CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761066Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

MEMORANDUM

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

DATE: 03/22/2018

TO: File for BLA 761066

THROUGH: Ping Ji, Ph.D.

FROM: Bhawana Saluja, Ph.D.

SUBJECT: Amendment to Clinical Pharmacology Primary Review

APPLICATION/BIOLOGIC: BLA 761066/ (b) (4) (SB4)

Reference is made to the BLA 761066 submission by the Applicant, Samsung Bioepis Co., Ltd., received May 25, 2017, and the Clinical Pharmacology Review dated February 15, 2018. At the time of archiving the review, this reviewer stated that the OSIS inspection of the bioanalytical site (b) (4) had identified significant findings including, but not limited to, the validation of the bioanalytical assay used for determination of etanercept concentrations in human serum for Study SB4-G11-NHV (archived on February 12, 2018). Specifically, the findings relate to the (b) (4) stability assessment of the bioanalytical assay used for Study SB4-G11-NHV. Accordingly, the OSIS reviewers recommended that analytical data from Study SB4-G11-NHV not be accepted for Agency review. Based on OSIS review and findings, DPARP issued the following information request (IR) to the applicant for bioanalytical assay method used for determination of etanercept concentrations in human serum for Study SB4-G11-NHV on February 21, 2018 –

"The Office of Study Integrity and Surveillance (OSIS) recently inspected the bioanalytical site (b) (4) utilized for analysis of subject samples collected in Study SB4-G11-NHV. The inspection identified (b) (4)

The applicant responded to the IR on March 9, 2018. Following the review of this response, OSIS submitted an amendment to the previous EIR review on March 22, 2018, and concluded that the stability assessments (b) (4) for SB4 in human and RA sera are reliable and should be accepted for further Agency review. For details refer to the OSIS review by Drs. Gajendiran Mahadevan and Ruben Ayala (archived on March 22, 2018).

Based on this new information and conclusions from OSIS, the Office of Clinical Pharmacology concludes that the PK data provided by Samsung, support a demonstration of PK similarity between SB4 and US-licensed Enbrel, and the PK component of the scientific bridge to justify the relevance of the comparative data generated using EU-approved Enbrel to support a demonstration of no clinically meaningful differences between SB4 and US-licensed Enbrel.

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/s/

BHAWANA SALUJA
03/23/2018

PING JI
03/23/2018

CLINICAL PHARMACOLOGY REVIEW

BLA	761066
Submission Date	05/25/2017
Proposed Brand Name	(b) (4)
Nonproprietary Name	SB4
Applicant	Samsung Bioepis Co., Ltd.
Submission Type; Code	351(k); standard review
Formulation; Strength(s)	25 and 50 mg Single-dose Pre-filled Syringe
Proposed Indications	• Rheumatoid Arthritis (RA) • Polyarticular Juvenile Idiopathic Arthritis (JIA) • Psoriatic Arthritis (PsA) • Ankylosing Spondylitis (AS) • Plaque Psoriasis (PsO)
Proposed Dosage Regimens	• Adult RA, AS and PsA: 50 mg once weekly • Adult PsO: 50 mg twice weekly for 3 months, followed by 50 mg once weekly • JIA and Pediatric PsO (patients who weigh 63 kg or more): 50 mg once weekly
Clinical Pharmacology Reviewer	Bhawana Saluja, Ph.D.
Clinical Pharmacology Team Leader	Anshu Marathe, Ph.D.
OCP Division	Division of Clinical Pharmacology II
OND Division	Division of Pulmonary, Allergy, and Rheumatology Products

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1. Executive Summary

Samsung submitted a Biologic License Application (BLA) for SB4, a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human p75 tumor necrosis factor receptor (TNFR2) linked to the Fc portion of human immunoglobulin G1 (IgG1), under Section 351(k) of the Public Health Service Act (42 U.S.C. 262(k)). The applicant is seeking approval for SB4 as a biosimilar to US-licensed Enbrel® (BLA 103795) and licensure for the following approved indications for US-Enbrel®:

- Rheumatoid Arthritis (RA)
- Polyarticular Juvenile Idiopathic Arthritis (JIA) in patients aged 2 years or older
- Psoriatic Arthritis (PsA)
- Ankylosing Spondylitis (AS)
- Plaque Psoriasis (PsO) in patients 4 years and older

SB4 drug product is supplied as (b) (4) a 50 mg/mL solution for injection, which is clear to opalescent, colorless to pale yellow, sterile and preservative-free solution for injection. It is intended for subcutaneous administration, and is presented in a pre-filled syringe (PFS).

The clinical development for SB4 relevant to US submission included two clinical studies (SB4-G11-NHV and SB4-G31-RA). Pharmacokinetic (PK) similarity of SB4 to US-licensed Enbrel® was evaluated in a pivotal three-part, two-way crossover PK similarity study to compare the PK, safety, tolerability, and immunogenicity of SB4, EU-approved Enbrel® and US-licensed Enbrel® in healthy subjects (Study SB4-G11-NHV). PK and immunogenicity were also assessed for SB4 and EU-approved Enbrel® in patients with active rheumatoid arthritis (RA) (Study SB4-G31-RA).

PK similarity was demonstrated between SB4 and US-licensed Enbrel® in Study SB4-G11-NHV. The study also established the PK portion of the scientific bridge between SB4, US-licensed Enbrel®, and EU-approved Enbrel®, which supports the use of EU-approved Enbrel® in the comparative clinical study (Study SB4-G31-RA). The clinical pharmacology results add to the totality of evidence to support a demonstration of biosimilarity of SB4 and US-licensed Enbrel®.

Study SB4-G11-NHV was conducted at a single center (Berlin PAREXEL International GmbH, Berlin), and the pharmacokinetic and immunogenicity assays for this study were conducted at one bioanalytical laboratory (b) (4). Since the results of this study are considered pivotal to support the determination of biosimilarity of the proposed biosimilar (SB4) to US-licensed Enbrel®, the Office of Clinical Pharmacology recommended inspection of the clinical and bioanalytical sites. The Office of Study Integrity and Surveillance (OSIS) recommended accepting the clinical site data without an on-site inspection of the clinical site (PAREXEL International GmbH, Berlin). Refer to OSIS Memorandum (DARRTS dated 08/21/2017) for further details. OSIS recently DARRTed their review (DARRTS dated 02/12/2018) for the bioanalytical site utilized for determination of etanercept concentrations in human serum in Study SB4-G11-NHV. Among other things, the OSIS reviewers identified significant findings including, but not limited to, the validation of the bioanalytical assay used to determine etanercept concentrations in human serum in Study SB4-G11-NHV. Specifically, the findings relate to the (b) (4) stability assessment of the bioanalytical assay used for Study SB4-G11-NHV. For details refer to the OSIS review by Drs. Gajendiran Mahadevan and Ruben Ayala. Accordingly, the OSIS reviewer recommended that (b) (4) repeat the (b) (4)

(b) (4) prior to accepting the data from Study SB4-G11-NHV for further review. At this time, the implications of the recent recommendations from OSIS as they relate to the bioanalytical site are being evaluated, and the Agency may contact the applicant and request additional information to address the issues identified by OSIS. Accordingly, this review may be updated with an addendum at a later date with any potential new information that impacts the assessment on PK similarity of SB4 to the US-licensed Enbrel®.

