Adverse event	4 (3.2)	1 (0.8)
Subject lost to follow-up	0	1 (0.8)
Withdrew consent	3 (2.4)	4 (3.4)

Source: Adapted from SB4-G31-RA 52 Week CSR, Table 10-1, page 64
Adapted from SB4-G31-RA 100 Week CSR, Table 10-1, page 48
Reviewer JMP analysis, ADSL datasets using variables CMP24FL, CMP52FL, CMP100FL, DSREAS, DSEREAS, ACTARM

Two hundred and forty-five subjects from Poland and the Czech Republic continued in the open-label extension period of the study, 119 (48.6%) subjects previously treated with EU-Enbrel who transitioned to SB4 and 126 (51.4%) subjects who continued on SB4. Of these, 232

(94.7%) subjects completed the study through Week 100. Subjects who discontinued the open-label extension did so for reasons of withdrawal of consent, adverse event, and loss to follow-up; these were generally balanced between the treatment groups with numerical differences due to small numbers of subjects.

Protocol violations
Through Week 52, there were 211 major protocol deviations reported in 157 subjects (80 randomized to SB4, 77 to EU-Enbrel). Subjects were excluded from the per-protocol sets if they had major protocol deviations that affect the efficacy assessment. Seventy-three subjects (40 SB4, 33 EU-Enbrel) were excluded from PPS1 and 78 subjects (42 SB4, 36 EU-Enbrel) were excluded from PPS2 due to major protocol deviations. As presented in Table 11, the proportions of subjects with protocol deviations were similar between treatment groups for those deviations that led to exclusion from the per-protocol sets and those that did not result in exclusion from the PPS. The proportions of subjects with major protocol deviations were also similar between treatment groups in the OLE. Overall, the patterns of subject disposition did not appear to favor or disfavor SB4.

Table 11: Summary of Major Protocol Deviations by Treatment Group, Randomized Population SB4-G31-RA and OLE

	SB4 N = 299 n (%)	EU-Enbrel N = 297 n (%)
Subjects with at least 1 major protocol deviation	80 (26.8)	77 (25.9)
Excluded from Per-protocol set 1	40 (13.4)	33 (11.1)
Concomitant medication criteria	10 (3.3)	15 (5.1)
Eligibility and entry criteria	7 (2.3)	4 (1.3)
Investigational product compliance	9 (3.0)	2 (0.7)
Study procedures criteria	15 (5.0)	15 (5.1)
Others[a]	52 (17.4)	51 (17.2)
Concomitant medication criteria	1 (0.3)	1 (0.3)
Eligibility and entry criteria	1 (0.3)	4 (1.3)
Investigational product compliance	15 (5.0)	12 (4.0)
Study procedures criteria	41 (13.7)	38 (12.8)
Excluded from Per-protocol set 2	42 (14.0)	36 (12.1)
Concomitant medication criteria	11 (3.7)	16 (5.4)
Eligibility and entry criteria	7 (2.3)	4 (1.3)
Investigational product compliance	10 (3.3)	3 (1.0)
Study procedures criteria	15 (5.0)	15 (5.1)
Others[b]	53 (17.7)	51 (17.2)
Eligibility and entry criteria	1 (0.3)	4 (1.3)
Investigational product compliance	15 (5.0)	13 (4.4)
Study procedures criteria	41 (13.7)	38 (12.8)
Open-Label Extension	SB4/SB4 N = 126 n (%)	EU-Enbrel/SB4 N = 119 n (%)
Subjects with at least 1 major protocol	8 (6.3)	8 (6.7)

deviation during OLE		
Concomitant medication criteria	0	3 (2.5)
Investigational product compliance	8 (6.3)	4 (3.4)
Study procedures criteria	0	1 (0.8)

[a] Major protocol deviations which did not lead to exclusion from PPS1
[b] Major protocol deviations which did not lead to exclusion from PPS2
Source: Adapted from SB4-G31-RA 52 Week CSR, Table 10-2, page 65 and 100 Week CSR, Table 10-2, page 49

6.1.4 Analysis of Primary Endpoint(s)

Study SB4-G31-RA met the pre-specified similarity criterion for the primary endpoint of ACR20 response at Week 24 (Table 12). As discussed above, the primary analysis specified in the protocol was the ACR20 response at Week 24 based on the Per-protocol Set 1, which included all FAS subjects who completed the Week 24 visit and had an adherence (from baseline to Week 24) within the range 80-120% of both the expected number of IP injections and the expected sum of MTX doses without any major protocol deviations that affected the efficacy assessment. As requested by the Agency at the pre-BLA meeting on 23-June-2016, the Applicant provided the primary analysis on the full analysis set and also calculated 90% CIs for the differences in ACR20 responses to control the overall type I error rate at 5%.

The ACR20 response rate at Week 24 was 73.6% for the SB4 treatment group and 71.7% for the EU-Enbrel treatment group, based on the FAS (Table 12). The 90% CI for the adjusted treatment difference fell within the protocol-specified equivalence margin of [-15%, 15%], as well as within the equivalence margin recommended by FDA to have a lower bound no greater in magnitude than -12%. The protocol-specified primary analysis on the PPS1 also fell within the specified equivalence margin. Sensitivity analyses were conducted to evaluate the effect of missing data and were consistent with the primary analysis. For further details on the statistical considerations for the analysis of the efficacy endpoints, refer to Dr. Ginto's statistical review.

Table 12: SB4-G31-RA ACR20 Response at Week 24

	SB4 n (%)	EU-Enbrel n (%)	Adjusted Difference Rate	95% Confidence Interval	90% Confidence Interval
Full Analysis Set	N=299	N=297			
Responder	220 (73.6)	213 (71.7)	1.66%	(-5.50%, 8.82%)	(-4.35%, 7.67%)
Per Protocol	N=247	N=236			
Responder	193 (78.1)	190 (80.5)	-2.37%	(-9.54%, 4.80%)	

Subjects with missing ACR20 response at Week 24 considered non-responders in FAS analysis
Source: Adapted from SB4-G31-RA 52 Week CSR Table 11-5, page 72, and Table 11-6, page 74.
Reviewer JMP analysis, ADEF dataset using variables FASFL, PPS1FL, ARM, PARAM, AVISIT, AVALC

6.1.5 Analysis of Secondary Endpoints(s)

The results of the comparative analyses of secondary endpoints also support the demonstration of similarity between SB4 and US-licensed Enbrel. Secondary endpoints included ACR50 and ACR70 responses at Weeks 24 and 52, as well as ACR20 responses at Week 52, DAS28 and EULAR responses at Weeks 24 and 52, major clinical response at Week 52, and change from baseline in mTSS at Week 52. These analyses are presented in Table 13 below. While a

numerically greater proportion of ACR20/50/70 responders is observed in the SB4 treatment group, the confidence interval for the difference rates includes 0, supporting a similar response in both treatment groups. Change from baseline values of the DAS28 at Week 24 were compared between treatment groups using the ANCOVA method. The 95% CIs at Weeks 24 and 50 were within the FDA recommended equivalence margin of [-0.5, 0.5], supporting a similar change in DAS28 between the treatment groups. Mean changes from baseline in the components of the ACR composite endpoint and the DAS28 were also similar between the treatment groups. Major clinical response, defined as an ACR70 response for 6 consecutive months, was achieved by a similar proportion of subjects in each treatment group at Week 52. EULAR good and moderate responses were also generally comparable between groups at Weeks 24 and 52. Change in mTSS, an assessment of radiographic progression of joint damage, was evaluated at Week 52. The change from baseline for each treatment group are listed in Table 13 below. The adjusted treatment difference in LSMeans for the change in mTSS at Week 52 was -0.27 (95% CI: -0.8, 0.26), supporting the similar efficacy of SB4 and EU-Enbrel.

Table 13: SB4-G31-RA Secondary Endpoints, Full Analysis Set

	SB4 (N=299)		EU-Enbrel (N=297)		Difference (95% CI)
ACR responses	n/n'	%	n/n'	%	
ACR50 Week 24	128/299	42.8	116/297	39.1	3.8 (-3.9, 11.6)
ACR70 Week 24	69/299	23.1	59/297	19.9	3.3 (-3.2, 9.7)
ACR20 Week 52	210/299	70.2	195/297	65.7	4.5 (-2.9, 11.9)
ACR50 Week 52	143/299	47.8	125/297	42.1	5.5 (-2.3, 13.3)
ACR70 Week 52	91/299	30.4	73/297	24.6	5.9 (-1.1, 12.9)
DAS28-ESR	LSM	SE	LSM	SE	
DAS28 Week 24	-2.625	0.0837	-2.553	0.0835	0.072 (-0.1, 0.3)
DAS28 Week 52	-2.974	0.0842	-2.856	0.0847	0.118 (-0.1, 0.3)
EULAR response	n/n'	%	n/n'	%	
Good Week 24	92/287	32.1	81/272	29.8	
Moderate Week 24	158/287	55.1	159/272	58.5	
Good Week 52	108/259	41.7	85/246	34.6	
Moderate Week 52	132/259	51.0	139/246	56.5	
Major Clinical Response	n/n'	%	n/n'	%	
Week 52	54/259	20.8	45/246	18.3	
Change in mTSS	Change from baseline n'=250		Change from baseline n'=228		
Week 52	0.45		0.74		

CI=Confidence interval, LSM=Least squares mean, mTSS=modified Total Sharp Score, N=Number of subjects in the per-protocol set, n=Number of responders, n'=Number of subjects with an assessment, SE=Standard error
Adapted from SB4-G31-RA 52 Week CSR Table 11-8 page 75, Table 11-11 page 77, Table 14.2-6.3 page 706, Table 14.2-5.5 pages 698-699, Table 14.2-5.6 page 700, Table 11-12 page 80

In the OLE, the proportions of subjects with an ACR20/50/70 response were similar at Week 52 (extended baseline) in the group that continued treatment with SB4 and the group that transitioned from EU-Enbrel to SB4. The ACR20/50/70 responses were similar at Weeks 76 and 100 as shown in Table 14. The mean changes from baseline in DAS28 score at Week 52 (extended baseline), Week 76, and Week 100 were also similar between the treatment groups. There were small numerical differences in proportions of EULAR good and moderate responses at extended baseline (45.6% and 48.0% in SB4/SB4, 37.8% and 54.6% in EU-Enbrel/SB4,

respectively). At Week 100, the proportion of subjects with EULAR good, moderate or no response was 48.8%, 44.6%, and 6.6%, respectively, in the SB4/SB4 treatment group and 54.8%, 34.8%, and 10.4%, respectively in the EU-Enbrel/SB4 group.

Table 14: SB4-G31-RA OLE Secondary Endpoints, Extended Population

	SB4/SB4 (N=126)		EU-Enbrel/SB4 (N=119)	
ACR responses	n/n'	%	n/n'	%
ACR20 Week 52	99/125	79.2	98/119	82.4
ACR50 Week 52	65/125	52.0	64/119	53.8
ACR70 Week 52	48/125	38.4	39/119	32.8
ACR20 Week 76	102/125	81.6	90/117	76.9
ACR50 Week 76	74/125	59.2	62/117	53.0
ACR70 Week 76	49/125	39.2	44/117	37.6
ACR20 Week 100	95/122	77.9	91/115	79.1
ACR50 Week 100	73/122	59.8	70/115	60.9
ACR70 Week 100	52/122	42.6	48/115	41.7
DAS28-ESR	Mean change from baseline		Mean change from baseline	
DAS28 Week 52	- 2.8		- 2.8	
DAS28 Week 76	- 2.9		- 2.9	
DAS28 Week 100	- 2.9		- 3.0	
Change in mTSS	Mean change from baseline n'=108		Mean change from baseline n'=104	
Week 100	0.48		1.00	

mTSS=modified Total Sharp Score, N=Number of subjects in the per-protocol set, n=Number of responders, n'=Number of subjects with an assessment
Adapted from SB4-G31-RA 100 Week CSR Table 11-5 page 56, Table 14.2-3.1 pages 144-149, Table 11-6 pages 58-59

The mean change in mTSS at Week 52 was similar between treatment arms (0.51 in the EU-Enbrel/SB4 group and 0.49 in the SB4/SB4 group). At Week 100, there was a numerically higher mean change in the EU-Enbrel/SB4 group as compared to the SB4/SB4 group; this is driven in part by 1 subject with a mean change of 45 in the EU-Enbrel/SB4 group and 1 subject with a mean change of -31 in the SB4/SB4 group. Mean change from baseline at Week 100 was 0 in both treatment groups, further supporting the demonstration of no clinically meaningful differences between SB4 and EU-Enbrel.

