

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761066Orig1s000**

**NON-CLINICAL REVIEW(S)**

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

**PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION**

Application number: 761066  
Supporting document/s: SDN # 1 and 8  
Applicant's letter date: October 25, 2018  
CDER stamp date: October 25, 2018  
Product: SB4 (a proposed biosimilar to US-licensed  
Enbrel®)  
Indication: Rheumatoid Arthritis, Polyarticular Juvenile  
Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing  
Spondylitis, Plaque Psoriasis  
Applicant: Samsung Bioepis Co., Ltd  
Review Division: Division of Pulmonary Allergy and  
Rheumatology Products  
Reviewer: Ijeoma Uzoma, Ph.D.  
Supervisor/Team Leader: Timothy Robison, Ph.D., DABT  
Division Director: Sally Seymour, MD  
Project Manager: Brandi Wheeler, PharmD

*Template Version: September 1, 2010*

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# 1 Executive Summary

## 1.1 Introduction

BLA 761066 was resubmitted by Samsung Bioepis on October 25, 2018, under section 351(k) of the Public Health Services Act (PHS Act) to support registration of SB4 as a biosimilar to US-licensed Enbrel<sup>®</sup> (etanercept) after receiving a Complete Response to the initial BLA submission. Etanercept is a dimeric soluble form of the p75 TNF receptor that can bind TNF molecules. Etanercept inhibits binding of TNF- $\alpha$  and TNF- $\beta$  (lymphotoxin alpha [LT- $\alpha$ ]) to cell surface TNF receptors, rendering TNF biologically inactive. US-licensed Enbrel<sup>®</sup> (US-Enbrel) is a subcutaneously administered product, originally developed by Immunex Corporation (BLA 103795, Approval date November 2, 1998), indicated for the treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, ankylosing spondylitis, and plaque psoriasis. Samsung Bioepis Co. intends to obtain indications for SB4 identical to the indications of the reference product that are not subject to orphan exclusivity and are supported by the current presentations of SB4: Rheumatoid arthritis, Juvenile Idiopathic Arthritis in patients that weigh over 63 kg (138 lbs.) from ages 2 and older, Psoriatic Arthritis, Ankylosing Spondylitis, and Plaque Psoriasis in patients that weigh over 63 kg (138 lbs.) from ages 4 and older. This review describes recommended changes in the proposed labeling for the product.

## 1.2 Brief Discussion of Nonclinical Findings

See review dated February 12, 2018.

## 1.3 Recommendations

### 1.3.2 Additional Nonclinical Recommendations

There are no outstanding PharmTox issues.

### 1.3.3 Labeling

The product label submitted by the Sponsor was consistent with the innovator product as well as the approved etanercept biosimilar Erelzi. In Section 8.1, 8.2, and 13.1, “etanercept” was changed to “etanercept products” or “SB4” as appropriate.

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/s/  
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IJEOMA K UZOMA  
04/16/2019 11:18:27 AM

TIMOTHY W ROBISON  
04/16/2019 05:34:43 PM  
I concur

## Pharmacology and Toxicology Secondary Review for BLA 761066

TO: BLA 761066 (SB4 as a biosimilar to US-licensed Enbrel® [etanercept])

FROM: Timothy W. Robison, Ph.D., D.A.B.T.  
Pharmacology and Toxicology Team Leader  
Division of Pulmonary, Allergy, and Rheumatology Products

DATE: March 16, 2018

BLA 761066 was submitted by Samsung Bioepis Co. on May 25, 2017 under section 351(k) of the Public Health Service Act (PHS Act) to support licensure of SB4 as a biosimilar to US-licensed Enbrel® (etanercept). US-licensed Enbrel® is a subcutaneously administered product, originally developed by Immunex Corporation (BLA 103795, Approval date November 2, 1998), indicated for the treatment of Rheumatoid Arthritis, Polyarticular Juvenile Idiopathic Arthritis in patients aged 2 years or older, Psoriatic Arthritis, Ankylosing Spondylitis, and Plaque Psoriasis in patients 4 years or older. Samsung Bioepis Co. intends to obtain indications for SB4 identical to the indications of the reference product that are not subject to orphan exclusivity and are supported by the current presentations of SB4: Rheumatoid arthritis, Juvenile Idiopathic Arthritis in patients that weigh over 63 kg (138 lbs.) from ages 2 and older, Psoriatic Arthritis, Ankylosing Spondylitis, and Plaque Psoriasis in patients that weigh over 63 kg (138 lbs.) from ages 4 and older.

Dr. Ijeoma Uzoma's review dated February 12, 2018 focused on three in vivo nonclinical studies submitted in support of a demonstration of biosimilarity of SB-4 to US-licensed Enbrel®: 1) a primary pharmacology study evaluating efficacy in a collagen antibody-induced arthritis mouse model comparing SB4 vs US-licensed Enbrel and EU-approved Enbrel (Study # CAIA-e007), 2) a single-dose PK study conducted in SD rats comparing SB4 vs. EU-approved Enbrel (Study # RD00407), and 3) a 4-week repeat-dose toxicity study in monkeys comparing SB4 vs US-licensed Enbrel (US-Enbrel) and EU-approved Enbrel (EU-Enbrel) (Study # 264-004).

The design of the nonclinical program (i.e., pharmacology study in mice, pharmacokinetic study in rats, 28-day toxicology study in monkeys, and safety assessments of extractables and leachables) for SB4 was discussed under Pre-IND 113462 (see meeting minutes dated March 23, 2012 and June 23, 2016).

The SB4 product formulation differs from the US-licensed Enbrel® formulation; see Dr. Uzoma's review for further details. There were no issues with excipients in the SB4 product formulation.

In the comparative efficacy study using the collagen antibody-induced arthritis mouse model, no differences in efficacy were observed between SB4, EU-approved Enbrel, or US-licensed Enbrel®.

In a single-dose subcutaneous pharmacokinetic study in male Sprague-Dawley rats, pharmacokinetic profiles were demonstrated to be comparable between SB4 and EU-approved Enbrel at a dose of 1 mg/kg.

The pivotal 28-day comparative repeat-dose toxicology study of SB4, EU-Enbrel, and US-Enbrel was conducted in Cynomolgus monkeys (3/sex/group) that received subcutaneous doses of 1 or 15 mg/kg administered twice per week. A separate vehicle-control group received the SB4 vehicle. There was one unscheduled death of a male monkey in the 15 mg/kg US-Enbrel group on Day 17. There were microscopic findings in the thoracic cavity that included pericardial adhesion/inflammation/fibrosis, inflammation of the epicardium, thrombus of the ventricle of the heart, and thrombus of the lung. The presence of bacterial colonies in the heart and pericardium were identified by hematoxylin and eosin and Giemsa staining. The cause of death was attributed to preexisting bacterial infection exacerbated by the immunosuppressive effects of etanercept.

Microscopic findings in SB4, EU-Enbrel and US-Enbrel treated animals at study termination were generally comparable. Expected treatment-related immunosuppressive microscopic findings included atrophy of the mandibular LN and decreased follicular lymphocytes of the mesenteric LB and spleen. One male in the 15 mg/kg SB4 group had findings consistent with macrophage activation syndrome in the spleen (increased numbers of enlarged macrophages with granular cytoplasm and cell debris and/or intact RBC or leukocytes), liver (sinusoidal leukocytosis), and mesenteric and mandibular lymph nodes (subcapsular sinuses and sinusoids contained macrophages that were enlarged with granular cytoplasm) that were considered test article related. Sinusoidal leukocytosis of the liver was observed for one female in the 1 mg/kg EU-Enbrel group, two females in the 15 mg/kg EU-Enbrel group, one female in the 1 mg/kg US-Enbrel group, and one female in the 15 mg/kg US-Enbrel group; this finding may have been a weak signal of macrophage activation syndrome.

In general, systemic exposures ( $AUC_{0-72}$  and  $C_{max}$ ) in the SB4 treated animals were comparable to those for EU-Enbrel and US-Enbrel treated monkeys. The decreased systemic exposures in 1 mg/kg-treated animals on Day 25 were likely due to the development of ADAs. The development of ADAs in 1 mg/kg/dose SB4 treated animals on Day 22 and at study termination, were generally comparable to those observed in EU-Enbrel and US-Enbrel treated monkeys. However, in the 15 mg/kg SB4 treated females, 0/3 were positive for ADA on Day 22 or at study termination.

Overall, the toxicology and toxicokinetic data submitted in BLA 761066 demonstrate the similarity of SB4 and US-licensed Enbrel<sup>®</sup> formulation from the nonclinical pharmacology and toxicology perspective and support a demonstration that SB4 is biosimilar to US-licensed Enbrel<sup>®</sup>.

I concur with Dr. Uzoma's review dated February 12, 2018 that recommends approval of SB4 from the nonclinical Pharmacology and Toxicology perspective. Dr. Uzoma's review recommended changes to the Sponsor's proposed labeling that were made to allow consistency with the labeling for US-licensed Enbrel<sup>®</sup> and approved biosimilar product,

ERELZI® (BLA 761042, Sandoz, Inc., approved August 30, 2016). The labeling format complies with the Pregnancy and Lactation Labeling Rule (PLLR) that was approved for the reference product, US-licensed Enbrel® on July 11, 2017.