1.1 Recommendations

The Office of Clinical Pharmacology 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.

Labeling Recommendations

Please refer to Section 3 – Detailed Labeling Recommendations.

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology Findings

The clinical development for SB4 included two clinical studies: a pivotal three-part, two-way crossover PK similarity study of SB4, EU-approved Enbrel® and US-licensed Enbrel® in healthy male subjects (Study SB4-G11-NHV), and a comparative efficacy and safety study of SB4 and EU-approved Enbrel® in patients with moderate-to-severe RA (Study SB4-G31-RA).

In Study SB4-G11-NHV, 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 PK parameters (i.e., AUC_{inf}, AUC_t, and C_{max}) were all within the acceptance interval of 80.00 - 125.00%, as presented in Table 1. These pairwise comparisons met the pre-specified criteria for PK similarity between SB4, US-licensed Enbrel® and EU-approved Enbrel®. A scientific PK bridge was therefore established to support the relevance of the data generated using EU-approved Enbrel® in the comparative clinical study (Study SB4-G31-RA). For details refer to section 2.2.3.

Table 1 Summary Results of the Comparison of the Pharmacokinetic Parameters between Test and References Products (Study SB4-G11-NHV)

PK Parameter	Geometric LS Means		%GLSM Ratio (90% CI)
Part A - SB4 and EU-approved Enbrel® (n=42)			
	SB4	*EU-approved Enbrel®*	
AUC_{inf} (µg.h/mL)	729.371	736.391	99.0 (94.7 - 103.6)
AUC_t (µg.h/mL)	688.853	698.494	98.6 (94.2 - 103.3)
C_{max} (µg/mL)	3.319	3.201	103.7 (98.5 - 109.2)
Part B - SB4 and US-licensed Enbrel® (n=44)			
	SB4	*US-licensed Enbrel®*	
AUC_{inf} (µg.h/mL)	794.463	785.891	101.1 (95.8 - 106.7)
AUC_t (µg.h/mL)	749.543	742.437	101.0 (95.4 - 106.9)
C_{max} (µg/mL)	3.613	3.463	104.4 (97.7 - 111.4)
Part C - EU-approved Enbrel® and US-licensed Enbrel® (n=42)			
	EU-approved Enbrel®	*US-licensed Enbrel®*	
AUC_{inf} (µg.h/mL)	735.360	731.657	100.5 (91.5 - 110.4)
AUC_t (µg.h/mL)	700.560	691.766	101.3 (92.3 - 111.1)
C_{max} (µg/mL)	3.408	3.300	103.3 (94.7 - 112.7)

(Source: BLA 761066, Module 5.3.3.1, Study SB4-G11-NHV)

In Study SB4-G31-RA, serum trough concentrations assessed at treatment period 1 (up to Week 24) in a subset of patients (i.e., n=79; SB4: n=41, EU-approved Enbrel®: n=38) were generally comparable between SB4 and EU-approved Enbrel® treatment groups. The incidence of immunogenicity at Week 52 for SB4 and EU-approved Enbrel® treatment groups were 1% (3/299) and 13.2 % (39/297) respectively. Since the incidence of immunogenicity in the PK subset was low, the impact of immunogenicity on PK remains unclear. For details refer to section 2.3.1.

Overall, the submitted clinical pharmacology data support a demonstration of PK similarity among SB4, EU-approved Enbrel® and US-licensed Enbrel®.

2. Question Based Review

2.1 General Attributes

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of this drug?

SB4 is being developed as a proposed similar biological product to Enbrel® (etanercept).

During the clinical development of SB4, key regulatory interactions with the Applicant occurred in context of the clinical pharmacology program:

1. Pre-IND meeting held on February 22, 2012 discussed the study design of the pivotal PK similarity study in heathy subjects and PK similarity assessment in the comparative clinical study;
2. BPD Type 4 meeting held on May 26, 2016 discussed the content of PK similarity data from two clinical studies to support the comparative clinical development plan in the proposed BLA submission.

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

SB4 drug substance is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 kilodalton (p75) tumor necrosis factor receptor (TNFR) linked to the Fc portion of human IgG1. The Fc component of SB4 contains the CH2 domain, the CH3 domain and hinge region, but not the CH1 domain of IgG1. SB4 is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian cell expression system. It consists of 934 amino acids (molecular formula - $C_{2224}H_{3472}N_{618}O_{701}S_{36}$) and has a molecular weight of approximately 130 kilodaltons (Source – BLA 761066, Module 3.2.S.3.1).

SB4 injection drug product is presented in a single-dose pre-filled syringe is clear to opalescent, colorless to pale yellow, sterile, and preservative-free solution for injection presented in a pre-filled syringe.

Table 2 Composition of SB4 Drug Product

Component	Nominal Quantity/mL	Function	Quality Standard
Etanercept	50 mg	Active substance	In-house
Sucrose	10.0 mg	(b) (4)	Ph. Eur./NF
Sodium chloride	8.18 mg		Ph. Eur./USP/JP
Sodium phosphate monobasic monohydrate	1.038 mg		USP
Sodium phosphate dibasic heptahydrate	0.665 mg		USP
Water for injection	*q.s.*		Ph. Eur./USP

(Source: BLA 761066, Module 3.2.P.1, Description and composition of the drug product)

2.1.3 What are the proposed mechanism of action and therapeutic indication(s)?

SB4 is a dimeric soluble form of the p75 TNF receptor that can bind TNF molecules.

In the US, SB4 is intended to be licensed for five indications currently approved for US-licensed Enbrel®. These indications are RA, Polyarticular Juvenile Idiopathic Arthritis (JIA) in patients aged 2 years or older, Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS) and Plaque Psoriasis (PsO). SB4 is not intended to be licensed for pediatric patients (PsO and JIA) weighing less than 63 kg.

2.1.4 What are the proposed dosages and routes of administration?

The proposed dosages and route of administration for the listed indications are identical to those approved for US-licensed Enbrel® (BLA 103795), as outlined in Table 3.

Table 3 Proposed Dosage and Routes of Administration for SB4

Indication	Dosage and Administration
Adult RA and PsA	50 mg once weekly with or without methotrexate (MTX)
AS	50 mg once weekly
Adult PsO	50 mg twice weekly for 3 months, followed by 50 mg once weekly
Pediatric PsO and JIA (patients who weigh 63 kg or more)	50 mg once weekly

Abbreviations: AS, ankylosing spondylitis; JIA, polyarticular juvenile idiopathic arthritis PsA, psoriatic arthritis; PsO, plaque psoriasis; RA, rheumatoid arthritis
(Source: USPI ENBREL® (etanercept), Revised 10/2017, Amgen)

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

The clinical development for SB4 included two completed clinical studies, SB4-G11-NHV and SB4-G31-RA as listed in Table 4 below.