6.1.6 Other Endpoints

For further details on the statistical analyses, the reader is referred to the statistical review.

6.1.7 Subpopulations

For further details on the subpopulation analyses the reader is referred to the statistical review.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable to this submission.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Refer to Dr. Ginto's detailed statistical review.

6.1.10 Additional Efficacy Issues/Analyses

The Applicant's sensitivity analysis for key primary and secondary efficacy endpoints to account for missing data demonstrated results consistent with primary analysis. FDA's analysis of key primary and secondary efficacy endpoints was consistent with the Applicant's analysis. Refer to Dr. Ginto's detailed statistical review.

7 Review of Safety

Safety Summary

The submitted safety and immunogenicity data from SB4-G31-RA, supported by the data from the single-dose PK similarity study SB4-G11-NHV, are adequate to support the demonstration of no clinically meaningful differences in safety and immunogenicity between SB4 and US-licensed Enbrel. The safety database submitted for SB4 is adequate to provide a reasonable descriptive comparison between the two products. The safety risks identified are consistent with the known adverse event profile of US-licensed Enbrel. There were no notable differences between SB4 and EU-approved Enbrel in treatment-emergency adverse events (TEAEs), serious adverse events (SAEs), adverse events leading to discontinuation, or deaths between the treatment groups. No cases of drug-induced liver injury based on Hy's law criteria were reported in the SB4 clinical program. In addition, transitioning of non-treatment naïve patients, i.e., patients previously treated with EU-approved Enbrel, to SB4 does not appear to result in an increase of clinically significant adverse reactions. This would support the safety of a clinical scenario where non-treatment naïve patients undergo a single transition to SB4.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary safety data were derived from Study SB4-G31-RA, the comparative clinical study in which 596 subjects with RA were randomized to treatment with SB4 or EU-approved Enbrel. In the OLE, conducted at sites in Poland and the Czech Republic, all subjects received open-label treatment with SB4, providing an assessment of safety and immunogenicity in 119 subjects who underwent a single transition from EU-approved Enbrel to SB4 to address the safety of the clinical scenario where non-treatment naïve patients transition to SB4. The OLE also provides longer term safety and immunogenicity data for 126 subjects who continued to receive SB4 for up to 100 weeks. In addition, supportive safety and immunogenicity information was provided from the single dose PK study, Study SB4-G11-NHV, in 138 healthy subjects.

The safety database for SB4 includes 734 subjects exposed to at least one dose of study drug, of whom 509 subjects received at least one dose of SB4. Overall, the safety database is adequate to provide a reasonable comparative safety assessment and supports a determination

that there are no clinically meaningful differences between the proposed biosimilar, SB4, and the comparator product, EU-approved Enbrel.

Safety data is derived from clinical studies that included EU-approved Enbrel as a comparator product. As discussed above, Samsung Bioepis has provided robust comparative analytical data and clinical PK bridging data between US-licensed Enbrel and EU-approved Enbrel to justify the relevance of comparative data, including safety data, generated using EU-approved Enbrel to support a demonstration of the biosimilarity of SB4 to US-licensed Enbrel.

7.1.2 Categorization of Adverse Events

An AE was defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which did not necessarily have to have a causal relationship with this treatment. An AE could therefore be an unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product. Pre-existing conditions which worsened during the study were reported as AEs. AEs were classified in intensity by the Investigator into the following categories: mild (usually transient and did not interfere with subject's daily activities), moderate (low level of inconvenience or concern to the subject and could interfere with daily activities), and severe (interrupted the subject's usual daily activity).

SAE was defined as an event that resulted in death, was life-threatening (including events which put patients at risk of death at the time of the event but not events which may have caused patient death if more severe), required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, was medically important, or resulted in a congenital anomaly/birth defect.

Adverse events of special interest (AESI) included serious infection and TB. In response to an Agency request, the Applicant submitted an additional analysis of events previously associated with treatment with etanercept as described in the Warnings and Precautions section of the Enbrel USPI. The Applicant identified the associated preferred terms for the events described in the USPI based on Standardized MedDRA Queries (SMQ).

Adverse events were coded using MedDRA version 16.0.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

As discussed at the pre-BLA meeting on 26-May-2016, a pooled safety analysis of the two clinical studies was not justified due to differences in study design and population. All reported AEs are presented per individual study.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The safety population across the SB4 clinical studies consists of 596 adult male and female patients with moderately to severely active rheumatoid arthritis and 138 healthy adult subjects. Patients with RA received 50 mg SB4 or EU-approved Enbrel weekly via subcutaneous injection in combination with oral methotrexate and folic acid for up to 52 weeks in the double-blind portion of the study. Two hundred and forty-five (245) patients with RA continued to receive 50 mg SB4 SC weekly for up to an addition 48 weeks in the OLE. Healthy subjects received single doses of SB4, EU-approved Enbrel, or US-licensed Enbrel.

In Study SB4-G31-RA, the mean exposure to investigational product (IP) during the double-blind period was similar between subjects receiving SB4 (338.9 days) as compared to subjects receiving EU-approved Enbrel (323.5 days) as shown in Table 15. Compliance with IP was high in both treatment groups. The mean total number of IP doses administered and mean cumulative doses in the SB4 and EU-approved Enbrel treatment groups were similar, with a numerically greater mean number of doses administered and mean cumulative dose in the SB4 treatment group. Cumulative doses of methotrexate at weeks 24 and 52 were also similar, but numerically higher in the SB4 treatment group.

Table 15: SB4-G31-RA Exposure, Double-Blind period

	SB4 N=299	EU-Enbrel N=297
Exposure (days)		
Mean (SD)	338.9 (58.0)	323.5 (87.5)
Min, Max	34, 371	14, 371
Mean Cumulative dose IP (SD), mg	2430.3 (470.5)	2317.2 (662.7)
Mean IP doses administered (SD), n		
Week 24	24.1 (3.0)	23.2 (5.0)
Week 52	48.6 (9.4)	46.3 (13.3)
Mean Cumulative dose MTX (SD), mg		
Week 24	372.9 (115.5)	359.8 (128.1)
Week 52	758.5 (264.3)	725.4 (296.1)

Source: Adapted from SB4-G31-RA 52 Week CSR Table 12-1, page 90; Table 14-3-1.2, page 741
Reviewer JMP analysis, ADSL dataset, variables RANFL, ACTARM, EXDAYS, NUMIP24, NUMIP52, CMPIP24, CUMIP, CUMMTX24, CUMMTX52

In the OLE, the mean exposure to IP was similar between subjects who continued on SB4 (685.2 days) and subjects who transitioned from EU-approved Enbrel to SB4 (682.9 days). The mean cumulative dose of IP was similar between treatment groups (4866.7 mg in the SB4/SB4 group and 4870.6 mg in the EU-Enbrel/SB4 group), as was the mean cumulative dose of IP after Week 52 (2302.0 mg and 2292.4 mg, respectively), based on reviewer analysis. The exposure to MTX was also similar between treatment groups in the OLE. The mean cumulative dose of MTX through Week 52 in the subjects who entered the OLE was 874.5 mg for the SB4/SB4 group and 859.0 mg for the EU-Enbrel/SB4 group. The mean cumulative MTX dose through Week 100 was 1639.5 mg and 1604.3 mg, respectively.

In Study SB4-G11-NHV, 138 healthy subjects received single doses of IP as shown in Table 16. One hundred and thirty-two (95.7%) subjects received two doses of IP and completed the study.

Table 16: SB4-G11-NHV Exposure, by Study Part

Subjects who received single doses of:	Part A	Part B	Part C
SB4, N	46	45	
EU-approved Enbrel, N	45		45
US-licensed Enbrel, N		46	43

Source: Reviewer JMP analysis, ADSL dataset, variables RANDFL, ARM, TRT01A, TRT02A

The overall exposure of subjects was balanced between the treatment arms throughout the controlled and extension studies.

7.2.2 Explorations for Dose Response

Study SB4-G31-RA studied a single dose regimen of etanercept 50 mg subcutaneously weekly. This is the approved dose of Enbrel for treatment of RA. Dose-exploration studies were not conducted or required for this application.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable to the current BLA.

7.2.4 Routine Clinical Testing

Routine clinical testing included assessment of ECGs and clinical laboratory studies, including clinical chemistry, hematology, inflammatory markers, serology, and urinalysis, as presented in the schedule of assessments in Appendix 1 and Appendix 2.

7.2.5 Metabolic, Clearance, and Interaction Workup

No special metabolic, clearance and interaction workup studies were conducted for this application. For further details, please refer to Section 4.4 Clinical Pharmacology.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

SB4 is a proposed biosimilar to US-licensed Enbrel. The safety profile of SB4 was assessed in the context of the known adverse event profile of US-licensed Enbrel, as well as other DMARDs and biologics.

7.3 Major Safety Results

A summary of AEs across the controlled studies is found in Table 17. No new safety signals were identified in the SB4 treatment arm compared with the known adverse event profile of etanercept. Three deaths occurred in subjects who received SB4 in Study SB4-G31-RA, 2 due to malignancy and one due to cardiopulmonary failure. There were no other deaths in the clinical program. Overall, there were no major differences in AEs, SAEs, and AEs leading to discontinuation between the treatment groups.

Table 17: Summary of TEAEs: Controlled Studies

	Rheumatoid Arthritis Study SB4-G31-RA Double-blind Period		Healthy Subjects Study SB4-G11-NHV		
Subjects with ≥ 1:	SB4 N=299	EU-Enbrel N=297	US-Enbrel N=89	EU-Enbrel N=90	SB4 N=91
Deaths	2 (0.7)	0	0	0	0
SAEs, n (%)	18 (6.0)	15 (5.1)	0	0	0
TEAE leading to IP discontinuation, n (%)	16 (5.4)	20 (6.7)	2 (2.2)	2 (2.2)	1 (1.1)
TEAEs, n (%)	175 (58.5)	179 (60.3)	34 (38.2)	33 (36.7)	41 (45.1)
Severe TEAEs, n (%)	14 (4.7)	11 (3.7)	1 (1.1)	1 (1.1)	0
AESI, n (%)	1 (0.3)	5 (1.7)	-[a]	-[a]	-[a]

[a] AESI were not defined for Study SB4-G11-NHV
Source: Adapted from SB4-G31-RA 52 Week CSR Table 14.3.1-1.1, page 1087
Reviewer JMP analysis, ADAE dataset, variables SAFFL, TRTEMFL, ACTARM, AESDTH, AESER, AESEV, AEACN

7.3.1 Deaths

There were 2 deaths reported in subjects treated with SB4 during the double-blind portion of SB4-G31-RA. One death was due to gastric adenocarcinoma and one death was due to cardiopulmonary failure. The death due to gastric adenocarcinoma occurred in a 63 year old female who experienced cardiopulmonary arrest in setting of hospitalization complicated by ileus, deep vein thrombosis, peritoneal carcinomatosis, and wound dehiscence with surgical repair. The death due to cardiopulmonary failure occurred in a 75 year old male with a history of hypertension who died during sleep; autopsy revealed cardiorespiratory failure, heart hypertrophy, and general late atherosclerosis. Neither death was determined to be related to the IP by the Investigator.