Dr. Uzoma's review dated February 16, 2018 evaluated the safety of observed extractables and leachables from the container closure system.

**Recommendation:** From the nonclinical perspective, approval of the application is recommended.

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TIMOTHY W ROBISON  
03/16/2018

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

**PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION OF  
EXTRACTABLES AND LEACHABLES FROM THE CONTAINER CLOSURE SYSTEM  
(PREFILLED SYRINGE)**

Application number: 761066

Supporting document/s: SDN 1 and SDN 20

Applicant's letter date: May 25, 2017 and January 12, 2018

CDER stamp date: May 25, 2017 and January 12, 2018

Product: SB4 (a proposed biosimilar to US-licensed  
Enbrel®)

Indication: Rheumatoid Arthritis, Polyarticular Juvenile  
Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing  
Spondylitis, Plaque Psoriasis

Applicant: Samsung Bioepis Co., Ltd

Review Division: Division of Pulmonary Allergy and  
Rheumatology Products

Reviewer: Ijeoma Uzoma, Ph.D.

Supervisor/Team Leader: Timothy Robison, Ph.D., DABT

Division Director: Badrul Chowdhury, MD, Ph.D.

Project Manager: Brandi Wheeler, PharmD

*Template Version: September 1, 2010*

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# 1 Executive Summary

## 1.1 Introduction

BLA 761066 was submitted by Samsung Bioepis Co., Ltd on May 25, 2017, under section 351(k) of the Public Health Services Act (PHS Act) to support registration of SB4 as a biosimilar to US-licensed Enbrel® (etanercept). This review provides a safety evaluation of extractables and leachables for the SB4 container closure system. The overall nonclinical toxicology evaluation and labeling recommendations for this application are provided in a separate review.

## 1.2 Brief Discussion of Nonclinical Findings

The primary container closure system (CCS) for the SB4 drug product (DP) is the (b) (4) glass syringe with a 29-gauge thin-wall staked-in needle and a rigid needle shield, which is closed with (b) (4) plunger stopper. This CCS is a marketed device that is used with other FDA-approved drug products. The manufacturer has done extraction studies with this device.

To demonstrate compatibility of the container closure system with the DP, the Sponsor conducted extractables and leachables studies to evaluate if chemical compounds from the DP container closure system migrated into the SB4 solution.

A variety of analytical techniques were used for the identification and measurement of extractables and leachables that included semi-volatile organic compounds (SVOC), volatile organic compounds (VOC), non-volatile organic compounds (NVOC), and metals.

In forced extraction studies, high temperature and/or harsh solvents were used with the syringe components, listed above, in order to determine the compounds most likely to be extracted from the container closure components.

Forced extraction studies on (b) (4) glass syringe with a 29-gauge thin-wall staked-in needle and a rigid needle shield identified 23 extracted metals or organic compounds that were subsequently analyzed as potential leachables.

Leachables were identified and measured using stability samples under real time or accelerated conditions for up to 12 months. Observed levels of leachables were not considered to pose any safety concerns. Additional stability samples under real time conditions with time points up to 36 months are ongoing and will be provided when available.

## 1.3 Recommendations

### 1.3.1 Approvability

Leachables from the container closure system appear to pose no significant safety concerns to patients. The leachables study was ongoing at the time of this review and results for later time points will be reported over the product shelf life.

### 1.3.2 Additional Nonclinical Recommendations

None

## 2 Drug Information

### 2.1 Drug

CAS Registry Number (Optional): 185243-69-0 (etanercept)

Proper Name: To be determined

Code Name: SB4

Molecular Formula/Molecular Weight:  $C_{2224}H_{3472}N_{618}O_{701}S_{36}$  / 130 kDa (homodimer)

Structure or Biochemical Description:

SB4 is a homodimer of a chimeric protein genetically engineered by fusing the extracellular ligand binding domain of human TNFR2/p75 to the Fc domain of human IgG1. The Fc component comprises the hinge, CH2 and CH3 regions, but the CH1 region is excluded. SB4 consists of 934 amino acids (467 for the single chain) and has MW of approximately 130 kDa.

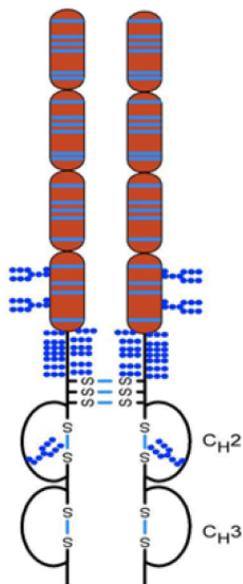
Amino Acid Sequence:

1	LPAQVAFTPY	APEPGSTCRL	REYYDQTAQM	CCSKCSPGQH	AKVFCTKTS
51	TVCDSCEDST	YTQLWNWVPE	CLSCGSRCSS	DQVETQACTR	EQNRICTCRP
101	GWYCALSKQE	GCRLCAPLRK	CRPGFGVARP	GTETSDVVCK	PCAPGTFST
151	TSSTDICRPH	QICNVVAIPG	<u>N</u> ASMDAVCTS	TSPTRSMAPG	AVHLPQPVST
201	RSQHTQPTPE	PSTAPSTSFL	LPMGSPPPAE	GSTGDEPKSC	DKTHTCPPCP
251	<b>APELLGGPSV</b>	<b>FLFPPKPKDT</b>	<b>LMISRTPEVT</b>	<b>CVVVDVSHED</b>	<b>PEVKFNWYVD</b>
301	<b>GVEVHNAKTK</b>	<b>PREEQYNSTY</b>	<b>RVVSVLTVLH</b>	<b>QDWLNGKEYK</b>	<b>CKVSNKALPA</b>
351	<b>PIEKTISKAK</b>	<b>GQPREPQVYT</b>	<b>LPPSREEMTK</b>	<b>NQVSLTCLVK</b>	<b>GFYPSDIAVE</b>
401	<b>WESNGQPENN</b>	<b>YKTTTPVLDS</b>	<b>DGSFFLYSKL</b>	<b>TVDKSRWQQG</b>	<b>NVFSCSVME</b>
451	<b>ALHNHYTQKS</b>	<b>LSLSPGK</b>			

Extracellular ligand-binding domain of the human TNFR: Normal letters  
**Fc domain of human IgG1: Bold letters**  
N-linked glycosylation site: Boxed letters  
Potential O-linked glycosylation site: Normal letters underlined  
*Cysteine residues: Italics*

(Excerpted from the Sponsor's submission)

Schematic Structure of SB4:



(Excerpted from the Sponsor’s submission)

Pharmacologic Class: Tumor Necrosis Factor Blocker

## 2.2 Relevant INDs, NDAs, BLAs and DMFs

Application #	Description	Sponsor	Date
PIND 113462	IND application in support of clinical testing of SB4 in the U.S.	Samsung Bioepis	3/4/2016 (PIND Submission date)

DMFs for primary packaging components:

[Redacted content] (b) (4)

## 2.3 Drug Formulation

The SB4 drug product will be provided as a 25 mg/ 0.50 mL and a 50 mg/mL solution for subcutaneous administration, supplied in a pre-filled syringe. The SB4 drug product formulation is not identical to that of the reference product and differs from the marketed US-Enbrel formulation with inclusion of the sodium phosphate monobasic monohydrate (b) (4) and sodium phosphate dibasic heptahydrate (b) (4). This formulation also lacks L-arginine monohydrochloride (b) (4) in the US-Enbrel formulation.

Component (50 mg)	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	<i>q.s.</i>		Ph.Eur./USP

(Excerpted from the Sponsor's submission)

Component (25 mg)	Nominal Quantity/Unit	Function	Quality Standard
Etanercept	25 mg	Active substance	In-house
Sucrose	5.0 mg	(b) (4)	Ph.Eur./NF
Sodium chloride	4.09 mg		Ph.Eur./USP/JP
Sodium phosphate monobasic monohydrate	0.519 mg		USP
Sodium phosphate dibasic heptahydrate	0.333 mg		USP
Water for injection	<i>q.s.</i>		Ph.Eur./USP

(Excerpted from the Sponsor's submission)

## 2.4 Comments on Novel Excipients

There are no novel excipients in the SB4 drug product.

## 2.5 Comments on Impurities/Degradants of Concern

Impurities appear to pose no safety concerns.

## 2.6 Proposed Clinical Population and Dosing Regimen

The proposed therapeutic indications for SB4 are identical to the indications of the reference product that are not subject to orphan exclusivity and are supported by the current presentations of SB4:

- Rheumatoid arthritis (RA)
- Juvenile Idiopathic Arthritis (JIA) in patients that weigh over 63 kg (138 lbs.) from ages 2 and older,
- Psoriatic Arthritis (PsA)
- Ankylosing Spondylitis (AS)
- Plaque Psoriasis (PsO) in patients that weigh over 63 kg (138 lbs.) from ages 4 and older.