Study SB4-G11-NHV was the pivotal three-part, two-way crossover PK-similarity study comparing SB4, EU-approved Enbrel® and US-licensed Enbrel® in healthy male subjects. In addition, PK of SB4 and EU-approved Enbrel® was also assessed in patients with moderate-to-severe RA in Study SB4-G31-RA.

This clinical pharmacology reviewer primarily focused on the pivotal PK similarity study (SB4-G11-NHV). The PK and immunogenicity in the comparative efficacy study (SB4-G31-RA) were also reviewed.

Table 4 Listing of Clinical Studies

Study ID	Design	Objectives	Subjects	Treatments	Endpoints
Clinical Pharmacology Study					
SB4-G11-NHV	R, SB, 3-part, cross-over	PK, safety, and immunogenicity	138 healthy male subjects	50 mg SC 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)	AUC_{inf}, AUC_t and C_{max}
Comparative Clinical Study					
SB4-G31-RA	R, DB, PG TP1 (Wk 0-52)	Efficacy, safety, immunogenicity and PK	596 RA patients	50 mg SC once weekly: • SB4; n=299 • EU-Enbrel®; n=297	ACR20 at 24 weeks
	R, OL, TP2 (switching) (Wk 52-100)	Safety and immunogenicity	245 RA patients	50 mg SC once weekly: • SB4 cont. (SB4/SB4); n=126 • EU-Enbrel® switch (Enbrel®/SB4); n=119	Safety, Immunogenicity

Abbreviations: R, randomized; DB, double blind; OL, open label; PG, parallel group; TP, treatment period; SB, single blind; SD, single dose; SC, subcutaneous
(Source: BLA 761066, Module 2.7.6 - Synopses of Individual Studies)

2.2.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

PK (AUC_{inf}, AUC_t, and C_{max}) was assessed as primary endpoint in the Study SB4-G11-NHV to evaluate and compare the PK profiles of SB4, EU-approved Enbrel® and US-licensed Enbrel® in healthy male subjects. Safety, tolerability and immunogenicity were the secondary endpoints. Study SB4-G31-RA was the comparative efficacy trial in patients with moderate-to-severe RA. Therefore, the primary efficacy endpoint was the proportion of patients achieving a 20% or greater improvement in the American College of Rheumatology (ACR) clinical response (ACR20 criteria) at Week 24. Safety, immunogenicity and PK at steady-state (C_{trough}), in a subset of patients (i.e., n=79; SB4: n=41, EU-approved Enbrel®: n=38), were also evaluated.

2.2.3 What are the PK characteristics of the drug?

2.2.3.1 What are the single dose and multiple dose pharmacokinetic characteristics for SB4?

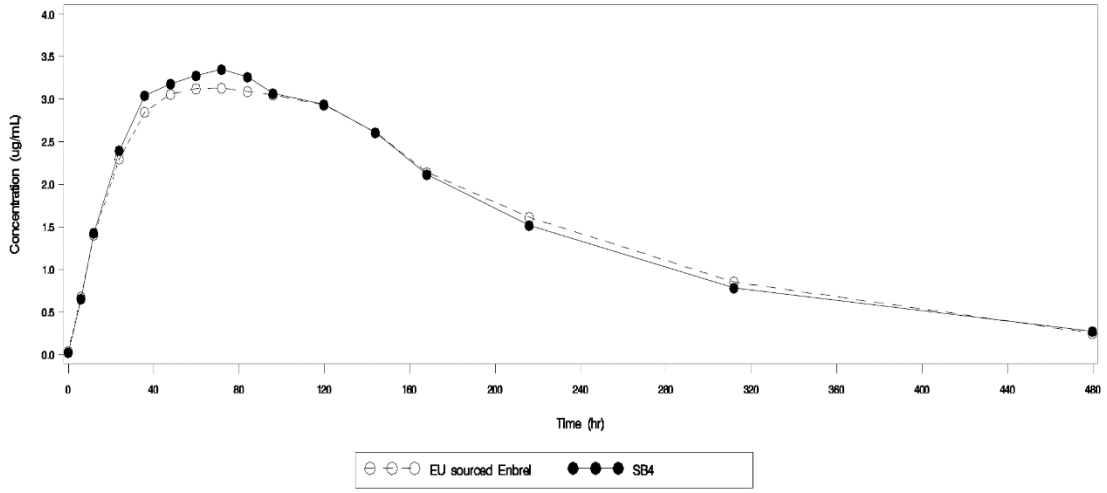
Single-Dose PK

The pivotal PK similarity Study SB4-G11-NHV was a randomized, single-blind, three-part, two-period, two-sequence, single-dose, cross-over study comparing the pharmacokinetic profiles a single-dose 50 mg SC injection of the test product SB4 and US-licensed Enbrel® and EU-approved Enbrel® in 138 healthy male subjects. In this study, healthy male subjects received one single dose of 50 mg of the study drug subcutaneously (SC) followed by a washout period of at least 35 days and were then crossed over to receive another single dose of 50 mg SC of the comparator product. The PK, safety, tolerability, and immunogenicity of SB4, EU-approved Enbrel® and US-licensed Enbrel® were assessed.

The pairwise comparisons 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) met the pre-specified acceptance criteria for PK similarity (90% CIs for the ratios of geometric mean of AUC_{inf}, AUC_t, and C_{max} were within the interval of 80.00 to 125.00%) as summarized in (Table 5).

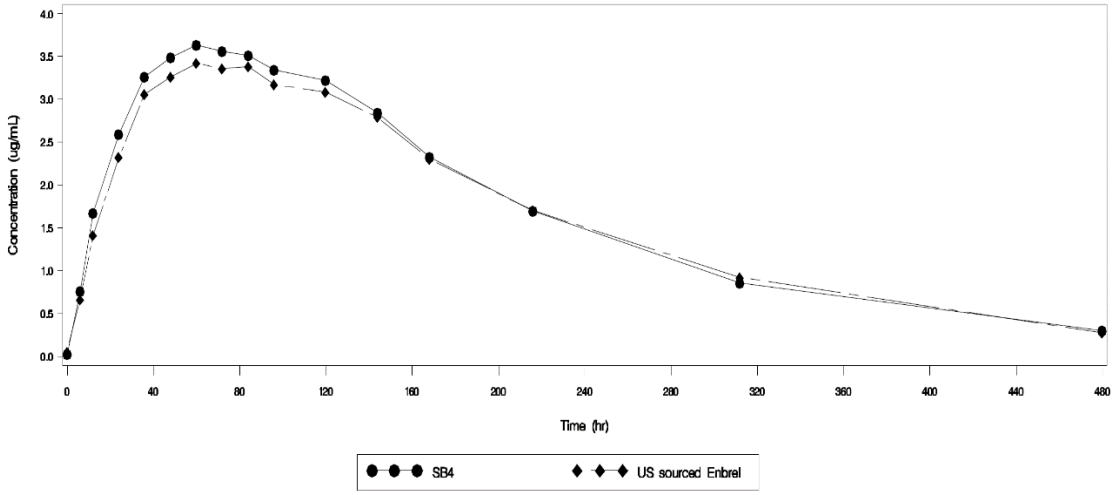
The mean serum concentration-time profiles of SB4, EU-approved Enbrel® or US-licensed Enbrel® treatment groups in Parts A, B and C of the Study SB4-G11-NHV are presented in Figure 1-3.