In the OLE period, there was 1 subject treated with SB4 throughout both periods who died of metastatic hepatic cancer. The event of metastatic hepatic cancer was determined to be related to IP.

There were no deaths reported in the healthy subjects in Study SB4-G11-NHV.

Deaths observed in the SB4 clinical program were few and not clustered by cause of death. Based on review of the submitted narratives, the subjects who died due to gastric adenocarcinoma and cardiopulmonary failure had medical comorbidities that may have

increased their risk of death. These findings support the similar safety profiles between EU-approved Enbrel and SB4.

7.3.2 Nonfatal Serious Adverse Events

Study SB4-G31-RA
Thirty-three (33) subjects reported 38 treatment emergent SAEs as displayed in Table 18. Overall, SAEs were balanced between treatment groups, occurring in 6.0% of the subjects treated with SB4 and 5.1% of the subjects treated with EU-approved Enbrel. Treatment emergent SAEs that occurred in greater than one subject included cellulitis, which occurred in 2 subjects treated with EU-approved Enbrel, and rheumatoid arthritis, which occurred in 1 subject in each treatment group. All other treatment emergent SAEs were singular events by preferred term. A greater proportion of subjects reported serious infections and events within the gastrointestinal disorders SOC in the EU-approved Enbrel treatment group, while a greater proportion of subjects in the SB4 group reported events within the hepatobiliary disorders, cardiac disorders, neoplasms benign, malignant, and unspecified, and reproductive system and breast disorders SOCs; however, differences were due to small numbers of subjects.

Table 18: Treatment Emergent SAEs, Safety Population Study SB4-G31-RA

System organ class Preferred term	SB4 N=299 n (%)	EU-Enbrel N=297 n (%)
Number of subjects with TE SAEs	**18 (6.0)**	**15 (5.1)**
Infections And Infestations	**1 (0.3)**	**5 (1.7)**
Cellulitis	0	2 (0.7)
Appendicitis	0	1 (0.3)
Erysipelas	0	1 (0.3)
Liver Abscess	1 (0.3)	0
Peritonitis	1 (0.3)	0
Pneumonia	0	1 (0.3)
Hepatobiliary Disorders	**4 (1.3)**	**0**
Bile Duct Stone	1 (0.3)	0
Cholangitis	1 (0.3)	0
Cholecystitis	1 (0.3)	0
Cholelithiasis	1 (0.3)	0
Gallbladder Perforation	1 (0.3)	0
Cardiac Disorders	**3 (1.0)**	**1 (0.3)**
Acute Myocardial Infarction	1 (0.3)	0
Atrial Fibrillation	1 (0.3)	0
Cardiopulmonary Failure	1 (0.3)	0
Coronary Artery Disease	0	1 (0.3)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	**3 (1.0)**	**1 (0.3)**
Adenocarcinoma Gastric	1 (0.3)	0
Breast Cancer	1 (0.3)	0
Invasive Ductal Breast Carcinoma	0	1 (0.3)
Lung Cancer Metastatic	1 (0.3)	0
Gastrointestinal Disorders	**0**	**3 (1.0)**
Enterocolitis	0	1 (0.3)
Gastritis	0	1 (0.3)

Gastroesophageal Reflux Disease	0	1 (0.3)
Musculoskeletal And Connective Tissue Disorders	**2 (0.7)**	**1 (0.3)**
Rheumatoid Arthritis	1 (0.3)	1 (0.3)
Still's Disease Adult Onset	1 (0.3)	0
Reproductive System And Breast Disorders	**3 (1.0)**	**0**
Ovarian Cyst	1 (0.3)	0
Uterine Polyp	1 (0.3)	0
Vaginal Prolapse	1 (0.3)	0
Blood And Lymphatic System Disorders	**0**	**1 (0.3)**
Neutropenia	0	1 (0.3)
Eye Disorders	0	**1 (0.3)**
Chorioretinopathy	0	1 (0.3)
General Disorders And Administration Site Conditions	**1 (0.3)**	**0**
Device Failure	1 (0.3)	0
Injury, Poisoning And Procedural Complications	**0**	**1 (0.3)**
Femoral Neck Fracture	0	1 (0.3)
Nervous System Disorders	**1 (0.3)**	**0**
Syncope	1 (0.3)	0
Skin And Subcutaneous Tissue Disorders	**1 (0.3)**	**0**
Psoriasis	1 (0.3)	0
Vascular Disorders	**0**	**1 (0.3)**
Hypertensive Crisis	0	1 (0.3)

Source: Reviewer JMP analysis ADAE dataset using variables TRTEMFL, AESER, AESOC, AEDECOD, ACTARM, USUBJ
Adapted from SB4-G31-RA 52 Week CSR Table 14.3.1-1.5, pages 1293-1295

In the OLE, 8 subjects reported SAEs, 6 subjects (4.8%) who received SB4 in the double-blind portion of the study and continued on SB4 in the OLE and 2 subjects (1.7%) who transitioned from EU-approved Enbrel to SB4. All SAEs were singular events. SAEs reported in the group that continued on SB4 include cervical polyp, deep vein thrombosis, hepatic cancer, osteoarthritis, pneumonia, and renal oncocytoma. SAEs reported in the group that transitioned from EU-approved Enbrel to SB4 included abdominal pain and bronchitis.

While a numerically greater proportion of subjects in the SB4 treatment group experienced treatment emergent SAEs during the double-blind and OLE periods, differences between treatment groups were due to differences in small numbers of subjects (3 subjects in the double-blind period and 4 in the OLE). No new safety signals were identified. These findings support the similar safety profiles between EU-approved Enbrel and SB4.

Study SB4-G11-NHV
There were no SAEs reported in the healthy subjects in Study SB4-G11-NHV.

7.3.3 Dropouts and/or Discontinuations

Thirty-six (36) subjects reported 50 TEAEs leading to discontinuation of study drug; these were generally balanced between treatment groups as shown in Table 19. Events that occurred in more than one subject included injection site erythema, injection site hypersensitivity, rheumatoid arthritis, breast cancer/invasive ductal breast carcinoma, neutropenia, and pneumonia. Other events occurred in single subjects.

Table 19: TEAEs leading to IP discontinuation, Safety Population SB4-G31-RA

System organ class Preferred term	SB4 N=299 n (%)	EU-Enbrel N=297 n (%)
Number of subjects with TEAEs leading to discontinuation of IP	**16 (5.4)**	**20 (6.7)**
General Disorders And Administration Site Conditions	**2 (0.7)**	**7 (2.4)**
Injection Site Erythema	1 (0.3)	4 (1.3)
Injection Site Hypersensitivity	1 (0.3)	1 (0.3)
Injection Site Dermatitis	0	1 (0.3)
Injection Site Reaction	0	1 (0.3)
Musculoskeletal And Connective Tissue Disorders	**3 (1.0)**	**5 (1.7)**
Rheumatoid Arthritis	2 (0.7)	5 (1.7)
Still's Disease Adult Onset	1 (0.3)	0
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	**4 (1.3)**	**1 (0.3)**
Basal Cell Carcinoma	1 (0.3)	0
Breast Cancer	1 (0.3)	0
Hemangioma of Liver	1 (0.3)	0
Invasive Ductal Breast Carcinoma	0	1 (0.3)
Lung Cancer Metastatic	1 (0.3)	0
Skin And Subcutaneous Tissue Disorders	**1 (0.3)**	**2 (0.7)**
Alopecia	0	1 (0.3)
Dry Skin	0	1 (0.3)
Erythema	0	1 (0.3)
Pruritus	0	1 (0.3)
Rash Papular	1 (0.3)	0
Infections And Infestations	**2 (0.7)**	**1 (0.3)**
Pneumonia	1 (0.3)	1 (0.3)
Liver Abscess	1 (0.3)	0
Peritonitis	1 (0.3)	0
Investigations	**1 (0.3)**	**2 (0.7)**
Lymphocyte Count Decreased	0	1 (0.3)
Neutrophil Count Decreased	1 (0.3)	0
Transaminases Increased	0	1 (0.3)
Blood And Lymphatic System Disorders	**1 (0.3)**	**1 (0.3)**
Neutropenia	1 (0.3)	1 (0.3)
Leukopenia	1 (0.3)	0
Thrombocytopenia	1 (0.3)	0
Hepatobiliary Disorders	**2 (0.7)**	**0**
Cholangitis	1 (0.3)	0
Cholecystitis	1 (0.3)	0
Cholelithiasis	1 (0.3)	0
Gallbladder Perforation	1 (0.3)	0
Cardiac Disorders	**2 (0.7)**	**0**
Acute Myocardial Infarction	1 (0.3)	0
Cardiopulmonary Failure	1 (0.3)	0
Gastrointestinal Disorders	**0**	**2 (0.7)**
Abdominal Pain	0	1 (0.3)
Gastric Ulcer	0	1 (0.3)
Reproductive System And Breast Disorders	**1 (0.3)**	**1 (0.3)**
Breast Induration	0	1 (0.3)

Breast Mass	1 (0.3)	0
Eye Disorders	0	**1 (0.3)**
Chorioretinopathy	0	1 (0.3)
Injury, Poisoning And Procedural Complications	**0**	**1 (0.3)**
Femoral Neck Fracture	0	1 (0.3)

Source: Reviewer JMP analysis ADAE dataset using variables AEACN 'Drug Withdrawn', AESOC, AEDECOD, TRT01A, USUBJ
Adapted from SB4-G31-RA 52 Week CSR Table 14.3.1-1.7 pages 1297-1299

Treatment was interrupted due to TEAEs in 64 subjects, generally balanced between the treatment groups (30 subjects in the EU-Enbrel group, 34 subjects in the SB4 treatment group). The most frequently reported AEs leading to study drug interruptions were upper respiratory tract infection (8 SB4, 4 EU-Enbrel), bronchitis (4 SB4, 3 EU-Enbrel), ALT increased (4 SB4, 2 EU-Enbrel), urinary tract infection (3 SB4, 3 EU-Enbrel), nasopharyngitis (2 SB4, 3 EU-Enbrel), pharyngitis (1 SB4, 2 EU-Enbrel), and viral infection (3 SB4). Other events by PT were reported in 2 or fewer subjects. TEAEs leading to study treatment interruption were generally similar in frequency and types of events reported between treatment groups.

In the OLE, 6 subjects experienced 8 AEs leading to discontinuation of IP. Four subjects who continued on SB4 in the OLE experienced events of hepatic cancer (1), renal oncocytoma (1), drug intolerance (1), and rash and peripheral edema (1), while 2 subjects who underwent a single transition from EU-approved Enbrel to SB4 in the OLE reported congestive cardiac failure (1), and oral candidiasis and thrombocytopenia (1). All events were singular by preferred term. Treatment was interrupted due to AEs for 34 subjects in the OLE (20 SB4/SB4, 14 EU-Enbrel/SB4). The most frequently reported AEs leading to treatment interruption were within the Infections and Infestations SOC. TEAEs leading to study treatment discontinuation and interruption in the OLE were generally similar in frequency and types of events reported between treatment groups.