The FDA approved the expanded use of Enbrel® for pediatric patients from ages 4 to 17 with the chronic moderate-to-severe plaque psoriasis in November 2016. (b) (4)

(b) (4) it was determined that the Sponsor needs to develop their pediatric presentation with clinical studies under PREA.

The US-licensed Enbrel dosage for adult patients with Rheumatoid Arthritis or Psoriatic Arthritis is 50 mg once weekly with or without methotrexate. For Ankylosing Spondylitis, the treatment regimen is 50 mg once weekly. For adults with Plaque Psoriasis, the dosage is 50 mg twice weekly for 3 months, followed by 50 mg once weekly. For patients aged 2 years or older with Polyarticular Juvenile Idiopathic Arthritis, the treatment regimen is 0.8 mg/kg weekly, with a maximum dose of 50 mg per week.

Proposed subcutaneous doses for SB4 are listed in the table below.

Patient Population	Recommended Dose and Frequency
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 or JIA (patients who weigh 63 kg or more)	50 mg once weekly

(Excerpted from the Sponsor's submission)

## 2.7 Regulatory Background

Samsung Bioepis Co submitted the initial meeting request for PIND 113462 on September 23, 2011 (received September 26, 2011) for the development of SB4 as a proposed biosimilar to US-Enbrel, for the same patient populations and dosing regimen as the reference product.

Nonclinical program for SB4 discussed under the Pre-IND:

Meeting minutes dated March 23, 2012: Recommended a GLP compliant 4-week comparative toxicology and TK study in Cynomolgus monkeys with US-licensed Enbrel and SAIT-104. The following parameters should be included: clinical signs, body weight, hematology, immunophenotyping of lymphocytes, clinical chemistry, gross pathology, organ weights, histopathology, and toxicokinetics. A complete battery of organs and tissues should be submitted for histopathological examination. An appropriate control group should be included. A SC dose of 15 mg/kg given twice weekly is recommended for US-licensed Enbrel and SAIT104. A group size of 3 monkeys/sex/group is recommended. FDA confirmed that that a recovery period is not required. A pharmacokinetic study in cynomolgus monkeys should be incorporated into the toxicology study. The pharmacokinetic method should be GLP compliant and validated.

Additional Nonclinical comments were as follows:

If after review of data we conclude that SAIT104 is similar to Enbrel from a nonclinical perspective, reproductive toxicology, immunotoxicity, safety pharmacology and an evaluation of the carcinogenic potential will likely not be needed.

Meeting minutes dated June 23, 2016: Agreed that the in vivo nonclinical studies (Efficacy study in BALB/c mice, PK study in SD rats, and 4-week comparative toxicology study in monkeys) were sufficient for a 351(k) application.

A safety assessment of extractables and leachables with the pre-filled syringe (PFS) should be available with the BLA.

On May 25, 2017 Samsung Bioepis Co submitted the 351(k) BLA 761066 for registration of SB4 as a biosimilar to US-Enbrel.

A nonclinical IR was sent to the Sponsor on December 12, 2017 requesting that the finalized reports of the extractables and leachables studies be submitted to the BLA.

A second nonclinical IR was sent to the Sponsor on January 10, 2018 requesting that complete documentation of the batches/lots and purity of US-licensed Enbrel® and EU-licensed Enbrel® be submitted to the BLA.

### **3 Studies Submitted**

#### **3.1 Studies Reviewed**

1. Section 3.2.P.2.4 of the BLA submission for the Container Closure System
2. SB4 DP Container Closure Extractable Study Report (Study No. 14-00519-N1)
3. Determination of the Leachable Amount of Chemical Compounds, Which Migrate Into Sponsor Drug Product Formulation From Both Real Time and Accelerated Stability Samples (Study No. 14-00321-N2)

Study Reports 2 and 3 were provided in response to the Information Request dated December 12, 2017.

#### **3.2 Studies Not Reviewed**

None

#### **3.3 Previous Reviews Referenced**

Pharmacology and Toxicology Review of BLA 761066 dated February 13, 2018

## **11 Integrated Summary and Safety Evaluation**

The prefilled syringe sub-assembly (PFS-SA) is the primary container closure system for the Drug Product. The PFS-SA consists of a (b) (4) glass syringe with a 29-gauge thin-wall staked-in needle and a rigid needle shield, which is closed with (b) (4) plunger stopper. Accessories (needle safety shield, extended finger flange and plunger rod) and a label are added to the PFS-SA to produce the

Accessorized Prefilled Syringe (APFS). The components of the PFS that are in direct contact with the SB4 solution are the glass syringe barrel, the rubber plunger stopper, the stainless-steel needle, and the inner rubber part of the rigid needle shield. (b) (4)

. None of the accessories are in contact with the Drug Product solution or part of the fluid path of the delivery system. The secondary packaging includes a unit tray and lid stock to secure the Drug Product during transportation, an opaque paperboard unit carton to protect the Drug Product from light exposure, and package inserts.

The container closure system for SB4 is the (b) (4) glass syringe with a 29-gauge thin-wall staked-in needle and a rigid needle shield, which is closed with (b) (4) plunger stopper, is a marketed device that is used with other FDA-approved drug products. The concerns for leachables were generally considered minimal for this marketed, approved device.

The studies performed to demonstrate compatibility of the container closure system with the drug product, consisted of standard extractables and leachables studies evaluating if chemical compounds from the DP container closure system may migrate into the SB4 solution.

### **Extractables Study:**

**Study title:** Determination of the extractable amount of chemical compounds from critical Components of Container and Delivery Device (Study No. 14-00519-N1)

The Test Article used in this study consisted of the following components:

- 1) Syringe barrel with stacked needle shield CAS/Code Number 47294426; Lot/Batch 3277267
- 2) Plunger Stopper 1 pack CAS/Code Number 47375910; Lot/Batch number 3162187

Test article components (1 and 2) were separately extracted in solutions (b) (4) and drug placebo at 50° +/- 2° C for 72 +/- 2 hours, except the drug placebo which was at 37° +/- 2° C for 72 +/- 2 hours, to identify compounds for monitoring in leachable studies.

For each sample, the test article components were extracted by immersion in the extraction solution at a ratio of 3 cm<sup>2</sup> surface area per mL solution. The test articles and controls were analyzed for metals, volatiles, semi-volatiles, non-volatiles, organic acids, non-target NVOC, acetates, and formates. Methods used for detection included ICP-OES for metal content, GC/MS for VOC and SVOC, LC/MS for NVOC and organic acids, LC chromatogram UV-Vis detection for non-target peaks, and IC for acetate and formate formation. The Sponsor's Analytical Matrix table below illustrates the methods used in the extractables study.

**Table 1: Analytical Methodology Matrix for Extraction Studies**

Extraction Solution	Extraction Condition	ICP	GC/MS		LC/MS		LC/UV	IC
		Metals	VOC	SVOC	NVOC	Organic Acids	NVOC	Acetate and Formate
(b) (4)	50 ± 2 °C for 72 ± 2 hours	X	X	X	X	X	X	X
	50 ± 2 °C for 72 ± 2 hours	X	X* See 10.2.2	X	X	X	X	X* See 10.6.2
	50 ± 2 °C for 72 ± 2 hours	X	X	X	X	X	X	X* See 10.6.3
	50 ± 2 °C for 72 ± 2 hours	X	X	X	X	X	X	X
	37 ± 2 °C for 72 ± 2 hours	X	X	X	X	X	X	X* See 10.6.5

X – Test was performed  
 X\* - matrix interference with assay

**Results of Extraction Studies:**



The maximum potential clinical exposure was calculated by the Sponsor based on the extractable concentration and the maximum syringe fill volume of (b) (4) mL.

**Table 2: The Maximum Amount of Elements Detected and Identified in Extractables**

Element	CAS	Maximum Amount (b) (4)
(b) (4)		

(Excerpted from Sponsor’s Study Report)

**Table 3: The Maximum Amount of Organic Compounds Detected and Identified in Extractables**

Organic Compound	CAS	Maximum Amount (b) (4)	Tolerable Exposure Level (mg/day)	Safety Margin
(b) (4)			0.14	1.1
(b) (4)			49	2944
(b) (4)			49	2944
(b) (4)			49	2944
(b) (4)			49	2944
(b) (4)			1.16	2095
(b) (4)			10.5	2120
(b) (4)			21.14	291506
(b) (4)			0.56	472
(b) (4)			35	27242

(Excerpted from Sponsor’s Study Report)

**Leachables Study**

**Study Title:** Determination of the Leachable Amount of Chemical Compounds, Which Migrate into Sponsor Drug Product Formulation From Both Real Time and Accelerated Stability Samples (14-00321-N2)

Purpose: Determine the amounts of chemical compounds from the DP container closure system that migrate into SB4 DP when stored at multiple time points under real time (2-8 °C) and under accelerated (ambient) conditions, and to evaluate changes in the compounds and / or their levels over shelf-life.