Figure 1 Mean Serum Drug Concentration-time Profiles following a Single 50 mg SC Dose of SB4 or EU-approved Enbrel® in Healthy Male Subjects (Part A, Study SB4-G11-NHV)



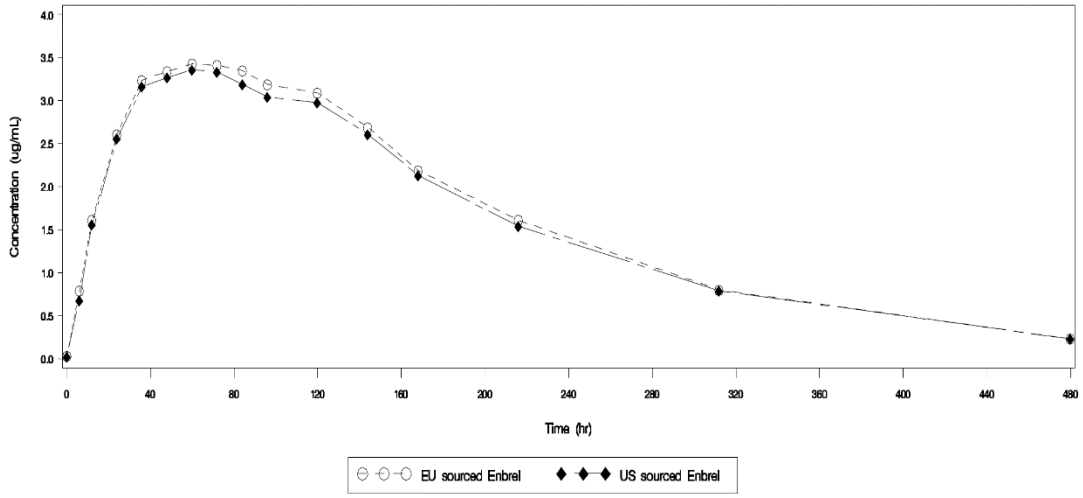
(Source: BLA 761066, Module 5.3.3.1 CSR SB4-G11-NHV)

Figure 2 Mean Serum Drug Concentration-time Profiles following a Single 50 mg SC Dose of SB4 or US-Licensed Enbrel® in Healthy Male Subjects (Part B, Study SB4-G11-NHV)



(Source: BLA 761066, Module 5.3.3.1 CSR SB4-G11-NHV)

Figure 3 Mean Serum Drug Concentration-time Profiles following a Single 50 mg SC Dose of EU-approved Enbrel® or US-Licensed Enbrel® in Healthy Male Subjects (Part C, Study SB4-G11-NHV)



(Source: BLA 761066, Module 5.3.3.1 CSR SB4-G11-NHV)

Table 5 Geometric Means, Ratios of Geometric Means and 90% Confidence Intervals for the Comparison of the PK Parameters between Test and References Products (Study SB4-G11-NHV)

PK Parameters[a]	Geometric Mean[a]			90% CI[b]
	Test	Reference	Ratio T/R (%)	
PART A: SB4 (T, n= 42) *vs* EU-approved Enbrel® (R, n=42)				
AUC_{inf} (µg.h/mL)	729.371	736.391	99.0	94.7 - 103.6
AUC_t (µg.h/mL)	688.853	698.494	98.6	94.2 - 103.3
C_{max} (µg/mL)	3.319	3.201	103.7	98.5 - 109.2
PART B: SB4 (T, n=44) *vs* US-licensed Enbrel® (R, n= 44*)*				
AUC_{inf} (µg.h/mL)	794.463	785.891	101.1	95.8 - 106.7
AUC_t (µg.h/mL)	749.543	742.437	101.0	95.4 - 106.9
C_{max} (µg/mL)	3.613	3.463	104.4	97.7 - 111.4
PART C: EU-approved Enbrel® (T, n=42) *vs* US-licensed Enbrel® (R, n= 42)				
AUC_{inf} (µg.h/mL)	735.360	731.657	100.5	91.5 - 110.4
AUC_t (µg.h/mL)	700.560	691.766	101.3	92.3 - 111.1
C_{max} (µg/mL)	3.408	3.300	103.3	94.7 - 112.7

[a]Data are presented as the geometric means for Test Product and Reference Products based on Least Squares Mean of log-transformed parameter values. [b]90% CI: Lower and upper limits of 90% confidence interval of the geometric men ratio.
(Source: BLA 761066, Module 5.3.3.1, CSR SB4-G11-NHV)

The Study SB4-G11-NHV comprised of three parts (Part A, B and C). In each part, comparison between SB4 and EU Enbrel® (Part A), between SB4 and US Enbrel® (Part B), and between EU Enbrel® and US Enbrel® (Part C) was performed. Among the 138 healthy male subjects randomized in Study SB4-G11-NHV, 46 subjects were assigned in each of the three parts. Ten subjects (4, 2, and 4 in Part A, B and C, respectively) were excluded from the PK analysis. Of these 10 subjects, 6 subjects were excluded because they discontinued from the study prematurely, and consequently had an incomplete PK profile. The remaining 4 subjects were excluded because the PK analyses because they had non-zero baseline concentrations of greater than 5% of C_{max} in Period 2.

Independent PK analyses were conducted by the reviewer and the 90% CI of the geometric mean ratio of AUC_{inf}, AUC_t, and C_{max} were all within the PK similarity criteria range of 80.00-125.00% for the pairwise comparisons among SB4, EU-approved Enbrel®, and US-licensed Enbrel®.

Multiple-Dose PK

The PK of SB4 and EU-approved Enbrel® was also assessed in the comparative efficacy Study SB4-G31-RA. This prospective Phase 3 study was designed to compare the efficacy, safety and immunogenicity between SB4 and EU-approved Enbrel® in combination with MTX to treat subjects with moderate-to-severe RA who have had an inadequate response to MTX therapy.