Study SB4-G11-NHV
In Study SB4-G11-NHV, 5 subjects discontinued treatment due to AEs. AEs leading to discontinuation occurred following treatment with US-licensed Enbrel in 2 subjects, EU-approved Enbrel in 2 subjects, and SB4 in 1 subject. All AEs leading to discontinuation were non-serious. One subject in each treatment group experienced AEs within the Infections and Infestations SOC (oral herpes, nasopharyngitis, and tooth abscess). Other AEs leading to discontinuation were ligament rupture (US-Enbrel) and ALT increased (EU-Enbrel). All AEs leading to discontinuation were singular by preferred term.

AEs leading to treatment discontinuation and interruption were consistent with the enrolled population of subjects with rheumatoid arthritis, as well as the known safety profile of etanercept. These findings support the similar safety profiles between US-licensed Enbrel and SB4.

7.3.4 Significant Adverse Events

Protocol specified AESI included tuberculosis and serious infections in SB4-G31-RA. Latent TB was reported in 24 subjects, 11 (3.7%) subjects randomized to SB4 and 13 (4.4%) subjects randomized to EU-approved Enbrel. None of the events of latent TB were treatment-emergent and there were no reported events of active tuberculosis.

Serious events within the Infections and Infestations SOC were reported by 6 subjects (1 SB4, 5 EU-Enbrel) during the DB period. Additionally, 1 subject each experienced serious events of cholangitis and enterocolitis; these were included in the reviewer analysis of serious infections which identified 2 (0.7%) subjects in the SB4 treatment group and 6 (2.0%) subjects in the EU-approved Enbrel group with reported serious infection. Cellulitis was reported by 2 subjects receiving EU-approved Enbrel. Other events were singular and included enterocolitis, erysipelas, appendicitis, and pneumonia (1 subject each in EU-approved Enbrel group), and cholangitis (1 subject on SB4), and liver abscess and peritonitis (1 subject on SB4).

In the OLE, there were 3 AESI reported in 2 (0.8%) subjects. One (0.8%) subject in the EU-Enbrel/SB4 treatment group reported 2 non-concurrent events (a serious event of bronchitis and a non-serious event of herpes zoster) and 1 (0.8%) subject in the SB4/SB4 group reported pneumonia.

There were no specified AESI for SB4-G11-NHV.

7.3.5 Submission Specific Primary Safety Concerns

In response to an Agency information request dated 19June2017, the Applicant provided data for events previously associated with treatment with etanercept and described in the Warnings and Precautions section of the Enbrel USPI. The Applicant investigated events with preferred terms derived from standardized MedDRA Queries. The FDA clinical reviewer conducted additional analyses to evaluate these events, as presented in Table 20 and discussed below.

Table 20: Treatment-Emergent AEs of Interest, Safety Population SB4-G31-RA

	Double-blind period		OLE[1]	
Subjects with ≥ 1:	SB4 N=299 n (%)	EU-Enbrel N=297 n (%)	SB4/SB4 N=126 n (%)	EU-Enbrel/SB4 N=119 n (%)
Opportunistic Infections[2]	3 (1.0)	1 (0.3)	0	2 (1.7)
Malignancies	4 (1.3)	1 (0.3)	1 (0.8)	0
Congestive Heart Failure	1 (0.3)	2 (0.7)	0	2 (1.7)
Cytopenias	23 (7.7)	20 (6.7)	3 (2.4)	2 (1.7)
Leukopenia/WBC Decreased	8 (2.7)	4 (1.3)	1 (0.8)	1 (0.8)
Lymphopenia/Lymphocyte Count Decreased	6 (2.0)	10 3.4)	1 (0.8)	0
Neutropenia/Neutrophil Count Decreased	6 (2.0)	6 (2.0)	1 (0.8)	0
Anemia[3]/Hemoglobin Decreased	7 (2.3)	3 (1.0)	0	0
Thrombocytopenia/Platelet Count Decreased	3 (1.0)	1 (0.3)	1 (0.8)	1 (0.8)
Demyelinating Disorders	0	0	1 (0.8)	0
Anaphylaxis/Hypersensitivity	0/0	0/1 (0.3)	0/1 (0.8)	0/0
Injection Site Reactions	11 (3.7)	52 (17.5)	0	0

[1] Treatment-Emergent in Part 2
[2] Herpes zoster
[3] Includes anemia of chronic disease
Source: Reviewer JMP analysis using ADAE dataset, variables TRTEMFL, TRTEMFL2, PERIOD, AESOC, AEDECOD, ACTARM, USUBJ

Subjects reporting opportunistic infections were balanced between the groups. Herpes zoster was the only reported opportunistic infection, based on reviewer analysis of PTs. Four subjects (SB4: 3, EU-Enbrel: 1) reported events of herpes zoster through the randomized period, while 2 subjects in the EU-Enbrel/SB4 treatment group reported herpes zoster in the OLE. The Applicant's SMQ analysis included infections that may not be opportunistic, such as nail candida, onychomycosis, and vulvovaginal candidiasis, however assessment via SMQ analysis did not alter the overall conclusions that opportunistic infections were generally similar during the double-blind period.

Malignancies occurred in 4 (1.3%) subjects receiving SB4 (gastric adenocarcinoma, breast cancer, metastatic lung cancer, and basal cell carcinoma) and 1 (0.3%) subject on EU-Enbrel (invasive ductal breast carcinoma). In the OLE, there was 1 (0.8%) subject in the SB4/SB4 group with hepatic cancer. There was no clustering by type of malignancy and the incidence of malignancies was low.

Congestive heart failure was reported by 1 (0.3%) subject in each treatment group (PTs cardiopulmonary failure and cardiac failure congestive), and, additionally, 1 (0.3%) subject in the EU-approved Enbrel group experienced cardiovascular insufficiency (reported term circulatory insufficiency). The latter subject was not included in the Applicant analysis. In the OLE, 2 (1.7%) subjects in the EU-Enbrel/SB4 arm experienced heart failure.

Treatment-emergent AEs of cytopenias were reported by a similar proportion of subjects in each treatment group (SB4: 23 (7.7%), EU-Enbrel: 20 (6.7%)), based on reviewer analysis which included anemia in the analysis. Lymphopenia/lymphocyte count decreased was the most commonly reported cytopenia (SB4: 6 (2.0%), EU-Enbrel: 10 (3.4%)). Numerical differences between treatment groups were observed for leukopenia/WBC decreased (SB4: 8 (2.7%), EU-Enbrel: 4 (1.3%)) and thrombocytopenia/platelet count decreased (SB4: 3 (1.0%), EU-Enbrel: 1 (0.3%)), and anemia/anemia of chronic disease/hemoglobin decreased (SB4: 7 (2.3%), EU-Enbrel: 3 (1.0%)), although differences were small. Neutropenia/neutrophil count decreased was reported by 6 (2.0%) subjects in each treatment group. In the OLE, treatment-emergent cytopenias were reported by 2 (1.7%) subjects in the EU-Enbrel/SB4 group and 3 (2.4%) subjects in the SB4/SB4 group, based on reviewer analysis. One subject in each group reported thrombocytopenia/platelet count decreased, while decreases in white blood cells (lymphocyte, neutrophil, leukopenia, white blood cells) were reported by 1 (0.8%) subject in the EU-Enbrel/SB4 group and 2 (1.6%) subjects in the SB4/SB4 group. Overall, AEs of cytopenias were similar in type and frequency across the treatment groups in the double-blind and OLE periods.

There were no events of demyelinating disorders in the double-blind period based on reviewer analysis. In the OLE, SMQ analysis identified 1 event of trigeminal neuralgia in a subject who continued on SB4. There were no cases of lupus-like syndromes or autoimmune hepatitis reported in Study SB4-G31-RA.

There were no cases of anaphylaxis as retrospectively assessed by NIAID/FAAN criteria up to Week 52 or in the OLE. Two subjects receiving SB4 experienced 3 non-serious events of eyelid edema which resolved without intervention. One of these subjects had cough (not concurrent with eyelid edema) and one subject had sneezing (concurrent) and rash (not concurrent). In the

EU-Enbrel group, 1 subject had cough and erythema (not concurrent). There were 11 events of injection site hypersensitivity reported in 3 subjects (SB4: 1, EU-Enbrel: 2); none of the events were serious. There was a single event of hypersensitivity in a subject receiving EU-approved Enbrel; the associated reported term was propolis allergy and the event was not considered related to the IP. In the OLE, there was 1 subject (SB4/SB4) who experienced drug hypersensitivity associated with use of sertraline. There were no AEs meeting criteria for anaphylaxis. Events of injection site hypersensitivity were similar between treatment groups and AEs of hypersensitivity were attributed to other exposures (propolis and sertraline).

Injection site reactions, where high-level group term (HLGT) of administration site reaction was considered injection site reaction, were reported by a greater proportion of subjects in the EU-approved Enbrel treatment group (17.5%) as compared to the SB4 group (3.7%) during the double-blind period. There were no ISR reported during the OLE period. None of the ISR were serious AEs. The most frequently reported ISR by PT was injection site erythema. While the numerical differences in observed ISR could be attributable to differences in formulations between SB4 and EU-Enbrel, these are not considered clinically meaningful and do not preclude a demonstration of no clinically meaningful differences between SB4 and US-licensed Enbrel.

Subjects with adverse events of interest as defined by events described in the Warnings and Precautions section of the Enbrel USPI were generally similar between the treatment groups with the exception of injection site reactions, which were more frequently reported by subjects receiving EU-approved Enbrel during the double-blind period.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Treatment emergent adverse events occurred in a similar proportion of subjects in each treatment group (SB4: 58.5%; EU-Enbrel: 60.3%) during the double-blind period as presented in Table 21. TEAEs within the Infections and Infestations SOC were the most frequently reported AEs and were reported by similar proportions of subjects in the SB4 and EU-approved Enbrel treatment groups. AEs within the Infections and Infestations SOC were generally balanced between the treatment groups by preferred term. Subjects receiving EU-approved Enbrel more frequently reported TEAEs within the General Disorders and Administration Site Conditions SOC (20.5%) as compared to subjects receiving SB4 (9.4%). Injection site erythema was the most frequently reported TEAE by PT within this SOC and was reported by 11.1% of subjects receiving EU-approved Enbrel as compared to 2.0% of those receiving SB4.

AEs events within the Hepatobiliary Disorders SOC were reported by 11 subjects receiving SB4 and not reported by any subjects receiving EU-approved Enbrel; the most frequently reported AE by preferred term was cholelithiasis (4 (1.3%) subjects), while 3 (1.0%) subjects reported cholecystitis or cholecystitis chronic, and 3 (1.0%) subjects reported liver disorder. Other reported PTs included bile duct stone, biliary colic, cholangitis, gallbladder perforation and transaminasemia in 1 (0.3%) subject each. In the Investigations SOC, similar proportions of

subjects overall experienced TEAEs of abnormal liver tests as determined by the following PTs: alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, hepatic enzyme increased, elevated alkaline phosphatase, and transaminases increased. Five subjects with AEs within the Hepatobiliary Disorders SOC, including 3 subjects with cholecystitis, 1 subject with biliary colic, and 1 subject with liver disorder, also reported AEs of abnormal liver tests. Analysis of the 11 subjects with AEs within the Hepatobiliary Disorders SOC shows that these subjects had a higher mean BMI (27.8 kg/m^2) and mean weight (76.5 kg) and were of older mean age (54 years) at baseline as compared to the overall population, however, the 5 subjects who experienced AEs of cholelithiasis and biliary duct stone had similar baseline BMI and weight as the overall population. Conclusions are limited by the small number of subjects who experienced hepatobiliary AEs. Hepatobiliary AEs were generally distributed across multiple PTs. Mean exposures to IP and MTX were lower in the subjects who experienced AEs within the Hepatobiliary SOC than in the overall group, supporting the conclusion that these events are not drug-related.