Test Article: SB4 DP (Lot/batch numbers: 14B13, 14C20, 14C26, 14C28)

Control Article: Drug Placebo

Methods: The container/closure system was exposed to the SB4 DP under real time storage conditions at 2 to 8 °C for time points of -1.5 Months, 3 Months, 6 Months, 12 Months,

18 Months, 24 Months, 30 Months and 36 Months, **or** under accelerated (ambient, 25°C) storage conditions for 3 months, 6 months, and 12 months.

Samples were prepared in triplicate. Controls (blank) were prepared with the same solution used in the test article extract preparations. The control solution was not in contact with the container closure system, while the test solutions were in contact with the CCS for the duration of the study.

The test article solutions were then analyzed by the following methods:

- ICP-OES analysis for trace metals
- GC/MC for VOC and SVOC
- LC/MS for NVOC and organic acids
- LC with UV scan for non-target NVOC
- IC for Acetate and Formate

Samples were monitored for chemicals identified as extractables; target analytes included [REDACTED]<sup>(b) (4)</sup>. In addition, the testing laboratory monitored for target chemicals from a library of known extractables and leachables.

**Table 4: Analytical Methodology Matrix table for the Leachable Study**

Test System	Storage Condition	Leaching Time Point	Target Analyte	ICP	IC	GC/MS	GC/MS	LC/MS	LC/UV	LC/MS
				Metals	Acetate and Formate	VOC	SVOC	NVOC	NVOC	Organic Acids
SB4 DP	Accelerated Aging (Ambient (25 ± 2°C) Adjusted for time stored at 2-8°C prior to chamber placement)	T=3 month equivalent at 2-8°C	(b) (4)	X	X	X	X	X	X	X
		T=6 month equivalent at 2-8°C		X	X	X	X	X	X	X
		T= 12 month equivalent at 2-8°C		X	X	X	X	X	X	X
	Refrigeration (2-8°C) Real Time Aging	T=~1.5 month (54 days)		X	X	X	X	X	X	X
		T=3 month		X	X	X	X	X	X	X
		T= 6 month		X	X	X	X	X	X	X
		T=12 month		X	X	X	X	X	X	X
		T= 18 month		X	X	X	X	X	X	X
		T= 24 month		X	X	X	X	X	X	X
		T=30 month		X	X	X	X	X	X	X
T= 36 month	X	X	X	X	X	X	X			

X = Test performed

The data described in this study report include all samples under accelerated aging conditions and samples up to 12 months under real time aging conditions. Real time samples from 18, 24, 30, and 36 months will be analyzed upon completion of again.

(b) (4) was observed at low levels in all samples of 1.5, 3 and 6 months but not in samples of 12 months. Therefore, (b) (4) was not considered to pose a safety risk. (b) (4) was observed in the accelerated aging samples at 6 months and 12 months at elevated levels. It was also observed in the drug solution blank. (b) (4) was observed in all samples at 1.5, 3, 6 and 12 months under real time and accelerated again conditions. No formate was observed in any sample.

**Table 5: Summary of Leachable Concentrations measured in SB4 DP under storage at 2 to 8° C and 25° C**

(b) (4)



The levels of  (b) (4) are considered qualified from a safety perspective based on the low estimated daily intakes from the extractable and leachable studies.

The design of the extractables and leachables studies were considered generally acceptable. Overall, there appear to be no nonclinical safety concerns for the SB4 formulation related to the levels of leachables from the pre-filled syringe primary container closure system leachables studies. It is noted that the CCS is a marketed,

approved device. The leachables study is ongoing and data from additional time points up to 36 months will be provided when available.

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/s/  
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IJEOMA K UZOMA  
02/16/2018

TIMOTHY W ROBISON  
02/16/2018  
I concur

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

**PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION**

Application number: 761066  
Supporting document/s: SND 1  
Applicant's letter date: May 25, 2017  
CDER stamp date: May 25, 2017  
Product: SB4 (a proposed biosimilar to US-licensed  
Enbrel®)  
Indication: Rheumatoid Arthritis, Polyarticular Juvenile  
Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing  
Spondylitis, Plaque Psoriasis  
Applicant: Samsung Bioepis Co., Ltd  
Review Division: Division of Pulmonary Allergy and  
Rheumatology Products  
Reviewer: Ijeoma Uzoma, Ph.D.  
Supervisor/Team Leader: Timothy Robison, Ph.D., DABT  
Division Director: Badrul Chowdhury, MD, Ph.D.  
Project Manager: Brandi Wheeler, PharmD

*Template Version: September 1, 2010*

**Disclaimer**

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# 1 Executive Summary

## 1.1 Introduction

BLA 761066 was submitted by Samsung Bioepis Co., Ltd on May 25, 2017, under section 351(k) of the Public Health Services Act (PHS Act) to support registration of SB4 as a biosimilar to US-licensed Enbrel<sup>®</sup> (etanercept). Etanercept is a dimeric soluble form of the p75 TNF receptor that can bind TNF molecules. Etanercept inhibits binding of TNF- $\alpha$  and TNF- $\beta$  (lymphotoxin alpha [LT- $\alpha$ ]) to cell surface TNF receptors, rendering TNF biologically inactive. US-licensed Enbrel<sup>®</sup> (US-Enbrel) is a subcutaneously administered product, originally developed by Immunex Corporation (BLA 103795, Approval date November 2, 1998), indicated for the treatment of Rheumatoid Arthritis, Polyarticular Juvenile Idiopathic Arthritis in patients aged 2 years or older, Psoriatic Arthritis, Ankylosing Spondylitis, and Plaque Psoriasis in patients 4 years or older. Samsung Bioepis Co. intends to obtain indications for SB4 identical to the indications of the reference product that are not subject to orphan exclusivity and are supported by the current presentations of SB4: Rheumatoid arthritis, Juvenile Idiopathic Arthritis in patients that weigh over 63 kg (138 lbs.) from ages 2 and older, Psoriatic Arthritis, Ankylosing Spondylitis, and Plaque Psoriasis in patients that weigh over 63 kg (138 lbs.) from ages 4 and older.

The FDA approved the expanded use of Enbrel<sup>®</sup> for pediatric patients from ages 4 to 17 with the chronic moderate-to-severe plaque psoriasis in November 2016. (b) (4)

it was determined that the Sponsor needs to develop their pediatric presentation with clinical studies under PREA.

## 1.2 Brief Discussion of Nonclinical Findings

The nonclinical development program for SB4 included: 1) a primary pharmacology study evaluating efficacy in a CAIA-mouse model comparing SB4 vs US-licensed Enbrel and EU-approved Enbrel (Study # CAIA-e007) 2) a single-dose PK study conducted in SD rats comparing SB4 vs. EU-licensed Enbrel (Study # RD00407) 3) a 4-week repeat-dose toxicity study in monkeys comparing SB4 vs US-licensed Enbrel (US-Enbrel) and EU-approved Enbrel (EU-Enbrel) (Study # 264-004).

In the comparative efficacy study with SB4 in the CAIA mouse model, no differences in efficacy were observed between SB4, EU-Enbrel, or US-Enbrel compared to vehicle-control treated mice.

In the single-dose subcutaneous comparative PK study with male Sprague-Dawley rats, PK profiles were demonstrated to be similar between SB4 and EU-Enbrel at a dose of 1 mg/kg.

The pivotal 28-day comparative repeat-dose toxicology study of SB4, EU-Enbrel, and US-Enbrel was conducted in cynomolgus monkeys that received subcutaneous doses

at 1 and 15 mg/kg administered twice per week. A concurrent control group was included in the study. There was one unscheduled death of a male in the 1 mg/kg US-Enbrel group. The animal was euthanized on Day 17 due to severe clinical signs including lethargy and difficulty breathing. Microscopic evaluation revealed acute/chronic inflammation/adhesion of the pericardium and heart and staining indicated the presence of bacterial colonies. The immunosuppressive effects of etanercept treatment may have exacerbated the severity of the infection. In general, microscopic findings were similar in the SB4, EU-Enbrel, and US-Enbrel treated animals.

In general, systemic exposure ( $AUC_{0-72}$  and  $C_{max}$ ) in the SB4 treated animals were comparable to EU-Enbrel and US-Enbrel treated monkeys. The decreased systemic exposure in 1 mg/kg-treated animals on Day 25 was likely due to the development of ADAs. The development of ADAs in SB4 treated animals occurred at similar incidences compared to EU-Enbrel and US-Enbrel treated monkeys.

Collectively, there was no evidence in the 28-day comparative repeat-dose toxicity study of SB4, US-Enbrel and EU-Enbrel, conducted in cynomolgus monkeys, to indicate potential safety concerns associated with SB4 administration. The toxicokinetic profile of SB4 was considered reasonably comparable to that of US-Enbrel and EU-Enbrel in cynomolgus monkeys.

The nonclinical pharmacology, pharmacokinetic, and repeat-dose toxicity data submitted in support of the BLA demonstrate similarity (i.e., comparable exposures and safety profiles) between SB4 and EU-Enbrel and US-Enbrel from the nonclinical Pharmacology and Toxicology perspective.