A total of 596 patients with moderate-to-severe RA were randomized in a 1:1 ratio to receive either 50 mg SB4 (n=299) or 50 mg EU-approved Enbrel® (n=297) once weekly for 52 weeks via self-administered SC injection.

The primary endpoint of the study was the proportion of subjects achieving a 20% or greater improvement in ACR clinical response at Week 24. PK analysis was performed in a subset of patients (PK Subset - n=79; SB4: n=41, EU-approved Enbrel®: n=38). Serum drug concentrations were determined at baseline, and prior to dosing at Weeks 2, 4, 8, 12, 16 and 24 with additional samples at Week 8 (24, 48, 72, 96, and 168 hours after administration). As shown in Table 6, the PK measures showed similar inter-subject variability (%CV) for both SB4 and EU-approved Enbrel® groups; %CV in C_{trough} values ranged from 45.2 to 53.9 and 42.4 to 65.7, for SB4 and EU-approved Enbrel® groups, respectively. Even with the observed inter-subject variability in the PK measures, the values of C_{trough} and C_{max} for SB4 treatment group were generally comparable to those for EU-approved Enbrel® in the small patient PK subset (Table 6).

Table 6 Mean (Min, Max) Value of Serum Concentrations of SB4 and EU-approved Enbrel® (PK Subset, Study SB4-G31-RA)

Visit (Week)	SB4			EU-approved Enbrel®		
	C_{trough} (µg/mL) Mean (Min, Max)	CV%	n	C_{trough} (µg/mL) Mean (Min, Max)	CV%	n
2	2.42 (0.00, 4.75)	45.2	35	2.64 (0.36, 5.53)	42.4	36
4	2.64 (0.00, 5.72)	49.1	36	2.07 (0.50, 4.56)	55.9	36
8	2.89 (0.00, 5.75)	53.9	36	2.21 (0.00, 5.46)	65.7	35
12	2.86 (0.45, 6.31)	48.6	34	2.30 (0.37, 4.56)	49.4	36
16	2.54 (0.00, 5.46)	53.8	34	2.31 (0.00, 5.84)	57.7	35
24	2.75 (0.68, 5.82)	46.5	34	2.56 (0.46, 6.36)	50.6	33
	Week 8 PK Parameters Mean (Min, Max)	**CV%**	**n**	**Week 8 PK Parameters** Mean (Min, Max)	**CV%**	**N**
AUC_τ (µg·h/mL)	676.38 (121.68, 1142.11)	37.7	36	520.90 (98.09, 1145.02)	50.1	34
C_{min} (µg/mL)	2.60 (0.00, 5.23)	53.2	36	1.83 (0.00, 5.24)	59.5	35
C_{max} (µg/mL)	5.14 (0.89, 7.76)	35.1	36	4.08 (0.90, 9.64)	52.2	35

(Source: BLA 761066, Module 5.3.5.1, CSR SB4-G31-RA)

2.3 Intrinsic Factors

2.3.1 Immunogenicity

2.3.1.1 How was the immunogenicity assessed and what was the incidence of the formation of the anti-drug antibody?

Immunogenicity samples were analyzed using validated ADA assays based on a tiered approach. Only confirmed anti-drug antibody (ADA) positive samples were then assessed for neutralizing antibodies (NAbs). The measurement of ADA was accomplished using electrochemiluminescence (ECL) method, and measurement of NAb was accomplished using cell-based assay method in Study SB4-G11-HNV and a ligand-binding assay in Study SB4-G31-RA. The drug tolerance for the assays was in the range of 2 µg/mL. Refer to the OBP review for detailed information regarding assay validation and analysis of clinical study samples.

In the PK similarity study SB4-G11-NHV, samples were collected pre-dose, and 4 weeks after first injection of study treatments for assessment of immunogenicity. Table 7 summarizes the immunogenicity

results by treatment group. In Part A (SB4 vs. EU-approved Enbrel®) of the study, antibodies to EU-approved Enbrel® were detected in 3 subjects on Day 29 post-dose. Of the subjects who had confirmed positive ADA, NAb was detected in one subject. In Part B (SB4 vs. US-licensed Enbrel®) of the study, antibodies to US-licensed Enbrel® were detected in 4 subjects on Day 29 post-dose. Of the subjects who had confirmed positive ADA, none of the subjects had a positive result for NAb. In Part C (US-licensed Enbrel® vs. EU Enbrel®) of the study, antibodies were detected in 10 subjects; 6 subjects in US-licensed Enbrel® and 4 subjects in EU-approved Enbrel® on Day 29 post-dose. Of the subjects who had confirmed positive ADA, none of the subjects had a positive result for NAb. While small differences in the proportion of subjects with ADA positive response were evident after single dose administration in Study SB4-G11-NHV, it should be noted that assessment of immunogenicity after multiple dose in Study SB4-G31-RA is considered clinically more relevant.

In study SB4-G31-RA, blood samples were collected at baseline and Weeks 2, 4, 8, 12, 16, 24, and 52 for assessment of serum ADA and NAb (in ADA positive subjects only) formation and titers in response to SB4 and EU-approved Enbrel®. The incidences of ADA in SB4 and EU-approved Enbrel® treatment groups were not comparable at each specific time point of measurement during the 52 weeks of treatment. A total of 3 (1.0%) subjects in the SB4 group and 39 (13.2%) subjects in the EU-approved Enbrel® were tested positive for ADA during this period (Table 8).

It should be noted that the range of drug tolerance of the ECL method (2 µg/mL) overlapped with the range of observed PK concentrations; therefore, the incidence of ADA maybe underestimated with the assay. For details see the OBP review by Dr. Brian Janelsins. For the comparative efficacy study (SB4-G31-RA), the etanercept concentrations in the PK subset varied between 0.0-6.36 µg/mL (Table 6).

Table 7 Incidence of Anti-Drug Antibody (ADA) in the Clinical Studies SB4-G11-NHV by Treatment Group (SB4, EU-approved Enbrel®, US-licensed Enbrel®)

	Part A		Part B		Part C	
	SB4	EU sourced Enbrel®	SB4	US sourced Enbrel®	EU sourced Enbrel®	US sourced Enbrel®
	N = 23	N = 23	N = 23	N = 23	N =23	N = 23
Result	n/n' (%)	n/n' (%)	n/n' (%)	n/n' (%)	n/n' (%)	n/n' (%)
ADA						
Positive	0/22 (0.0)	3/23 (13.0)	0/23 (0.0)	4/22 (18.2)	4/22 (18.2)	6/22 (27.3)
Negative	22/22 (100.0)	20/23 (87.0)	23/23 (100.0)	18/22 (81.8)	18/22 (81.8)	16/22 (72.7)
Nab						
Positive	0	1/3 (33.3)	0	0/4 (0.0)	0/4 (0.0)	0/6 (0.0)
Negative	0	2/3 (66.7)	0	3/4 (75.0)	4/4 (100.0)	5/6 (83.3)
Non-specific positive	0	0/3 (0.0)	0	1/4 (25.0)	0/4 (0.0)	1/6 (16.7)