The proportions of subjects reporting other TEAEs were similar by both SOC and PT between the SB4 and EU-approved Enbrel treatment groups.

Table 21: Treatment-Emergent Adverse Events (≥ 2% incidence), Safety Population SB4-G31-RA

System organ class Preferred term	SB4 N=299 n (%)	EU-Enbrel N=297 n (%)
Number of subjects with TEAEs	**175 (58.5)**	**179 (60.3)**
Infections and Infestations	**85 (28.4)**	**76 (25.6)**
Upper Respiratory Tract Infection/Viral Upper Respiratory Tract Infection	26 (8.7)	19 (6.4)
Nasopharyngitis	15 (5.0)	16 (5.4)
Pharyngitis/Pharyngitis Bacterial	6 (2.0)	8 (2.7)
Bronchitis	6 (2.0)	6 (2.0)
Urinary Tract Infection	5 (1.7)	7 (2.4)
Viral Infection	7 (2.3)	5 (1.7)
Rhinitis	6 (2.0)	4 (1.3)
General Disorders and Administration Site Conditions	**28 (9.4)**	**61 (20.5)**
Injection Site Erythema	6 (2.0)	33 (11.1)
Injection Site Reaction	1 (0.3)	8 (2.7)
Injection Site Rash	2 (0.7)	6 (2.0)
Investigations	**41 (13.7)**	**38 (12.8)**
Alanine Aminotransferase Increased	18 (6.0)	17 (5.7)
Aspartate Aminotransferase Increased	8 (2.7)	9 (3.0)
Lymphocyte Count Decreased	4 (1.3)	6 (2.0)
Musculoskeletal and Connective Tissue Disorders	**30 (10.0)**	**29 (9.8)**
Rheumatoid Arthritis	9 (3.0)	10 (3.4)
Arthralgia/Arthritis	6 (2.0)	5 (1.7)
Gastrointestinal Disorders	**22 (7.4)**	**30 (10.1)**
Diarrhea	5 (1.7)	7 (2.4)
Abdominal Pain Upper/Abdominal Pain	6 (2.0)	7 (2.4)
Nervous System Disorders	**23 (7.7)**	**22 (7.4)**
Headache	13 (4.3)	8 (2.7)

Dizziness	2 (0.7)	7 (2.4)
Skin and Subcutaneous Tissue Disorders	**25 (8.4)**	**26 (8.8)**
Erythema	2 (0.7)	10 (3.4)
Rash	6 (2.0)	4 (1.3)
Blood and Lymphatic System Disorders	**15 (5.0)**	**15 (5.1)**
Leukopenia	6 (2.0)	3 (1.0)
Respiratory, Thoracic and Mediastinal Disorders	**13 (4.3)**	**15 (5.1)**
Cough	4 (1.3)	10 (3.4)
Vascular Disorders	**14 (4.7)**	**12 (4.0)**
Hypertension	11 (3.7)	11 (3.7)
Injury, Poisoning and Procedural Complications	**9 (3.0)**	**9 (3.0)**
Hepatobiliary Disorders	**11 (3.7)**	**0**
Reproductive System and Breast Disorders	**9 (3.0)**	**2 (0.7)**
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	**8 (2.7)**	**5 (1.7)**
Cardiac Disorders	**5 (1.7)**	**6 (2.0)**
Eye Disorders	**6 (2.0)**	**3 (1.0)**
Psychiatric Disorders	**6 (2.0)**	**2 (0.7)**
Metabolism and Nutrition Disorders	**1 (0.3)**	**6 (2.0)**

Source: Reviewer JMP analysis ADAE dataset using variables TRTEMFL, AESOC, AEDECOD, ACTARM, USUBJ

The majority of TEAEs were mild or moderate in intensity. Severe TEAEs were reported by 14 (4.7%) subjects in the SB4 treatment group and 11 (3.7%) subjects in the EU-approved Enbrel group. The most frequently reported severe TEAEs were alanine aminotransferase increased (SB4: 2 (0.7%), Enbrel: 1 (0.3%)) and rheumatoid arthritis (SB4: 1 (0.3%), Enbrel: 2 (0.7%)). Gamma-glutamyltransferase increased and arthralgia were each reported by 2 (0.7%) subjects in the SB4 group, while alopecia and aspartate aminotransferase increased were reported by 1 (0.3%) subject in each treatment group. Other severe TEAEs were singular by PT. The frequencies and types of severe TEAEs were balanced between the treatment groups.

In the OLE, TEAEs were reported by 118 subjects, balanced between the treatment groups (SB4/SB4: 47.6%, EU-Enbrel/SB4: 48.7%). The most frequently reported TEAEs were upper respiratory tract infection (SB4/SB4: 7.9%, EU-Enbrel/SB4: 7.6%), pharyngitis (SB4/SB4: 7.1%, EU-Enbrel/SB4: 4.2%), rheumatoid arthritis (SB4/SB4: 5.6%, EU-Enbrel/SB4: 2.5%), bronchitis (SB4/SB4: 4.8%, EU-Enbrel/SB4: 5.9%), and nasopharyngitis (SB4/SB4: 4.8%, EU-Enbrel/SB4: 4.2%). TEAEs reported with greater frequency in the SB4/SB4 group with a difference of ≥ 3 subjects as compared to the EU-Enbrel/SB4 group were pharyngitis, laryngitis, viral infection, and rheumatoid arthritis, while dyspepsia and hypertension were more frequently reported by subjects in the EU-Enbrel/SB4 group. Severe TEAEs were reported by 4 (3.1) subjects in the SB4/SB4 treatment group and included hepatic cancer, pneumonia, osteoarthritis, and deep vein thrombosis. There were no AEs within the Hepatobiliary Disorders SOC. Overall, the frequencies and types of TEAEs reported in the OLE were similar between treatment arms. There was no increase in TEAEs in the subjects that transitioned from EU-approved Enbrel to SB4 as compared to the subjects who remained on SB4.

Study SB4-G11-NHV
In Study SB4-G11-NHV, 79 subjects experienced 167 TEAEs. There were 2 reported severe AEs including ligament rupture (US-licensed Enbrel) and diarrhea (EU-approved Enbrel). A numerically greater proportion of subjects reported TEAEs while receiving SB4 (45.1%) as compared to during the US-licensed Enbrel (38.2%) or EU-approved Enbrel treatment (36.7%)

periods. The most frequently reported TEAEs were headache (7 (7.9%) US-licensed Enbrel, 6 (6.7%) EU approved-Enbrel, and 7 (7.7%) SB4), nasopharyngitis (3 (3.4%) US-licensed Enbrel, 4 (4.4%) EU approved-Enbrel, and 7 (7.7%) SB4), and injection site reactions. Injection site reactions were reported by 14 subjects; 4 (4.4%) subjects experienced ISR while receiving EU-approved Enbrel, 5 (5.5%) while receiving SB4, and 6 (6.7%) while receiving US-licensed Enbrel. One subject reported ISR with more than one IP. All ISR were non-serious and all were mild except for one moderate intensity ISR. There were no new safety signals identified in Study SB4-G11-NHV.

7.4.2 Laboratory Findings

Clinical chemistry, hematology, and urinalysis assessments, as well as CRP and ESR measurements, were performed at Screening, Weeks 2, 4, 8, 12, 16, 24, 32, 40, and 52 in the controlled portion of SB4-G31-RA.

Hematology
There were no notable differences in mean and median values for hematology parameters (hemoglobin, hematocrit, platelets, leukocytes, neutrophils, lymphocytes, eosinophils, mean corpuscular volume) between the SB4 and EU-approved Enbrel groups. The most frequently observed post-baseline significant abnormalities in hematology parameters to Week 52 were increased neutrophil count (> 15 x 10^9/L) in 5 (1.7%) SB4-treated subjects and 2 (0.7%) EU-Enbrel treated subjects, and low neutrophils (< 1.2 x10^9/L) and low lymphocytes (< 0.5 x 10^9/L), each reported in 3 (1.0%) SB4-treated subjects and 4 (1.4%) EU-Enbrel treated subjects. Decreased hemoglobin was observed in 4 (1.4%) EU-Enbrel treated subjects, but no subjects treated with SB4. Other significant abnormalities in hematology parameters occurred in similar proportions of subjects in each treatment group.

Chemistry
There were small changes in mean and median values for biochemistry parameters (albumin, calcium, creatinine, glucose, LDH, phosphorous, potassium, sodium, ALT, AST, alkaline phosphatase, GGT, total bilirubin) over time, without notable differences between the SB4 and EU-approved Enbrel treatment groups. Based on reviewer analysis, at Week 52, the mean change from baseline in ALT was greater in the EU-approved Enbrel group (5.2 U/L) as compared to the SB4 group (4.1 U/L). Subjects with post-baseline ALT elevations ≥ 3x ULN were relatively balanced across the treatment groups (SB4: 17 (5.7%), EU-Enbrel: 12 (4.0%)). Eight subjects (SB4: 6 (2.0%), EU-Enbrel: 2 (0.7%)) had post-baseline ALT ≥ 3x ULN on more than one occasion. At Week 52, the mean change from baseline in AST was similar in the SB4 (3.8 U/L) and EU-approved Enbrel groups (4.0 U/L). Post-baseline AST ≥ 3x ULN occurred more frequently in subjects on SB4 (10 (3.3%) subjects), than EU-approved Enbrel (4 (1.3%) subjects based on reviewer analysis. At Week 52, the mean change from baseline in total bilirubin was similar in the SB4 (1.5 umol/L) and EU-approved Enbrel groups (1.4 umol/L). Total bilirubin elevations ≥ 2x ULN occurred on single occasions in 2 female Caucasian subjects on SB4 at Weeks 2 and 4. One of the subjects ([redacted]$^{(b)(6)}$) had elevated AST ≥ 3x ULN at Week 4, but also had alkaline phosphatase > 2x ULN, and therefore was not considered a possible Hy's law case. She later had 2 events of bile duct stone on study days 135 and 256. AEs related to abnormal liver function tests are discussed above under Common Adverse Events. During the OLE, there was one subject ([redacted]$^{(b)(6)}$) with laboratory values consistent with possible Hy's law, with elevations in AST ≥ 3x ULN and total bilirubin ≥ 2x ULN, however,

this subject had an SAE of hepatic cancer, providing an alternative explanation for the abnormal labs. No cases of drug-induced liver injury based on Hy's law criteria were reported in the SB4 clinical program. There was a numerically higher proportion of subjects with AST and ALT increases ≥ 3x ULN in the SB4 treatment group, however, mean changes from baseline were similar and the proportions of subjects with TEAEs of abnormal liver tests were balanced between the treatment groups.

Changes in inflammatory markers were generally similar between treatment groups. At Week 52, the mean change in CRP was similar in the EU-Enbrel and SB4 treatment groups (-8.6 and -8.4, respectively), while the mean change in ESR was slightly greater in the EU-Enbrel group (-22.8) compared to the SB4 group (-20.3).

Urinalysis
There were no notable differences in urinalysis parameters over time between treatment groups.

Study SB4-G11-NHV
In Study SB4-G11-NHV, clinically significant elevations in ALT (> 3x ULN) were observed in 1 subject each following single doses of SB4 and EU-Enbrel. The latter subject was withdrawn due to the AE. Other clinically significant lab abnormalities included increased CRP (> 1.5x ULN) in 1 subject each after receiving SB4 and EU-Enbrel; both subjects had concurrent illness.

Across the SB4 clinical program, the distribution of laboratory findings was generally balanced between the SB4 and EU-approved Enbrel treatment groups. No new or unexpected laboratory findings were observed in the SB4 clinical program.