### **1.3 Recommendations**

#### **1.3.1 Approvability**

SB4 is recommended for approval from the nonclinical toxicology perspective.

#### **1.3.2 Additional Nonclinical Recommendations**

None. There are no outstanding nonclinical issues.

#### **1.3.3 Labeling**

Labeling was evaluated for Sections 8.1 (Pregnancy), 8.2 (Lactation), 12.1 (Mechanism of Action), and 13 (Nonclinical Toxicology). Additions were denoted as underlined text. Deletions were denoted with ~~text~~. Labeling closely follows that for ENBREL<sup>®</sup> (BLA 103795) and ERELZI<sup>®</sup> (an approved Etanercept biosimilar, BLA 761042).

#### **8.1 Pregnancy**

##### Risk Summary

Available studies with use of etanercept during pregnancy do not reliably support an association between etanercept products and major birth defects. Clinical data are available from the Organization of Teratology Information Specialists (OTIS) ~~etanercept~~ Pregnancy Registry in women with rheumatic diseases or psoriasis and a Scandinavian

study in pregnant women with chronic inflammatory disease. Both the OTIS Registry and the Scandinavian study showed the proportion of liveborn infants with major birth defects was higher for women exposed to etanercept compared to diseased etanercept unexposed women. However, the lack of pattern of major birth defects is reassuring and differences between exposure groups (eg. disease severity) may have impacted the occurrence of birth defects (see Data). In animal reproduction studies with pregnant rats and rabbits, no fetal harm or malformations were observed with subcutaneous administration of etanercept during the period of organogenesis at doses that achieved systemic exposures 48 to 58 times the exposure in patients treated with 50 mg etanercept products once weekly (see Data).

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the United States, about 2-4% of liveborn babies have a major birth defect and about 15-20% of pregnancies end in miscarriage, regardless of drug exposure.

### Clinical Considerations

#### Fetal/Neonatal adverse reactions

The risk of fetal/neonatal adverse reactions with in utero exposure to etanercept products is unknown. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to etanercept products in utero [see Use in Specific Populations (8.4)].

### Data

#### *Human Data*

A prospective cohort pregnancy registry conducted by OTIS in the US and Canada between 2000 and 2012 compared the risk of major birth defects in liveborn infants of women with rheumatic diseases or psoriasis exposed to etanercept in the first trimester. The proportion of major birth defects among liveborn infants in the etanercept-exposed (N = 319) and diseased etanercept unexposed cohorts (N = 144) was 9.4% and 3.5%, respectively. The findings showed no statistically significant increased risk of minor birth defects and no pattern of major or minor birth defects.

A Scandinavian study compared the risk of major birth defects in liveborn infants of women with chronic inflammatory disease (CID) exposed to TNF-inhibitors during early pregnancy. Women were identified from the Danish (2004-2012) and Swedish (2006-2012) population based health registers. The proportion of major birth defects among liveborn infants in the etanercept-exposed (N=344) and CID etanercept unexposed cohorts (N = 21,549) was 7.0% and 4.7%, respectively.

Overall, while both the OTIS Registry and Scandinavian study show a higher proportion of major birth defects in etanercept-exposed patients compared to diseased etanercept unexposed patients, the lack of pattern of birth defects is reassuring and differences between exposure groups (e.g. disease severity) may have impacted the occurrence of birth defects.

Three case reports from the literature showed that cord blood levels of etanercept at delivery, in infants born to women administered etanercept during pregnancy, were between 3% and 32% of the maternal serum level.

#### *Animal Data*

In embryofetal development studies with etanercept administered during the period of organogenesis to pregnant rats from gestation day (GD) 6 through 20 or pregnant rabbits from GD 6 through 18, there was no evidence of fetal malformations or embryotoxicity in rats or rabbits at respective doses that achieved systemic exposures 48 to 58 times the exposure in patients treated with 50 mg etanercept products once weekly (on an AUC basis with maternal subcutaneous doses up to 30 mg/kg/day in rats and 40 mg/kg/day in rabbits). In a peri- and post-natal development study with pregnant rats that received etanercept during organogenesis and the later gestational period from GD 6 through 21, development of pups through post-natal day 4 was unaffected at doses that achieved exposures 48 times the exposure in patients treated with 50 mg etanercept products once weekly (on an AUC basis with maternal subcutaneous doses up to 30 mg/kg/day).

## 8.2 Lactation

### Risk Summary

Limited data from published literature show that etanercept is present in low levels in human milk and minimally absorbed by a breastfed infant. No data are available on the effects of etanercept products on the breastfed child or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SB4 and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.

## 12.1 Mechanism of Action

TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. It plays an important role in the inflammatory processes of RA, polyarticular JIA, PsA, and AS and the resulting joint pathology. In addition, TNF plays a role in the inflammatory process of PsO. Elevated levels of TNF are found in involved tissues and fluids of patients with RA, JIA, PsA, AS, and PsO.

Two distinct receptors for TNF (TNFRs), a 55 kilodalton protein (p55) and a 75 kilodalton protein (p75), exist naturally as monomeric molecules on cell surfaces and in soluble forms. Biological activity of TNF is dependent upon binding to either cell surface TNFR.

Etanercept products are dimeric soluble forms of the p75 TNF receptor that can bind TNF molecules. Etanercept products inhibit binding of TNF- $\alpha$  and TNF- $\beta$  (lymphotoxin alpha [LT- $\alpha$ ]) to cell surface TNFRs, rendering TNF biologically inactive. In *in vitro* studies, large complexes of etanercept with TNF- $\alpha$  were not detected and cells

expressing transmembrane TNF (that binds etanercept products) are not lysed in the presence or absence of complement.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of etanercept products or ~~its~~ their effect on fertility.

## 2 Drug Information

### 2.1 Drug

CAS Registry Number (Optional): 185243-69-0 (etanercept)

Proper Name: To be determined

Code Name: SB4

Molecular Formula/Molecular Weight:  $C_{2224}H_{3472}N_{618}O_{701}S_{36}$  / 130 kDa (homodimer)

#### Structure or Biochemical Description:

SB4 is a homodimer of a chimeric protein genetically engineered by fusing the extracellular ligand binding domain of human TNFR2/p75 to the Fc domain of human IgG1. The Fc component comprises the hinge, CH2 and CH3 regions, but the CH1 region is excluded. SB4 consists of 934 amino acids (467 for the single chain) and has MW of approximately 130 kDa.

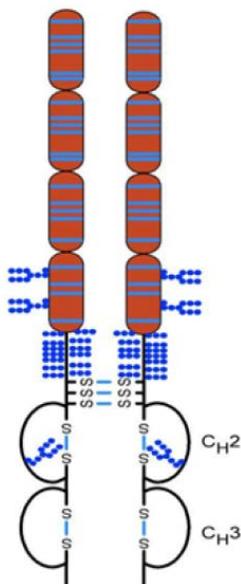
#### Amino Acid Sequence:

1	LPAQVAFTPY	APEPGSTCRL	REYYDQTAQM	CCSKCSPGQH	AKVFCTKTS
51	TVCDSCEDST	YTQLWNWVPE	CLSCGSRCSS	DQVETQACTR	EQNRICTCRP
101	GWYCALSKQE	GCRLCAPLRK	CRPGFGVARP	GTETSDVVCK	PCAPGTFS <u>N</u> T
151	TSSTDICRPH	QICNVVAIPG	<u>N</u> ASMDAVCTS	<u>T</u> SPTRSMAPG	AVHLPQPVST
201	<u>RSQHTQ</u> OPTPE	<u>P</u> STAPSTSFL	LPMGPSPPAE	<u>G</u> STGDEPKSC	<b>DKTHTCP</b> CP
251	<b>APELLGG</b> PSV	<b>FLFPPK</b> PKDT	<b>LMISRT</b> PEVT	<b>CVVVDV</b> SHED	<b>PEVKFN</b> WYVD
301	<b>GVEVHN</b> AKTK	<b>PREEQY</b> <u>N</u> STY	<b>RVVSVL</b> TVLH	<b>QDWLNG</b> KEYK	<b>CKVSNK</b> ALPA
351	<b>PIEKTIS</b> KAK	<b>GQPREP</b> QVYT	<b>LPPSRE</b> EMTK	<b>NQVSLT</b> CLVK	<b>GFYPSD</b> IAVE
401	<b>WESNGQ</b> PENN	<b>YKTTPP</b> VLDS	<b>DGSFFL</b> YSKL	<b>TVDKSR</b> WQQG	<b>NVFSCS</b> VMHE
451	<b>ALHNHY</b> TQKS	<b>LSLSPG</b> K			

Extracellular ligand-binding domain of the human TNFR: Normal letters  
**Fc domain of human IgG1: Bold letters**  
N-linked glycosylation site: Boxed letters  
 Potential O-linked glycosylation site: Normal letters underlined  
*Cysteine residues: Italics*

(Excerpted from the Sponsor’s submission)

Schematic Structure of SB4:



(Excerpted from the Sponsor’s submission)

Pharmacologic Class: Tumor Necrosis Factor Blocker

## 2.2 Relevant INDs, NDAs, BLAs and DMFs

Table 1: Relevant INDs and BLAs

Application #	Description	Sponsor	Date
PIND 113462	IND application in support of clinical testing of SB4 in the U.S.	Samsung Bioepis	3/4/2016 (PIND Submission date)
BLA 761042	BLA application for etanercept biosimilar (ERELZI®)	Sandoz, Inc	8/30/2016 (approval date)
BLA 103795 Reference No.: 98-0286	BLA application for innovator product, Enbrel®	Immunex Corp.	11/2/1998 (approval date)

## 2.3 Drug Formulation

The SB4 drug product will be provided as a 25 mg/ 0.50 mL and a 50 mg/mL solution for subcutaneous administration, supplied in a pre-filled syringe. The SB4 drug product formulation is not identical to that of the reference product and differs from the marketed US-Enbrel formulation with inclusion of the sodium phosphate monobasic monohydrate buffering agent and sodium phosphate dibasic heptahydrate buffering agent. This formulation also lacks L-arginine monohydrochloride (b) (4) in the US-Enbrel formulation.