(Source: BLA 761066, Module 5.3.3.1, CSR SB4-G11-NHV)

Table 8 Incidence of Anti-Drug Antibody (ADA) in the Clinical Studies SB4-G31-RA by Treatment Group (SB4, EU-approved Enbrel®)

Timepoint	Parameter	SB4 N=299			EU Enbrel® N=297			Total N=596		
		n'	n	(%)	n'	n	(%)	n'	n	(%)
Week 0	ADA	299	0	(0.0)	297	0	(0.0)	596	0	(0.0)
	NAb		0			0			0	
Week 8 overall[a]	ADA	299	2	(0.7)	296	38	(12.8)	595	40	(6.7)
	NAb		0			1			1	
Week 24 overall[a]	ADA	299	2	(0.7)	296	39	(13.2)	595	41	(6.9)
	NAb		0			1			1	
Week 52 overall[a]	ADA	299	3	(1.0)	296	39	(13.2)	595	42	(7.1)
	NAb		0			1			1	

#Overall ADA results at Week 8, Week 24 and Week 52 were determined as "Positive" if at least one ADA positive until the time point regardless the ADA result at Week 0 and "Negative" if no ADA positive until the time point regardless the ADA result at Week 0.
(Source: BLA 761066, Module 5.3.5.1, CSR SB4-G31-RA)

2.3.1.2 Does the immunogenicity affect the PK similarity of the therapeutic protein?

In the PK similarity study SB4-G11-NHV, 3 subjects tested positive to EU-approved Enbrel® in Part A, and 4 subjects tested positive to US-licensed Enbrel® in Part B of the study (Table 7). Therefore, the impact of ADA on SB4 PK was not evaluated as the ADA incidence is 0 for SB4 in Study SB4-G11-NHV.

In the comparative efficacy study SB4-G31-RA, mean serum trough concentrations and PK parameters from patients with positive ADA results generally fell within the trough concentration data and PK parameter ranges of patients with ADA-negative results (Table 9). It should be noted that the incidence of overall positive ADA was low in the PK Subset, i.e., 1 patient in the SB4 treatment group and 3 patients in the EU-approved Enbrel® treatment group. As shown in Table 9, for both SB4 and EU-approved Enbrel® sub-groups, the mean C_{trough} values were generally lower in ADA-positive subjects, as compared to the ADA negative subjects. However, due to the low incidence of overall positive ADA results in PK subset, the impact of the presence of ADA to the PK was remains unclear.

Table 9 Mean (Min, Max) Value of Serum Concentrations and PK Parameters of SB4 and EU-approved Enbrel® by Anti-Drug Antibody (ADA) Status (Study SB4-G31-RA)

	ADA-positive Subjects		ADA-Negative Subjects	
Visit (Week)	**SB4**	**EU-approved Enbrel®**	**SB4**	**EU-approved Enbrel®**
C_{trough} (µg/mL) Mean (Min, Max)				
2	2.14*	2.14 (0.89, 3.78)	2.43 (0.00, 4.75)	2.68 (0.36, 5.53)
4	1.08*	1.49 (0.93, 2.52)	2.69 (0.00, 5.72)	2.12 (0.50, 4.56)
8	1.60*	1.14 (0.68, 1.69)	2.92 (0.00, 5.75)	2.31 (0.00, 5.46)
12	-	1.80 (1.12, 2.15)	2.86 (0.45, 6.31)	2.35 (0.37, 4.56)
16	1.45*	2.00 (1.61, 2.50)	2.57 (0.00, 5.46)	2.34 (0.00, 5.84)
24	2.28*	2.13 (1.16, 3.54)	2.76 (0.68, 5.82)	2.60 (0.46, 6.36)
Day 8 PK Parameters Mean (Min, Max)				
AUC_{τ} (µg·h/mL)	494.37*	446.36 (231.43, 577.90)	681.58 (121.68, 1142.11)	528.11 (98.09, 1145.02)
C_{min} (µg/mL)	1.52*	1.14 (0.68, 1.69)	2.63 (0.00, 5.23)	1.89 (0.00, 5.24)
C_{max} (µg/mL)	4.10*	3.74 (1.98, 4.73)	5.17 (0.89, 7.76)	4.12 (0.90, 9.64)

* (n=1)
(Source: Adapted from BLA 761066, Module 5.3.5.1, CSR SB4-G31-RA)

2.3.1.3 Does the immunogenicity affect the efficacy comparison of the therapeutic protein?

In the comparative efficacy Study SB4-G31-RA, the proportion of patients achieving ACR20 response was 78.1% (193/247) and 80.5% (190/236) in the SB4 and EU Enbrel® treatment groups, respectively. The proportion of patients achieving ACR20 response who had an overall post-dose negative ADA result at Week 24 was 78.0% (191/245) and 81.6% (169/207), respectively. Additionally, the proportion of patients achieving ACR20 response who had an overall post-dose positive ADA result at Week 24 was 100% (2/2) and 72.4% (21/29), respectively. The ACR20 response rates at Week 24 were generally comparable between the two treatment groups regardless of ADA status over the 24-week treatment period. Overall, the ADA formation did not significantly affect the comparative efficacy between SB4 and EU-approved Enbrel®. It should be noted that there is a possibility of underestimation of ADA rate in Study SB4-G31-RA. Refer to the OBP review for information about the analytical method validation for assessment of immunogenicity. Refer to the Clinical review for further information on the efficacy comparison.

2.3.1.4 Does the immunogenicity affect the safety comparison of the therapeutic protein?

The overall incidence of injection site reactions was 3.4% (10/296) in the SB4 vs. 17.5% (45/257) in the EU Enbrel® treatment groups in patients with an overall post-dose negative ADA result and 33.3% (1/3) vs. 17.9% (7/39) in patients with an overall post-dose positive ADA result at Week 52. Refer to the Clinical review for further details.

2.4 General Biopharmaceutics

2.4.1 What is the *in vivo* relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?

The SB4 clinical formulation used in the pivotal PK similarity study (SB4-G11-NHV), and in the comparative efficacy study (SB4-G31-RA) was the same as the proposed to-be-marketed formulation. Refer to OBP review for more details.

2.5 Analytical Section

2.5.1 What are the analytical methods used to measure SB4 or Enbrel in serum?

Study SB4-G11-NHV - The serum concentrations of SB4, US-licensed Enbrel® and EU-approved Enbrel® were quantified using a validated Enzyme Linked ImmunoSorbent Assay (ELISA). A brief description of the ELISA assay: Mouse-Anti-Human s-TNF Receptor II was immobilized onto a 96-well microtiter sample plate. All unadsorbed sites were blocked with the addition of block/diluent buffer. Following this, 100 µL of blank, calibration standard, QC, and samples (all diluted at the 1 to 50 minimum required dilution) were dispensed onto the sample plate and incubated for 90 minutes with agitation. After washing the plate, an Anti-TNF receptor II Biotinylated Antibody solution was added and incubated for 90 minutes with agitation. After washing the plate, a Streptavidin-HRP solution was added and incubated for 30 minutes with agitation. After the final wash step, TMB substrate was added to the plate and incubated for 15 min. The reaction was stopped with a stop solution. Color develops in proportion to the amount of analyte (etanercept or SB4) in the sample. Plates were read on a plate reader with reading capabilities at 450 nm within 15 min.