7.4.3 Vital Signs

In SB4-G31-RA, mean and median values and changes from baseline for systolic blood pressure, diastolic blood pressure, heart rate, and body temperature were similar between SB4 and EU-approved Enbrel through the double-blind portion and the OLE. Clinically significant abnormal vital signs up to Week 52 occurred in 6 subjects receiving SB4 with clinically significant low systolic BP; other clinically significant abnormalities in vital signs occurred in similar proportions of subjects in each treatment group (Table 22). Clinically significant vital sign abnormalities reported in more than 1 subject at any timepoint during the double-blind period was low systolic BP reported in 4 (1.3%) subjects in the SB4 treatment group at Week 2.

Table 22: Clinically Significant Vital Signs Abnormalities Up to Week 52, Safety Population SB4-G31-RA

Vital Sign Parameter	Criteria	SB4 N=299 n (%)	EU-Enbrel N=297 n (%)
Mean Systolic Blood Pressure	Low (≤ 90 mmHg and change from baseline ≤ -20 mmHg)	6 (2.0)	0
	High (≥ 180 mmHg and change from baseline ≥ 20 mmHg)	1 (0.3)	1 (0.3)
Mean Diastolic Blood Pressure	Low (≤ 50 mmHg and change from baseline ≤ -15 mmHg)	2 (0.7)	1 (0.3)

	High (≥ 105 mmHg and change from baseline ≥ 15 mmHg)	1 (0.3)	0
Body Temperature	Low (≤ 35°C and change from baseline ≤ -1.1°C)	1 (0.3)	2 (0.7)
	High (≥ 38.3°C and change from baseline ≥ 1.1°C)	0	0
Heart Rate	Low (≤ 50 bpm and change from baseline ≤ -15 bpm)	2 (0.7)	0
	High (≥ 120 bpm and change from baseline ≥ 15 bpm)	0	0

Source: Adapted from SB4-G31-RA 52 Week CSR, Table 14.3-2.9, Pages 1057-1064

In the PK study, SB4-G11-NHV, no clinically meaningful changes over time or differences between treatment groups were noted for systolic blood pressure, diastolic blood pressure, heart rate, or body temperature based on the protocol-specified criteria for potentially clinically significant vital signs presented in Table 9-5 of CSR.

7.4.4 Electrocardiograms (ECGs)

ECGs were performed at Screening in Study SB4-G31-RA. Abnormalities not thought to be clinically significant were present in 50 subjects in the SB4 treatment group and 54 subjects in the EU-Enbrel treatment group. No follow-up ECGs were performed while on treatment during the study, however, there are no specific concerns regarding ECG changes based on experience with etanercept.

In Study SB4-G11-NHV, ECGs were performed at Screening, Day -1, with IP administration, and at 12, 24, 72, 168, and 480 hours after IP administration in periods 1 and 2. There were no relevant changes in ECG parameters over time. No subjects had QTcF intervals > 450 msec at any time point and no subjects had QTcF increases from baseline > 60 msec. No abnormalities were considered clinically relevant by the Investigator.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies with SB4 were submitted in the BLA.

7.4.6 Immunogenicity

Development of autoantibodies to the TNF receptor portion or other protein components of the Enbrel drug product has been described in subjects with RA, AS, PsA, and PsO. As described in the USPI for Enbrel, the clinical significance of these autoantibodies is unknown. In Studies SB4-G11-NHV and SB4-G31-RA, samples were tested for ADAs using an ELISA assay, and tested for neutralizing antibodies (NAb) using a validated cell-based NAb assay.

PK study
In Study SB4-G11-NHV, blood samples were collected pre-dose and 4 weeks after the first injection of study drug for determination of ADA and NAbs to etanercept as shown in Figure 1. Four subjects did not have samples at Period 2 Day 29 (1 EU-Enbrel/US-Enbrel, 1 SB4/EU-Enbrel, 1 US-Enbrel/EU- Enbrel, 1 US-Enbrel/SB4). One subject (SB4/US-Enbrel) had nonspecific ADA prior to receiving first dose of study drug, but did not subsequently have ADA. As presented in Table 23, no subjects developed ADA 4 weeks after SB4 dosing, while 7 (15.6%) subjects had ADA after receiving EU-approved Enbrel and 10 (22.7%) subjects developed ADA after US-licensed Enbrel. One subject (EU-Enbrel/SB4) developed NAb during

the study. Two subjects (1 each in US-Enbrel/EU-Enbrel and US-Enbrel/SB4) had NAb prior to dosing and at Period 2 Day 29, consistent with non-specific neutralizing antibodies. An assessment of the clinical impact of ADA is limited by the lack of ADA detected in subjects treated with SB4, however there was no observed impact of ADA on safety in the comparator groups.

Table 23: Antidrug Antibody Response in SB4-G11-NHV

	Part A		Part B		Part C	
Period 2 Day 29	SB4	EU-Enbrel	SB4	US-Enbrel	EU-Enbrel	US-Enbrel
N	22	23	23	22	22	22
ADA						
Positive (Ab-specific)	0	3 (13.0)	0	4 (18.2)	4 (18.2)	6 (27.3)
Negative	22 (100.0)	20 (87.0)	23 (100.00)	18 (81.8)	18 (81.8)	16 (72.7)
NAb						
Positive (Ab-specific)		1 (33.3)		0	0	0
Negative		2 (66.7)		3 (75.0)	4 (100.0)	5 (83.3)
Non-specific		0		1 (25.0)	0	1 (16.7)

ADA: anti-drug antibody; NAb: neutralizing antibody
NAb positive if Period 1 Day 1 NAb was negative and Period 2 Day 29 NAb was positive; NAb negative if Period 1 Day 1 NAb and Period 2 Day 29 NAb were negative; Non-specific positive if both Period 1 Day 1 NAb and Period 2 Day 29 NAb were positive
Reviewer JMP analysis ADIG dataset using variables PARAM 'ADA Serum P', AVISIT, AVALC, ARM, PARAM 'NAB Serum P', PARAM 'NAB Result'

Comparative Clinical Study in RA

In Study SB4-G31-RA, ADAs were detected in serum samples using a double antigen format assay specific for antibodies to etanercept. Immunogenicity samples were obtained at baseline and Weeks 2, 4, 8, 12, 16, 24, and 52. ADA results were defined as positive if the subject had at least 1 positive ADA result up to that timepoint, without regard to ADA result at Week 0. Samples in which ADAs were observed, underwent a NAb assay to evaluate the effect of the ADA on the ability of etanercept to provide competitive inhibition of TNFα.

No subjects had ADA observed at baseline. Forty-two subjects (39 (13.2%) EU-Enbrel, 3 (1.0%) SB4) developed ADA during the controlled portion of the study as presented in Table 24. While the reviewer notes the ADA incidence appears to be higher in the EU-approved Enbrel group compared to SB4, it is driven primarily by transient ADAs; only a single subject receiving EU-approved Enbrel had positive ADA on more than one occasion, while no subjects receiving SB4 had positive ADA on more than one occasion. Week 4 was the most frequent time point at which ADA were positive (33 subjects). ADA titers were generally low; 32 (74.4%) samples had titers that were ≤ 32. Neutralizing antibodies were observed in a single subject. The subject, who received EU-approved Enbrel, had ADA with neutralizing antibodies at Week 4, however subsequent ADA samples were negative.

In the OLE, 1 (0.8%) subject in the SB4 treatment group had non-neutralizing ADA at the Week 52 extended baseline visit; subsequent testing was negative for ADA. During the OLE, 2 subjects developed ADA, including 1 (0.8%) who underwent a single transition from EU-Enbrel to SB4 and 1 (0.8%) who remained on SB4; none of the ADA were neutralizing (Table 24). Of note, 19 subjects enrolled in the OLE (17 (14.3%) EU-Enbrel/SB4 and 2 (1.6%) SB4/SB4) had ADA during the DB period, but did not have ADA at the extended baseline nor during the OLE;

only 1 (0.8%) subject (EU-Enbrel/SB4) had positive ADA at more than one time point (Weeks 4 and 8).

Table 24: Anti-drug Antibody Response in SB4-G31-RA

	Parameter	SB4	EU-Enbrel
Week 0	N	299	297
	ADA +, n(%)	0	0
	NAb +, n(%)	0	0
Up to Week 8		299	296
	ADA +, n(%)	2 (0.7)	38 (12.8)
	NAb +, n(%)	0	1
Up to Week 24	N	299	296
	ADA +, n(%)	2 (0.7)	39 (13.2)
	NAb +, n(%)	0	1 (0.3)
Up to Week 52	N	299	296
	ADA +, n(%)	3 (1.0)	39 (13.2)
	NAb +, n(%)	0	1 (0.3)
OLE		SB4/SB4	EU-Enbrel/SB4
Week 52 (Extended Population)	N	126	119
	ADA +, n(%)	1 (0.8)	0
	NAb +, n(%)	0	0
Up to Week 100	N	126	117
	ADA +, n(%)	1 (0.8)[1]	1 (0.9)
	NAb +, n(%)	0	0

Positive if subject had at least one positive post-baseline ADA result (≥ 1:10) by time point indicated
[1] Excluding the subject with positive ADA at Week 52 Extended baseline (b) (6)
Source: Adapted from Summary of Clinical Pharmacology, Tables 14 and 15, pages 31-32
Reviewer JMP analysis, ADLB dataset using variables PARAM, AVALC, VISIT, ACTARM, USUBJ, TRTSEQA and ADSL dataset using variables ADA8, ADA24, ADA52, ACTARM

Assessment of the ADA impact on clinical outcomes and PK are limited by the low observed immunogenicity in the clinical studies with SB4. In addition, only 5 subjects with observed ADA (1 SB4, 4 EU-Enbrel) were included in the PK population. The proportion of subjects with an ACR20 response at Week 24 was somewhat lower in the subjects with ADA who received EU-Enbrel (61.5%) as compared to ADA negative subjects (73.5%), however the numbers of ADA positive patients was low to make definitive conclusions about the potential impact of the observed transient immunogenicity on clinical efficacy. Similarly, the number of subjects with ADA who received SB4 was too small to draw conclusions about impact on efficacy. The incidence of injection site reactions in the EU-Enbrel treated subjects with positive ADA up to Week 52 (17.9%) was similar to that in the overall EU-Enbrel group (17.5%). The incidence of injection site reactions in the SB4 group with positive ADA was higher (33.3%) as compared to the incidence in the overall SB4 treatment group (3.7%), however, this is based on 1 subject with an injection site reaction in a group of 3 subjects with ADA. The incidence of ADA in the OLE is similarly too small to assess an impact of ADA on clinical outcomes. Further, there were no cases of anaphylaxis.

The immunogenicity observed in Study SB4-G31-RA was low, with lower rates of immunogenicity observed in the SB4 treatment group as compared to the EU-approved Enbrel

treatment group. While the small numbers limit conclusions on the impact of ADA, the observed ADA were generally early and transient in nature and not associated with significant change in safety or efficacy.