**Table 2: Drug product formulation for a single dose of 50 mg or 25 mg of SB4**

<b>Component (50 mg)</b>	<b>Nominal Quantity/mL</b>	<b>Function</b>	<b>Quality Standard</b>
Etanercept	50 mg	Active substance	In-house
Sucrose	10.0 mg	[REDACTED] (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	<i>q.s.</i>		Ph.Eur./USP

(Excerpted from the Sponsor's submission)

<b>Component (25 mg)</b>	<b>Nominal Quantity/Unit</b>	<b>Function</b>	<b>Quality Standard</b>
Etanercept	25 mg	Active substance	In-house
Sucrose	5.0 mg	[REDACTED] (b) (4)	Ph.Eur./NF
Sodium chloride	4.09 mg		Ph.Eur./USP/JP
Sodium phosphate monobasic monohydrate	0.519 mg		USP
Sodium phosphate dibasic heptahydrate	0.333 mg		USP
Water for injection	<i>q.s.</i>		Ph.Eur./USP

(Excerpted from the Sponsor's submission)

## 2.4 Comments on Novel Excipients

There are no novel excipients in the SB4 drug product.

## 2.5 Comments on Impurities/Degradants of Concern

Impurities appear to pose no safety concerns.

## 2.6 Proposed Clinical Population and Dosing Regimen

The proposed therapeutic indications for SB4 are identical to the indications of the reference product that are not subject to orphan exclusivity and are supported by the current presentations of SB4:

- Rheumatoid arthritis (RA)
- Juvenile Idiopathic Arthritis (JIA) in patients that weigh over 63 kg (138 lbs.) from ages 2 and older,
- Psoriatic Arthritis (PsA)
- Ankylosing Spondylitis (AS)
- Plaque Psoriasis (PsO) in patients that weigh over 63 kg (138 lbs.) from ages 4 and older.

The FDA approved the expanded use of Enbrel® for pediatric patients from ages 4 to 17 with the chronic moderate-to-severe plaque psoriasis in November 2016. [REDACTED] (b) (4)

(b) (4) it was determined that the Sponsor needs to develop their pediatric presentation with clinical studies under PREA.

The US-licensed Enbrel dosage for adult patients with Rheumatoid Arthritis or Psoriatic Arthritis is 50 mg once weekly with or without methotrexate. For Ankylosing Spondylitis, the treatment regimen is 50 mg once weekly. For adults with Plaque Psoriasis, the dosage is 50 mg twice weekly for 3 months, followed by 50 mg once weekly. For patients aged 2 years or older with Polyarticular Juvenile Idiopathic Arthritis, the treatment regimen is 0.8 mg/kg weekly, with a maximum dose of 50 mg per week.

Proposed subcutaneous doses for SB4 are listed in the table below.

Patient Population	Recommended Dose and Frequency
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 or JIA (patients who weigh 63 kg or more)	50 mg once weekly

(Excerpted from the Sponsor's submission)

## 2.7 Regulatory Background

Samsung Bioepis Co submitted the initial meeting request for PIND 113462 on September 23, 2011 (received September 26, 2011) for the development of SB4 as a proposed biosimilar to US-Enbrel, for the same patient populations and dosing regimen as the reference product.

### Nonclinical program for SB4 discussed under the Pre-IND:

Meeting minutes dated March 23, 2012: Recommended a GLP compliant 4-week comparative toxicology and TK study in Cynomolgus monkeys with US-licensed Enbrel and SAIT-104. The following parameters should be included: clinical signs, body weight, hematology, immunophenotyping of lymphocytes, clinical chemistry, gross pathology, organ weights, histopathology, and toxicokinetics. A complete battery of organs and tissues should be submitted for histopathological examination. An appropriate control group should be included. A SC dose of 15 mg/kg given twice weekly is recommended for US-licensed Enbrel and SAIT104. A group size of 3 monkeys/sex/group is recommended. FDA confirmed that that a recovery period is not required. A pharmacokinetic study in cynomolgus monkeys should be incorporated into the toxicology study. The pharmacokinetic method should be GLP compliant and validated.

Additional Nonclinical comments were as follows:

If after review of data we conclude that SAIT104 is similar to Enbrel from a nonclinical perspective, reproductive toxicology, immunotoxicity, safety pharmacology and an evaluation of the carcinogenic potential will likely not be needed.

Meeting minutes dated June 23, 2016: Agreed that the in vivo nonclinical studies (Efficacy study in BALB/c mice, PK study in SD, and 4-week comparative toxicology study in monkeys) were sufficient for a 351(k) application.

A safety assessment of extractables and leachables with the pre-filled syringe (PFS) should be available with the BLA.

On May 25, 2017 Samsung Bioepis Co submitted the 351(k) BLA 761066 for registration of SB4 as a biosimilar to US-Enbrel.

A nonclinical IR was sent to the Sponsor on December 12, 2017 requesting that the finalized reports of the extractables and leachables studies be submitted to the BLA.

A second nonclinical IR was sent to the Sponsor on January 10, 2018 requesting that complete documentation of the batches/lots and purity of US-licensed Enbrel® and EU-licensed Enbrel® be submitted to the BLA.

### **3 Studies Submitted**

#### **3.1 Studies Reviewed**

- Evaluation of SB4 For Suppression of Collagen Antibody-Induced Arthritis In BALB/C Mice (Study No. CAIA-e007)
- Pharmacokinetic Study of SB4 In SD Rat (Study No. RD-00407)
- A 4-Week Repeat-Dose Toxicity Study of SB4 in Cynomolgus Monkeys (Study No. 2064-004)

#### **3.2 Studies Not Reviewed**

None

#### **3.3 Previous Reviews Referenced**

None

### **4 Pharmacology**

#### **4.1 Primary Pharmacology**

**Study # CAIA-e007: Evaluation of SB4 for Suppression of Collagen Antibody-induced Arthritis in BALB/c Mice**

Objective: To compare efficacy of SB4 versus reference products, EU-Enbrel and US-Enbrel, using the collagen antibody-induced, BALB/c mouse arthritis model (Study # CAIA-e007).

#### Methods:

To induce arthritis, female BALB/c mice (7 weeks old, body weight range of 16.2-19.0 g) were given 2 mg (0.2 mL) of ArthritoMab™, by tail vein injection, on Day 1 of the study. On Day 7, each animal was challenged with 50 µg LPS by IP injection. Treatment with SB4 (lot no.: PDR-112-12-137), EU-Enbrel (lot no.: F27600), and US-Enbrel (lot no.: 1026343) was administered by the intraperitoneal route, once daily at 3 day intervals, for a total of 5 doses (q3d x 5), on days 8, 12, 15, 19, and 22.

There were 10 treatment cohorts (n= 10/group). Group 1 received vehicle. Groups 2–4 received 1, 5, and 10 mg/kg SB4, respectively. Groups 5–7 received 1, 5, and 10 mg/kg EU-Enbrel, respectively. Groups 8–10 received 1, 5, and 10 mg/kg US-Enbrel, respectively.

Volume Changes, Mean Disease Burden AUC, and Disease Suppression: Day 8 total footpad volume (sum of the volumes of the right and left hindlimb paw footpads measured by plethysmography) for each animal was designated as the baseline for determining subsequent volume changes in that animal at later reassessments between Days 9 and 22. Mean disease burden was defined as the net AUC when plotting total footpad volume versus time. Mean disease suppression was defined as the percent decrease in the mean disease burden relative to the controls.

Clinical Scores based upon visible erythema and/or swelling: Maximum clinical score per animal on each day of observation was 60 (15 for each limb x 4). The AUC for clinical score vs time was determined for each animal (baseline subtraction was not performed).