SB4, US-licensed Enbrel® and EU-approved Enbrel® concentrations were determined on a standard curve obtained by plotting absorbance versus concentration using a five-parameter logistic curve-fitting program. The calibration curve range in human serum was 20.00 – 1000.00 ng/mL. The potential for variable matrix-related interferences was evaluated for SB4 in independent sources of normal (n=15), lipemic (n=5) and hemolyzed (n=5) matrices. No matrix effect in normal matrix samples was detected. In addition, there were no observed effects of hemolysis and lipemia. The specificity of the assay was evaluated by determining the accuracy and precision of US-licensed Enbrel®, EU-approved Enbrel® and SB4 quantification in the presence of soluble target/endogenous protein. The results demonstrated that up to 500 pg/mL TNF-alpha did not interfere with the detection of US-licensed Enbrel®, EU-approved Enbrel® and SB4. The validation results are shown in Table 10.

Table 10 Validation Summary for Enbrel® and SB4 Analytical PK Method (Study SB4-G11-NHV)

Bioanalytical Method Validation Report	Title: Method Validation for the Determination of SB4 and Enbrel® in Human Serum using ELISA (Report No. 8276853; Analytical Procedure Number - IC-12-065)		
Method Description	Matrix	Human serum	
	Primary Antibody	Mouse-Anti-Human sTNF Receptor II	
	Detection Method	ELISA with OD quantification MRD 1:50 (10 µL Sample + 490 µL Low Cross Buffer)	
	Sample Aliquot Volume	100 µL	
	Calibration Range	20.00 – 1000.00 ng/mL	
	Calibration Model	5 PL (regression)	
	Weighting Factor	Non weighted	
	ULOQ	1000.00 ng/mL	
	LLOQ	20.00 ng/mL	
Validation Assay Performance			
Analyte	**SB4**	**US-licensed Enbrel®**	**EU-approved Enbrel®**
Lots	12L11 SB4-14H04	1034016 1027240	G47931 H91657 F45454 203379
Lower Limit of quantitation (LLOQ)	20.00 ng/mL	20.00 ng/mL	20.00 ng/mL
LLOQ Mean Intra-run precision (%)	12.8 (n=6)	6.9 (n=6)	9.0 (n=6)
LLOQ Mean Intra-run accuracy (% RE)	3.9 (n=6)	-2.2 (n=6)	-2.7 (n=6)
LLOQ Inter-run precision (%)	19.8 (n=6)	15.9 (n=6)	12.4 (n=6)
LLOQ Inter-run accuracy (% RE)	11.1 (n=6)	-4.8 (n=6)	-3.1 (n=6)
QC concentrations (ng/mL)	20.00 (LLOQ), 60.00 (LQC), 400.00 (MQC), 750.00 (HQC), 1000.00 (ULOQ)		
QC Mean Intra-run precision (%)	LQC=4.1 MQC=7.2 HQC=7.6 ULOQ=19.1	LQC=4.7 MQC=3.0 HQC=8.1 ULOQ=10.2	LQC=6.0 MQC=2.7 HQC=9.1 ULOQ=10.6
QC Mean Intra-run accuracy (%)	LQC=18.4 MQC=12.2 HQC=1.9 ULOQ=2.7	LQC=1.4 MQC=-7.2 HQC=-9.8 ULOQ=-9.5	LQC=0.8 MQC=-8.4 HQC=-14.2 ULOQ=-18.1
QC Inter-run precision (%)	LQC=6.9 MQC=9.5 HQC=14.4	LQC=7.3 MQC=8.0 HQC=9.0	LQC=6.7 MQC=7.6 HQC=12.8

	ULOQ=12.1	ULOQ=11.4	ULOQ=11.2
QC Inter-run accuracy (%)	LQC=5.4 MQC=0.0 HQC=0.4 ULOQ=1.1	LQC=-1.2 MQC=-1.7 HQC=-12.4 ULOQ=-8.6	LQC=-6.1 MQC=-11.1 HQC=-10.9 ULOQ=-9.7
Dilution linearity	1 in 1000 dilution (in addition to 1 in 50 MRD)		
Short-term Stability	24 hours at room temperature		
Long-term Stability	In human serum - Up to 3 months and 24 months at <-10°C and <-50°C, respectively In rheumatoid arthritis serum - Up to 12 months at <-50°C		
Freeze-Thaw Stability	Five cycles at nominal <-50°C		

[Source: Adapted from BLA 761066, Module 5.3.1.4 - Method Validation for the Determination of SB4 and Enbrel® in Human Serum using ELISA]

Study SB4-G13-RA- The serum concentrations of SB4, US-licensed Enbrel® and EU-approved Enbrel® were quantified using a validated ELISA. A brief description of the ELISA assay: Anti-Human TNF RII/TNFRSF1B Biotinylated Antibody was immobilized onto a 96-well microtiter sample plate. All unadsorbed sites were blocked with the addition of block/diluent buffer. Following this, 100 µL of blank, calibration standard, QC, and samples (all diluted at the 1 to 200 minimum required dilution) were dispensed onto the sample plate and incubated for 90 minutes with agitation. After washing the plate, an Anti-Human TNF RII/TNFRSF1B Biotinylated Antibody solution was added and incubated for 90 minutes with agitation. After washing the plate, a Streptavidin-HRP solution was added and incubated for 30 minutes with agitation. After the final wash step, TMB substrate was added to the plate and incubated for 10 min. The reaction was stopped with a stop solution. Color develops in proportion to the amount of analyte (etanercept or SB4) in the sample. Plates were read on a plate reader with reading capabilities at 450 nm within 15 min.

SB4, US-licensed Enbrel® and EU-approved Enbrel® concentrations were determined on a standard curve obtained by plotting absorbance versus concentration using a four-parameter logistic curve-fitting program. The calibration curve range in human serum was 160.00 – 4000.00 ng/mL. The validation results are shown in Table 11.