In response to an Agency Information Request, the Applicant provided a reanalysis of the ADA results using a 1% false positive rate to calculate the confirmatory cut-point. The initial analysis was conducted using a confirmatory cutpoint of 35.1% signal inhibition, calculated based on a 0.1% false positive rate, however the Agency expressed concern that this may underestimate the number of patient samples with low levels of binding ADAs. In the reanalysis, the proportion of subjects with ADA up to Week 52 increased from 1.0% to 2.0% in the SB4 treatment group and from 13.2% to 23.3% in the EU-Enbrel group. In the OLE, the proportions of subjects with ADA based on the recalculated results were 1.6% in the SB4/SB4 group and 0.9% in the EU-Enbrel/SB4 group. In the reanalysis, an additional 10 subjects had positive ADA at more than one timepoint; all were prior to Week 24 with the exception of 1 subject in the SB4/SB4 group who was ADA positive at Weeks 8, 76, and 100. Following the single transition, the ADA incidence after Week 52 up to Week 100 was 0.8% in the SB4/SB4 group compared with 0.9% in the EU-Enbrel/SB4 group. NAb incidence was not determined for the newly ADA positive samples. Based on Applicant analysis, the trough concentrations and PK parameters from ADA positive subjects fell within the ranges of results for subjects without ADA and no significant interaction in ACR20/50/70 response rates at Weeks 24 and 52 between treatment and ADA status was reported based on the per-protocol populations. The incidence of injection site reactions in subjects with ADA using the higher cut-point was generally consistent with the analysis using the original cut-point.

Based on the immunogenicity data from the single dose healthy subjects and the repeat dose Study SB4-G31-RA, there does not appear to be an increased risk of development of ADAs with treatment with SB4 as compared to EU-approved Enbrel. The small numbers of subjects with ADA in the SB4 treatment group limit conclusions regarding impact on PK, safety, and efficacy, however there were no significant differences observed. Further, ADA formation did not increase following a single transition from EU-approved Enbrel to SB4.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Not applicable.

7.5.2 Time Dependency for Adverse Events

Not applicable.

7.5.3 Drug-Demographic Interactions

Analysis of TEAEs, SAEs, and AEs leading to discontinuation by demographic subgroups, including gender, race, ethnicity, and age, was similar to the safety profile of the overall study

population. This analysis is limited by the small number of non-Caucasian and non-female subjects enrolled in the study.

7.5.5 Drug-Drug Interactions

Not applicable for this application. No specific studies on the potential impact of drug interactions were conducted with SB4.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Lymphoma, has been identified as potential risk with US-licensed Enbrel and other TNF inhibitors as described in the Warnings and Precautions section of the US-licensed Enbrel USPI. There were a small number of malignancies reported in Study SB4-G31-RA. The incidence and types of these malignancies are expected for the study population and treatment.

7.6.2 Human Reproduction and Pregnancy Data

No clinical experience with SB4 in pregnant or breast-feeding women is available.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no reported cases of overdose in the clinical studies with SB4. Etanercept is not known to show a potential for drug dependence or abuse. Information on drug abuse and rebound after withdrawal is not provided in the US-licensed Enbrel USPI. The Applicant states that immunosuppression has to be maintained to suppress disease progression and modify the disease process, and if SB4 is withdrawn, it should be replaced by appropriate alternatives. This approach would be appropriate for most biologic and non-biologic DMARD therapies.

7.7 Additional Submissions / Safety Issues

All safety data from the clinical studies for SB4 were included in the original submission.

8 Postmarket Experience

SB4 was first approved in Korea in September 2015 and in the United Kingdom in Feb 2016. It is currently marketed in Korea, Canada, Norway, Denmark, Germany, Sweden, UK, France, Italy, Spain, Poland, Czech Republic, Estonia, Ireland, Portugal, and the Netherlands. There were approximately 11,000 patient years of treatment for SB4 from 01-July-2016 through 31-December-2016, and approximately 13,000 patient-years cumulatively from the international birth date on 07-Sept-2015 through 31-December-2016. No regulatory or Marketing

Authorization Holder actions have been taken for safety reasons and no new risk minimization activities have been performed.

The Applicant submitted the 3rd Periodic Safety Update Report (PSUR) as the 120 day safety update on 22Sept2017. The PSUR covers the reporting period 15Jan2017 through 14July2017 and provides exposure of approximately 20,700 additional patient-years. There were no actions taken for safety reasons and no new safety signals identified.

9 Appendices

9.1 Literature Review/References

FDA Guidance for Industry: "*Nonproprietary Naming of Biological Products*."

FDA Guidance for Industry: "*Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*."

FDA Guidance for Industry "*Scientific Considerations in Demonstrating Biosimilarity to a Reference Product.*"

Sampson HA et al., Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium *J Allergy Clin Immunol.* 2006 Feb;117(2):391-7

USPI Enbrel (etanercept), November 2017.

9.2 Labeling Recommendations

- Proprietary name
  The initially proposed proprietary name for SB4 was (b) (4). The Division of Medication Error Prevention and Analysis (DMEPA) found the name (b) (4) unacceptable due to similarity in spelling, pronunciation, and overlapping product characteristics with the marketed product, (b) (4) (b) (4) was also found to be unacceptable due to orthographic similarity and overlapping product characteristics with (b) (4) Most recently, the Applicant has proposed the name (b) (4) This name is currently under review.

- Non-proprietary/Proper name
  FDA has determined that the use of a distinguishing suffix in the nonproprietary name for Samsung's SB4 product is necessary to distinguish this proposed product from Enbrel (etanercept). As explained in FDA's draft Guidance for Industry, 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. Samsung proposed the following suffices: [redacted] (b) (4) these were determined to be unacceptable. Review of acceptable suffixes is ongoing.

- Physician Labeling
  At the time of this review, labeling discussions are ongoing.

9.3 Advisory Committee Meeting

An advisory committee meeting was not held for this application.

9.4 Financial Disclosure

Covered Clinical Studies (Name and/or Number): SB4-G31-RA and SB4-G11-NHV

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: **325 (1 investigator for SB4-G11-NHV, 324 for SB4-G31-RA)**		
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 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) **n/a**		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Appears this way on original

Appendix 1: SB4-G31-RA Schedule of Events

Assessments	Screening	Treatment period											
Visit	0	1 Randomisation	2	3	4	5	6	7	8	9	10	11 (EOT) or ET[2]	12[3]
Day (± visit window)	From -42	1	8 (± 1)	15 (± 1)	29 (± 3)	57 (± 5)	85 (± 5)	113 (± 5)	169 (±5)	225 (± 7)	281 (± 7)	365 (± 7)	393 (± 7)
Week	-6 to 0	0	1	2	4	8	12	16	24	32	40	52	56
Obtain informed consent[1]	✓												
Demographic information	✓												
Medical and surgical history	✓												
Physical examination, including height (Screening visit only) and weight[4]	✓											✓	
Abbreviated physical examination[4]		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Assessment of eligibility	✓	✓											
Chest X-ray[5]	✓												
X-ray (hands and feet)		✓										✓	
Pregnancy test[6]	✓	✓			✓	✓	✓	✓	✓	✓	✓	✓	
Vital signs[7]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Previous and concomitant medications[8]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse events[9]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
TB evaluation[10]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Twelve-lead electrocardiogram	✓												
IP injection site evaluation		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
EFFICACY ASSESSMENTS													
Pain Assessment, VAS[11]		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	
Subject Global Assessment VAS[11]		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	
Physician Global Assessment VAS		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	

Assessments	Screening	Treatment period											
Visit	0	1 Randomisation	2	3	4	5	6	7	8	9	10	11 (EOT) or ET[2]	12[3]
Day (± visit window)	From -42	1	8 (± 1)	15 (± 1)	29 (± 3)	57 (± 5)	85 (± 5)	113 (± 5)	169 (±5)	225 (± 7)	281 (± 7)	365 (± 7)	393 (± 7)
Week	-6 to 0	0	1	2	4	8	12	16	24	32	40	52	56
HAQ-DI[11]		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	
Swollen and tender joint counts[12]	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	
LABORATORY/SAFETY ASSESSMENTS													
TB test (QuantiFERON Gold test, Central laboratory)	✓												
Virology screen[13] (central laboratory)	✓												
Clinical chemistry[14], haematology (central laboratory) and urinalysis (local laboratory)	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	
C-reactive protein (central laboratory)	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	
Erythrocyte sedimentation rate (local laboratory)	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	
Rheumatoid factor (central laboratory)	✓								✓				
Pharmacokinetic assessment[15] (central laboratory)		✓		✓	✓	✓[16]	✓	✓	✓				
Anti-nuclear antibodies/anti-dsDNA antibodies		✓				✓			✓			✓	
Immunogenicity assay (central laboratory)		✓		✓	✓	✓	✓	✓	✓			✓	
INVESTIGATIONAL PRODUCT													
Randomisation		✓											
Dispense IP[17]		✓[18]	✓[18]	✓[18]	✓	✓	✓	✓	✓	✓	✓		
IP and MTX compliance review			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	

dsDNA= double-stranded deoxyribonucleic acid; EOT=End-of-Treatment; ET=Early Termination; HAQ-DI=Health Assessment Questionnaire – Disability Index; IP=investigational product; MTX=methotrexate; TB=tuberculosis; VAS=visual analogue scale

1. Informed consent must be obtained prior to any study related procedures.
2. Subjects who discontinue from the study at any time post-Day 1 will be required to have an ET Visit.
3. A follow-up telephone interview will be scheduled at Week 56 (or 4 weeks after ET) to collect adverse events and related concomitant medications.
4. Complete physical examination for Screening Visit, including height and weight; abbreviated physical examination at subsequent visits (the abbreviated physical examination must include cardiovascular and respiratory systems; other body systems to be examined at the discretion of the Investigator).
5. A chest X-ray, current or taken within 3 months prior to Screening, to exclude pulmonary infection.
6. Females only. Serum pregnancy test (central laboratory) at Screening and a urine pregnancy test (local laboratory) at each applicable visit thereafter.
7. Sitting after 5 minutes' rest, three measurements at 2-minute intervals.
8. Previous and concomitant medication at Screening and concomitant medication only at visits thereafter.
9. Adverse events and serious adverse events will be collected from the time of informed consent (even if this is prior to Visit 1).
10. If TB is suspected at any time during the study, chest X-ray and/or QuantiFERON Gold test should be performed.
11. Questionnaires must be completed at the Investigator site by the subject before any investigations or discussions about their disease with the clinic staff.
12. Joint assessor(s) will be independent to the rest of the study team.
13. Subjects with a negative hepatitis B surface antigen test and positive hepatitis B core antibody test must have hepatitis B virus DNA levels < 29 IU/mL (or 169 copies/mL) as determined by a polymerase chain reaction test to be enrolled in the study.
14. An alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transpeptidase or serum creatinine value > 2 times ULN should prompt repeat testing of all liver or renal function tests.
15. For pharmacokinetic subgroup only: blood samples for pharmacokinetic analysis will be collected at Weeks 0, 2, 4, 8, 12, 16 and 24 within 30 minutes prior to dosing with date and time of sampling accurately recorded (at each visit, samples should be taken at the same time of the day of first injection, within a window of ±3 h).
16. Additional samples for pharmacokinetic analysis will be collected at the following time points after the Week 8 injection: 24, 48, 72, 96 and 168 h after the injection of SB4 or Enbrel within a window of ±3 h.
17. Subjects will self-administer investigational product (SB4 or Enbrel) by subcutaneous injection weekly. On visit days, subjects are recommended to administrate IP at the study site which must be performed after completion of the scheduled assessments.
18. Administration of IP on Visit 1 (Randomisation), Visit 2 and Visit 3 must be performed at the study site under the supervision of the site staff.