Mice were euthanized on Day 22 and formalin-fixed left hind limbs were evaluated following hematoxylin and eosin staining. Five fields, 1) anterior-tibiotalus, 2) posterior-tibiotalus, 3) dorso-distal central tarsal, 4) ventro-distal central tarsal, and 5) dorsal tarsal-metatarsal, from each of the three step levels were examined. Five hallmarks of arthritis were assessed as follows: inflammation, pannus, cartilage damage, bone resorption, and periosteal change / exostosis. A score indicating the magnitude of arthritic progression (0 = normal, 1 = minimal, 2 = mild, 3 = moderate, 4 = marked, and 5 = severe) was assigned to each of the five metrics. The five hallmark scores were summed to give a composite score (maximum = 25 points) for each animal.

#### Results:

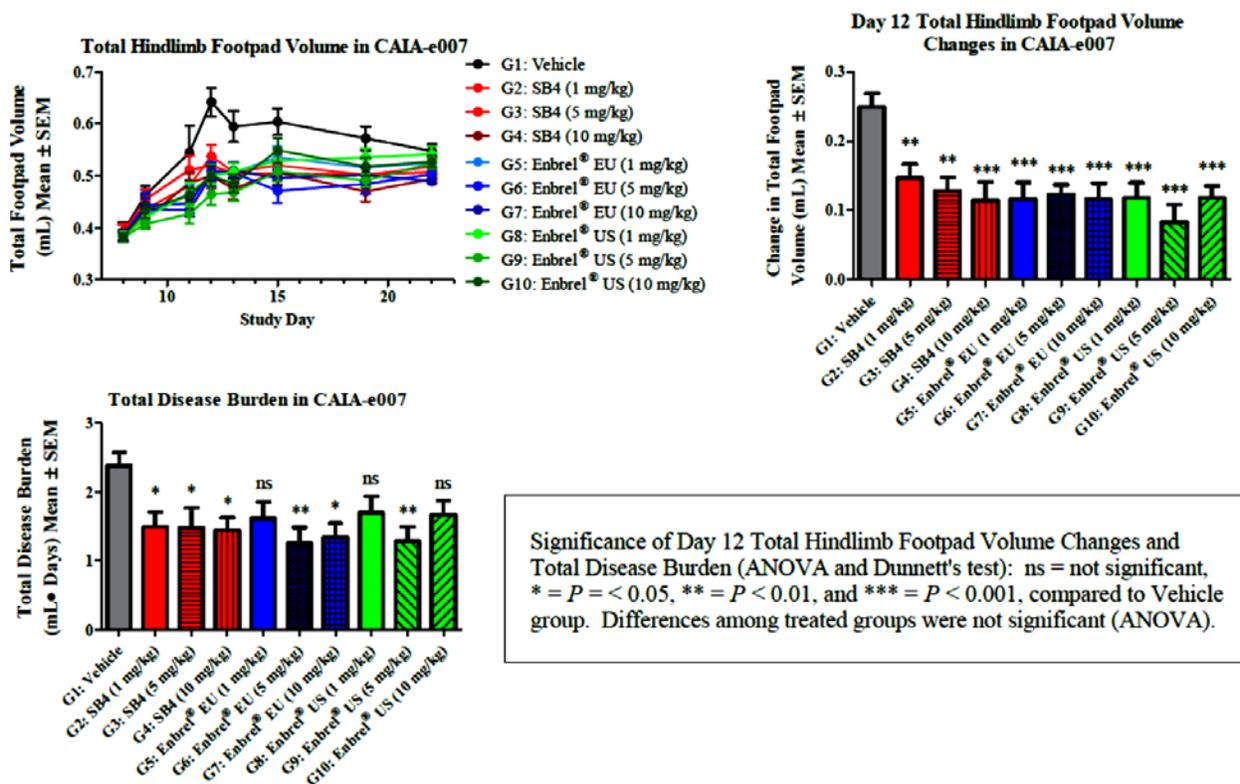
Responses to treatment based on Day 12 footpad volume (Figure 1):

After immunization with ArthritoMab™ vehicle-treated Group 1 control mice showed maximum swelling on Day 12 (Figure 1). Group 1 mean maximum change in total footpad volume on Day 12, relative to Day 8, was 0.249 mL. All treated groups had reduced group mean volume changes on Day 12 (Figure 1 and Table 3). SB4 (Groups

2–4) caused statistically significant reductions, on Day 12, that occurred in a dose dependent manner. All EU-Enbrel (Groups 5-7) and US-Enbrel (Groups 8-10) treatments also caused reductions in mean volume changes; however, there were no dose-response relationships. There were no significant differences between SB4, EU-Enbrel, US-Enbrel induced responses at the same doses and the magnitudes of response were similar.

Mean Disease Burden was significantly lower in SB4 treated groups at all doses, relative to controls, although there were no differences between doses. Mean Disease Burden was significantly repressed at the MD with EU-Enbrel and US-Enbrel. Mean Disease Burden was significantly repressed at the HD with EU-Enbrel. Mean disease suppression relative to the control group ranged from 37.2-39.3% with SB4 (dose-dependent manner), 32-47.2% with EU-Enbrel (lack of dose relationship), and 28.6-45.6% with US-Enbrel (lack of dose relationship). For each test article, there were no significant differences of disease burdens at the three dose levels. Observed treatment responses for SB4, EU-Enbrel, and US-Enbrel were comparable.

**Figure 1. Effects of SB4, EU-Enbrel, and US-Enbrel on the mean total hindlimb footpad volume and volume changes and total disease burden in the CAIA mouse model arthritis study**



**Table 3: Summary of total footpad Volume changes**

Group	n	Treatment Regimen				Total Arthritic Response										
						Mean Volume Change on Day 12			Mean Maximum Volume Changes			Mean Disease Burden Net AUC			Mean Disease Suppression	
		Agent	mg/kg	Route	Schedule	mL	SEM	Signif.	mL (Day)	SEM	Signif.	mL* day	SEM	Signif.	Percent	SEM
1	10	Vehicle	---	ip	q3d x 5 (start on Day 8)	0.25	0.02	---	0.28 (13)	0.02	---	2.38	0.20	---	0	8.3
2	10	SB4	1	ip	q3d x 5 (start on Day 8)	0.15	0.02	**	0.17 (13)	0.02	***	1.49	0.22	*	37.2	9.2
3	10	SB4	5	ip	q3d x 5 (start on Day 8)	0.13	0.02	**	0.16 (14)	0.03	***	1.48	0.29	*	37.6	12.3
4	10	SB4	10	ip	q3d x 5 (start on Day 8)	0.11	0.03	***	0.15 (15)	0.02	***	1.45 <sup>b</sup>	0.19	*	39.3	8.6
5	10	Enbrel <sup>®</sup> EU	1	ip	q3d x 5 (start on Day 8)	0.12	0.02	***	0.18 (17)	0.02	**	1.62	0.24	ns	32.0	10.3
6	10	Enbrel <sup>®</sup> EU	5	ip	q3d x 5 (start on Day 8)	0.12	0.01	***	0.15 (13)	0.01	***	1.26	0.23	**	47.2	9.7
7	10	Enbrel <sup>®</sup> EU	10	ip	q3d x 5 (start on Day 8)	0.12	0.02	***	0.16 (15)	0.02	***	1.35	0.20	*	43.1	8.2
8	10	Enbrel <sup>®</sup> US	1	ip	q3d x 5 (start on Day 8)	0.12	0.02	***	0.18 (19)	0.02	**	1.70	0.24	ns	28.6	10.2
9	10	Enbrel <sup>®</sup> US	5	ip	q3d x 5 (start on Day 8)	0.08	0.03	***	0.16 (19)	0.02	***	1.32	0.21	**	45.6	8.8
10	10	Enbrel <sup>®</sup> US	10	ip	q3d x 5 (start on Day 8)	0.12	0.02	***	0.18 (19)	0.02	**	1.67	0.21	ns	29.8	8.7

<sup>a</sup>Arthritis was induced with 2 mg/animal ArthritisMab<sup>®</sup> i.v. qd on Day 1, and 50 µg/animal LPS i.p. qd on Day 7. Baseline measurements from Day 8 were used to sort mice into groups with non-significant differences among mean hindlimb footpad volumes. Treatments with vehicle and test agents started on Day 8. Hindlimb footpad volumes were measured on Days 9, 11-13, 15, 19, and 22.

<sup>b</sup>In Group 4, the Disease Burden of Animal #7 was excluded as an outlier.

<sup>c</sup>Study Endpoint = 22 days

<sup>d</sup>Total Arthritic Response = an estimate of overall disease response based on total (left and right) hindlimb footpad swelling.

<sup>e</sup>n = number of animals in a group not dead from accidental or unknown causes, or euthanized for sampling prior to endpoint.

<sup>f</sup>Mean Volume Change on Day 12 = the mean difference (in mL) between total footpad volumes on Day 12 and Day 8.

<sup>g</sup>Mean Maximum Volume Changes = mean difference (in mL) between total footpad volumes on the day of maximal swelling and Day 8 in individual animals; (Day) = median day of the first instance of maximal swelling for individual mice in the group.

<sup>h</sup>Mean Disease Burden Net AUC = an estimate of mean disease burden (both hindlimb footpads) in each treatment group. Determined by measuring an initial total footpad volume for each animal to establish a baseline for the curve described by the total footpad volume over time, integrating the area under the curve (AUC) for each animal, and then calculating the group mean. AUC was calculated from data for Days 8-22.