Table 11 Validation Summary for Enbrel® and SB4 Analytical PK Method (Study SB4-G31-RA)

Bioanalytical Method Validation Report	Title: Validation of a Method for the Determination of SB4 and EU Enbrel® in Rheumatoid Arthritis Human Serum Using Enzyme-Linked Immunosorbent Assay (ELISA) (Report No. 8295685; Analytical Procedure Number - IC 13-080)	
Method Description	Matrix	Human serum
	Primary Antibody	Anti-Human TNF RII/TNFRSF1B Biotinylated Antibody
	Detection Method	ELISA with OD quantification MRD 1:200 [20 µL Sample + 180 µL Low Cross Buffer (MRD1) & then 30 µL MRD1 + 570 µL Low Cross Buffer]
	Sample Aliquot Volume	100 µL
	Calibration Range	160.00 – 4000.00 ng/mL
	Calibration Model	4 PL (regression)
	Weighting Factor	Non weighted
	ULOQ	4000.00 ng/mL
	LLOQ	160.00 ng/mL
Validation Assay Performance		
Analyte	**SB4**	**EU-approved Enbrel®**
Lots	12L11	203379
Lower Limit of quantitation (LLOQ)	160.00 ng/mL	160.00 ng/mL
LLOQ Mean Intra-run precision (% CV range)	2.3 to 10.1 (n=7)	2.2 to 15.2 (n=7)
LLOQ Mean Intra-run accuracy (% RE range)	-14.4 to 7.5 (n=7)	-14.8 to 2.8 (n=7)
LLOQ Inter-run precision (% CV)	10.4 (n=7)	10.2 (n=7)
LLOQ Inter-run accuracy (% RE)	-5.0 (n=7)	-6.6 (n=7)
QC concentrations (ng/mL)	160.00 (LLOQ), 480.00 (LQC), 1000.00 (MQC), 3000.00 (HQC), 4000.00 (ULOQ)	
QC Mean Intra-run precision (% CV range)	LQC= 1.7 to 8.6 MQC= 0.7 to 7.0 HQC= 3.7 to 11.6 ULOQ= 0.8 to 17.8	LQC= 1.0 to 11.3 MQC= 1.1 to 7.2 HQC= 4.0 to 14.9 ULOQ= 3.3 to 13.2
QC Mean Intra-run accuracy (% RE range)	LQC= −10.2 to −1.0 MQC= −10.2 to −0.7 HQC= −18.6 to −1.1 ULOQ= −15.6 to 1.2	LQC= −13.3 to 0.6 MQC= 0.2 to 13.6 HQC= −16.1 to 1.4 ULOQ= −14.5 to 5.0
QC Inter-run precision (%)	LQC= 6.5 MQC= 5.6	LQC= 7.5 MQC= 6.4

	HQC= 9.8 ULOQ=11.3	HQC= 9.6 ULOQ=10.3
QC Inter-run accuracy (%)	LQC= -6.4 MQC= -4.8 HQC= -10.3 ULOQ= -3.5	LQC= -4.8 MQC= -6.3 HQC= -6.1 ULOQ= -2.8
Dilution linearity	1 in 2000 dilution	
Short-term Stability	24 hours at room temperature	
Long-term Stability	Up to 12 months at <-50°C	
Freeze-Thaw Stability	Six cycles at nominal <-50°C	
Short-term Frozen Matrix Stability	SB4 37 days at ≤-50°C EU Enbrel® 56 days at ≤-50°C	

[Source: Adapted from BLA 761066, Module 5.3.1.4 - Validation of a Method for the Determination of SB4 and EU Enbrel® in Rheumatoid Arthritis Human Serum Using Enzyme-Linked Immunosorbent Assay (ELISA)]

2.5.2 What is the sample stability under conditions used in the PK similarity Study SB4-G11-NHV?

Pharmacokinetic samples from Study SB4-G11-NHV were stored and analyzed within the validated storage stability period and conditions for SB4, US-licensed Enbrel® and EU-approved Enbrel®.

Benchtop Stability (ambient temperature)
Based on the validation report submitted by the applicant, SB4, US-licensed Enbrel® and EU-approved Enbrel® were stable in human serum for 24 hours, respectively, at room temperature.

Freeze/Thaw Stability
Based on the validation report submitted by the applicant, the freeze-thaw stability for SB4, US-licensed Enbrel® and EU-approved Enbrel® was evaluated using QC samples subjected to three to five freeze (<-50°C) and thaw (ambient temperature) cycles. Results indicated that SB4, US-licensed Enbrel® and EU-approved Enbrel® were stable in human serum for at least five freeze/thaw cycles.

Long-term Storage Stability
The frozen stability for SB4, EU-approved Enbrel® and US licensed Enbrel® was evaluated for 92 days (3 months) when stored at <-10°C, and for 729 days (24 months) when stored at <-50°C. Results indicated that SB4, EU-approved Enbrel® and US licensed Enbrel® were stable in human serum for at least 92 days when stored at <-10°C, and for 729 days (24 months) when stored at <-50°C.

2.5.5 What is the result for the re-analysis of the incurred samples?

Pharmacokinetics samples from the pivotal PK study (Study SB4-G11-NHV) were re-analyzed for US-licensed Enbrel®, EU-approved Enbrel® and SB4 as part of the incurred sample reproducibility assessment. The results of the incurred sample reanalysis met the acceptance criterion demonstrating satisfactory reproducibility of the PK assay throughout the sample analysis period.

2.5.6 What are the findings from OSIS inspection?

The Office of Study Integrity and Surveillance (OSIS) inspection was requested for the clinical and bioanalytical sites of the pivotal clinical pharmacology Study SB4-G11-NHV. OSIS recommended accepting the clinical site data without an on-site inspection of the clinical site (PAREXEL International GmbH, Berlin). Refer to OSIS Memorandum (DARRTS dated 08/21/2017) for further details.

OSIS recently DARRTed their review (DARRTS dated 02/12/2018) for the bioanalytical site utilized for determination of etanercept concentrations in human serum in Study SB4-G11-NHV. Among other things, the OSIS reviewers identified significant findings including, but not limited to, the validation of the bioanalytical assay used to determine etanercept concentrations in human serum in Study SB4-G11-NHV. Specifically, the findings relate to the (b) (4) stability assessment of the bioanalytical assay used for Study SB4-G11-NHV. For details refer to the OSIS review by Drs. Gajendiran Mahadevan and Ruben Ayala. Accordingly, the OSIS reviewer recommended that (b) (4) prior to accepting the data from Study SB4-G11-NHV further review. At this time, the implications of the recent recommendations from OSIS as they relate to the bioanalytical site are being evaluated, and the Agency may contact the applicant and request additional information to address the issues identified by OSIS.

2.5.7 What bioanalytical methods are used to assess the immunogenicity?

Refer to Section 2.3.1.1 and the OBP review for information about the analytical method validation for assessment of immunogenicity.

3. Labeling Recommendations

In comparison to the US-licensed ENBREL USPI, the only labeling language changes proposed by the Applicant in Section 12.3 Pharmacokinetics of the SB4 label is the replacement of the term “ENBREL” with “etanercept”.

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

/s/

BHAWANA SALUJA
02/15/2018

ANSHU MARATHE
02/15/2018