Source: SB4-G31-RA Protocol Amendment 3. March 12, 2014, pages 11-13

Appendix 2: SB4-G31-RA OLE Schedule of Events

Assessments	Open-label, extension period					
Visit	11	12	13	14	15 (EOT) or ET[2]	16[3]
Day (± visit window)	365 (± 7)	449[4] (± 7)	533[4] (± 7)	617[4] (± 7)	701[4] (± 7)	729[4] (± 7)
Week	52	64	76	88	100	104
Obtain informed consent[1]	✓					
Physical examination[6]	✓[5]				✓	
Abbreviated physical examination[6]		✓	✓	✓		
Assessment of eligibility	✓					
X-ray (hand and feet)	✓[5]				✓	
Urine pregnancy test (local laboratory)[7]	✓[5]	✓	✓	✓	✓	
Vital signs[8]	✓[5]	✓	✓	✓	✓	
Concomitant medications	✓[5]	✓	✓	✓	✓	✓
Adverse events	✓[5]	✓	✓	✓	✓	✓
TB evaluation[9]	✓[5]	✓	✓	✓	✓	✓
IP injection site evaluation	✓[5]	✓	✓	✓	✓	
EFFICACY ASSESSMENTS						
Pain Assessment, VAS[10]	✓[5]		✓		✓	
Subject Global Assessment VAS[10]	✓[5]		✓		✓	
Physician Global Assessment VAS	✓[5]		✓		✓	
HAQ-DI[10]	✓[5]		✓		✓	
Swollen and tender joint counts[11]	✓[5]		✓		✓	
LABORATORY/SAFETY ASSESSMENTS						
Clinical chemistry, haematology (central laboratory) and urinalysis (local laboratory)	✓[5]	✓	✓	✓	✓	
C-reactive protein (central laboratory)	✓[5]		✓		✓	
Erythrocyte sedimentation rate (local laboratory)	✓[5]		✓		✓	
Anti-nuclear antibodies/anti-dsDNA antibodies (central laboratory)	✓[5]				✓	
Immunogenicity assay (central laboratory)	✓[5]		✓		✓	
INVESTIGATIONAL PRODUCT						
Dispense IP[12]	✓	✓	✓	✓		
IP and MTX compliance review	✓[5]	✓	✓	✓	✓	

dsDNA = double-strand deoxyribonucleic acid; ET = Early Termination; HAQ-DI = Health Assessment Questionnaire – Disability Index; IP = investigational product; MTX = methotrexate; TB = tuberculosis; VAS = visual analogue scale

Source: SB4-G31-RA Protocol Amendment 3.2. March 17, 2015, pages 11-13

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/s/

RACHEL GLASER
02/16/2018

NIKOLAY P NIKOLOV
02/16/2018

CLINICAL INSPECTION SUMMARY

Date	December 19, 2017
From	Min Lu, M.D., M.P.H., Medical Officer Janice Pohlman, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Rachel Glaser, M.D., Medical Officer Nikolay Nikolov, M.D., Clinical Team Leader Brandi Wheeler, Regulatory Project Manager Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
BLA	761066
Applicant	Samsung Bioepis Co., Ltd.
Drug	SB4, proposed biosimilar to Enbrel (etanercept)
NME	No
Therapeutic Classification	Tumor necrosis factor (TNF) blocker
Proposed Indication	Treatment of rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis, psoriatic arthritis (PsA), ankylosing spondylitis (AS), and plaque psoriasis (PsO)
Consultation Request Date	August 2, 2017
Summary Goal Date	January 15, 2018
Action Goal Date	March 23, 2018
BsUFA Date	March 25, 2018

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical sites (Drs. Leszczynski and Baranauskaite) were selected for inspection for Protocol SB4-G31-RA, entitled "A Randomized, Double-blind, Parallel Group, Multicenter Clinical Study to Evaluate the Efficacy, Safety, Pharmacokinetics and Immunogenicity of SB4 Compared to Enbrel in Subjects with Moderate to Severe Rheumatoid Arthritis despite Methotrexate Therapy". The study data derived from these clinical sites, based on the inspections, are considered reliable in support of the requested indication under this BLA.

The preliminary classification for the inspection of Dr. Leszczynski's site is Voluntary Action Indicated (VAI) due to protocol violations for altered ESR values at screening in six subjects. The protocol violations were reported in the clinical study report and these six subjects were excluded from all efficacy analyses in the study report in the BLA submission. The preliminary

classification for the inspection for Dr. Baranauskaite's site is No Action Indicated (NAI).

Preliminary classifications are based on communications with the ORA investigator. Inspection classification becomes final when the Establishment Inspection Report is received from the field, has been reviewed, and a letter is issued to the inspected entity. A clinical inspection summary addendum will be provided if review of the inspection report(s) indicates significant change in the classification for the inspection.

2. BACKGROUND

Enbrel® (etanercept) is a tumor necrosis factor (TNF) blocker approved for the treatment of rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (JIA) in patients aged 2 years or older, psoriatic arthritis (PsA), ankylosing spondylitis (AS), and plaque psoriasis (PsO) in patients 4 years or older.

In this application, the sponsor proposes SB4 as a biosimilar product to the US-licensed Enbrel® reference product under section 351(k) of the Public Health Service Act (PHS Act) for all indications for which US-licensed Enbrel® is currently approved.

The sponsor's clinical development program for SB4 included a clinical Phase 1 study (Study SB4-G11-NHV) to compare the pharmacokinetics (PK), safety, and immunogenicity between SB4 and Enbrel® and a clinical Phase 3 study (Study SB4-G31-RA) in RA patients to demonstrate similarity in efficacy, safety/tolerability, immunogenicity, and patient PK profiles between SB4 and Enbrel®.

The CDER review division selected two clinical sites for inspections for the Phase 3 clinical trial (Study SB4-G31-RA) based on the comparatively high number of enrolled subjects at each site with a relatively lower rate of subject discontinuation.

Protocol SB4-G31-RA

This was a Phase 3, multi-center, randomized, double-blind, active-controlled, parallel group study in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy.

The primary objective of the study was to demonstrate the equivalence of SB4 to Enbrel at Week 24, in terms of American College of Rheumatology 20% response criteria (ACR20) response rate in subjects with moderate to severe rheumatoid arthritis (RA) despite methotrexate (MTX) therapy.

The primary efficacy endpoint was the American College of Rheumatology 20% response criteria (ACR20) response at Week 24. ACR20 Responder is defined as a patient who has at least 20% improvement in both tender and swollen joint counts and at least 20% improvement in a minimum of 3 of the following 5 criteria: patient's assessment of arthritis pain, patient's global assessment of disease activity, physician's global assessment of disease activity, patient's assessment of physical function (Health Assessment Questionnaire-Disability Index), and an acute-phase reactant value (C-reactive protein or erythrocyte sedimentation rate).

The study main inclusion criteria included patients aged 18-75 years old, had been diagnosed as having RA according to the revised 1987 American College of Rheumatology (ACR) criteria for at least 6 months but not exceeding 15 years prior to Screening, had moderate to severe active disease despite MTX therapy, and had been treated with MTX for at least 6 months prior to randomization and be on a stable dose of MTX 10-25 mg/week given orally or parenterally for at least 4 weeks prior to Screening.

Study subjects were randomized into two study treatment arms to receive either SB4 50 mg or Enbrel 50 mg once-weekly for 52 weeks via subcutaneous injection. Subjects were enrolled in the study for up to 56 weeks after randomization, consisting of 52 weeks of active treatment and 4 weeks of safety follow-up. Patients who completed study SB4-G31-RA could enroll into an open-label, extension period (in Czech Republic and Poland). The extension period consisted of 48 weeks of active treatment and 4 weeks of safety follow-up to evaluate the long-term safety, tolerability, immunogenicity and efficacy of SB4 in patients with RA treated previously with SB4 or EU Enbrel.

The study screened 777 subjects and enrolled 596 subjects from the 73 clinical sites in Europe and Asia. The first subject signed informed consent June 11, 2013 and the last subject completed the last visit November 28, 2014.

3. RESULTS (by site):

Name of CI, Address	Site #, Protocol #, and # of Enrolled Subjects	Inspection Date	Classification
Piotr Leszczynski, M.D. Medyczne Centrum Hetmanska Indywidualna Specjalistyczna Praktyka Lekarska ul. Hetmanska 55/1 Poznan, NA 60-218 Poland	SB41018 SB4-G31-RA Subjects: 33	November 27-December 1, 2017	*VAI
Asta Baranauskaite, M.D. Hospital of Lithuanian University of Health Sciences Kaunas Clinics Eiveniu g. 2 Kaunas, NA LT-50009 Lithuania	SB40703 SB4-G31-RA Subjects: 19	December 4-7, 2017	*NAI

Key to Compliance Classifications
NAI (No Action Indicated) = No deviation from regulations.
VAI (Voluntary Action Indicated) = Deviation(s) from regulations.
OAI (Official Action Indicated) = Significant deviations from regulations. Data unreliable.
*Pending = Preliminary classification based on information in Form FDA 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

Clinical Study Site Investigators

1) Piotr Leszczynski, M.D. (Site #SB41018, Poznan, Poland)

The site screened 36 subjects and enrolled 33 subjects for Study Protocol SB4-G31-RA. An audit of 21 enrolled subjects' records was conducted. Of the 33 enrolled subjects, 32 subjects completed the study and one subject discontinued due to consent withdrawal (Subject #(b) (6)). The discontinuation data listing provided in the BLA were verified by review of source documents.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, electronic files, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected. Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and BLA subject line listings. There were no limitations during conduct of the clinical site inspection.

Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events was noted.

A Form FDA 483 was issued with the observations listed below at the end of inspection:

1) Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation.

   Specifically,
   For 5 of 33 subjects, the erythrocyte sedimentation rate value was altered to meet the protocol specified ESR ≥ 28 mm/h at screening. The altered ESR values at screening are as follows: Subject #(b) (6)- 40mm/h; Subject #(b) (6)-45mm/h; Subject #(b) (6)-46mm/h, Subject #(b) (6)-35mm/h and Subject #(b) (6)-41mm/h. The original ESR values on the source document were altered to meet the protocol specified ESR ≥ 28 mm/h. The five subjects were enrolled, randomized and received the study drug.

2) An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

   Specifically,
   Subject did not meet the eligibility criteria for enrollment in the randomization phase of the study: Subject #(b) (6) was screened on (b) (6). On (b) (6) the subject was diagnosed as having latent tuberculosis. On (b) (6) the subject was re-screened and enrolled. On (b) (6) the subject was randomized and received the study drug. However, the subject did not meet either the protocol specified ESR ≥ 28 mm/h or serum C-reactive protein ≥ 1.0 mg/dL at re-screening. The subject's serum C-reactive protein lab value was 0.1 mg/dL and the Erythrocyte Sedimentation Rate was determined as 26 mm/h.

OSI Reviewer's comments:

The above protocol violations were initially identified by routine monitoring that lead to sponsor's quality control audits at the site. A corrective action plan was subsequently instituted at the site. These six subjects were excluded from all efficacy analysis due to these protocol violations and their safety data were included in the safety analysis in the clinical study report in the BLA submission.

In general, except for protocol violations reported in the BLA submission for 6 of 33 subjects enrolled (21 subject records reviewed) at this clinical site appeared to be in compliance with Good Clinical Practices. Data submitted by this clinical site excluding these six subjects appear acceptable in support of this specific indication.

3) Asta Baranauskaite, M.D. (Site # SB40703, Kaunas, Lithuania)

The site screened 21 subjects and enrolled 19 subjects for Study Protocol SB4-G31-RA. An audit of all 19 enrolled subjects' records was conducted. All 19 enrolled subjects completed the study.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected. Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and BLA subject line listings. There were no limitations during conduct of the clinical site inspection.

Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events was noted.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear reliable in support of this specific indication.

{See appended electronic signature page}

Min Lu, M.D., M.P.H.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
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cc:
Central Doc. Rm.
Review Division /Medical Team Leader/ Nikolay Nikolov
Review Division/Medical Officer/ Rachel Glaser
Review Division /Project Manager/ Brandi Wheeler
OSI/DCCE/ Division Director/Ni Khin
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OSI/DCCE/Team Leader/ Susan Thompson
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/s/

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12/19/2017

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