<sup>i</sup>Mean Disease Suppression = Percent decrease in mean disease burden relative to vehicle-treated Control; calculated as the mean of the differences between Control mean AUC and the AUCs for individual treated animals, divided by the Control mean AUC and multiplied by 100; larger numbers indicate greater disease suppression relative to the Control group.

<sup>j</sup>Significance = determined with ANOVA and post hoc Dunnett's test: ns = not significant, \* = P ≤ 0.05, \*\* = P < 0.01, \*\*\* = P < 0.001, compared to Group 1.

Responses to treatment based on clinical scores (Figure 2 and Table 4):

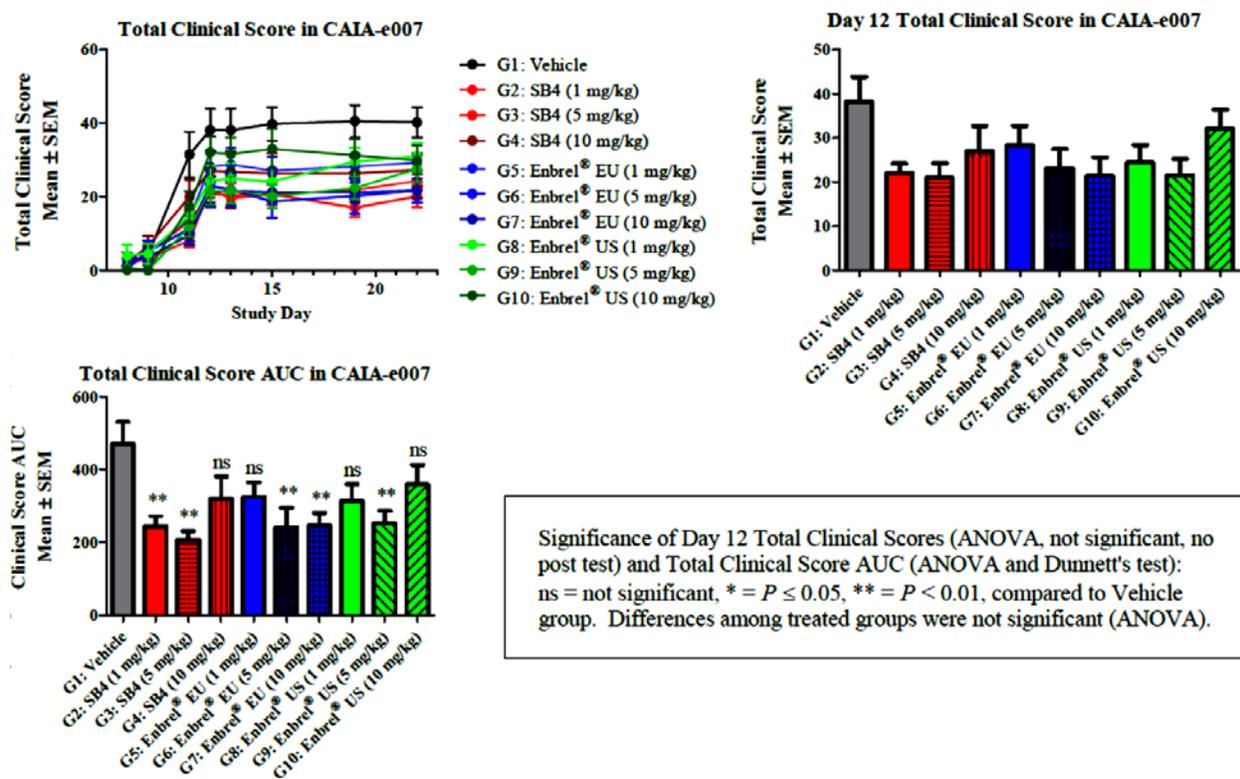
Clinical Score Response Results Summary:

The mean clinical score for the control group on Day 12 was 38.1. Clinical Scores for animals treated with SB4 were reduced relative to controls, ranging from 22-27%; however, the reduction in clinical scores lacked dose dependence and statistical significance. Treatment with EU-Enbrel and US-Enbrel also reduced clinical scores up to 28.2% and 32%, mean, respectively. SB4 reduced clinical scores by similar percentages as EU-Enbrel and US-Enbrel. Mean Clinical Score AUC was significantly reduced relative to controls at the LD and MD, whereas the clinical score at the HD was not statistically significantly relative to the controls. Treatment with EU-Enbrel caused significant

reduction at the MD and HD. Treatment with US-Enbrel caused significant reduction in clinical scores at the MD only.

Similarly, total clinical score AUCs were reduced significantly in the 1 and 5 mg/kg SB4 treatment groups, 5 and 10 mg/kg EU-Enbrel groups, and in the 5 mg/kg US-Enbrel group. There were no significant differences among the AUCs for the three test articles; therefore, treatment responses to the three test articles (total clinical score AUCs) were similar.

**Figure 2: Effects of SB4, EU-Enbrel, and US-Enbrel on mean total clinical scores**



**Table 4: Clinical Response Summary**

Group	n	Treatment Regimen				Total Arthritic Response									Toxicity		
						Mean Day 12 Clinical Score			Mean Maximum Clinical Score			Mean Clinical Score AUC			Mean BW Nadir (Day)	TR	NTR
		Agent	mg/kg	Route	Schedule	Score	SEM	Signif.	Score (Day)	SEM	Signif.	Score	SEM	Signif.			
1	10	Vehicle	---	ip	q3d x 5 (start on Day 8)	38.1	5.8	---	43.4 (13.5)	4.3	---	471.1	59.7	---	---	0	0
2	10	SB4	1	ip	q3d x 5 (start on Day 8)	22.0	2.2	ns	26.1 (19)	2.8	*	244.2	27.8	**	---	0	0
3	10	SB4	5	ip	q3d x 5 (start on Day 8)	20.9	3.4	ns	24.4 (15)	2.7	**	206.7 <sup>b</sup>	23.5	**	---	0	0
4	10	SB4	10	ip	q3d x 5 (start on Day 8)	27.0	5.7	ns	30.9 (17)	5.0	ns	320.5	60.7	ns	---	0	0
5	10	Enbrel <sup>®</sup> EU	1	ip	q3d x 5 (start on Day 8)	28.2	4.5	ns	34.4 (19)	3.3	ns	324.4	40.5	ns	---	0	0
6	10	Enbrel <sup>®</sup> EU	5	ip	q3d x 5 (start on Day 8)	23.0	4.5	ns	26.1 (12)	4.3	*	240.9	54.2	**	---	0	0
7	10	Enbrel <sup>®</sup> EU	10	ip	q3d x 5 (start on Day 8)	21.4	4.2	ns	23.0 (19) <sup>b</sup>	2.5	**	246.0 <sup>c</sup>	34.4	**	---	0	0
8	10	Enbrel <sup>®</sup> US	1	ip	q3d x 5 (start on Day 8)	24.4	4.0	ns	31.8 (22)	3.6	ns	314.9	45.1	ns	---	0	0
9	10	Enbrel <sup>®</sup> US	5	ip	q3d x 5 (start on Day 8)	21.5	3.7	ns	28.6 (19)	3.4	*	252.1	35.4	**	---	0	0
10	10	Enbrel <sup>®</sup> US	10	ip	q3d x 5 (start on Day 8)	32.1	4.3	ns	36.3 (15)	4.8	ns	359.1	53.7	ns	---	0	0

<sup>a</sup> Arthritis was induced with 2 mg/animal ArthritoMab<sup>®</sup> i.v. qd on Day 1, and 50 µg/animal LPS i.p. qd on Day 7. Baseline measurements from Day 8 were used to sort mice into groups with non-significant differences among mean hindlimb footpad volumes. Treatments with vehicle and test agents started on Day 8. Mice were evaluated for clinical signs of arthritis on Days 8, 9, 11, 12, 13, 15, 19, and 22.

<sup>b</sup> In Group 7, the Mean Maximum Clinical Score and Mean Clinical Score AUC of Animal #6 was excluded as an outlier.

<sup>c</sup> In Group 3, the Mean Clinical Score AUC of Animal #3 was excluded as an outlier.

Study Endpoint = 22 days

Total Arthritic Response = an estimate of overall disease response based on total clinical scores.

n = number of animals in a group not dead from accidental or unknown causes, or euthanized for sampling prior to endpoint.

Mean Day 12 Clinical Score = the mean of the individual total clinical scores for all animals in a group on Day 12. Scored from 0 to 60 (15 per limb); calculated as the sum of four limbs; each limb scored for sum of: (a) one point for each red or swollen digit (maximum 5 points per paw possible); (b) 5 points for each swollen footpad; and (c) 5 points for each swollen ankle.

Mean Maximum Clinical Score = the mean of the maximum total clinical scores for individual animals in a group. (Day) = median day of the first instance of maximal clinical score for individual mice in the group.

Mean Clinical Score AUC = an estimate of clinical disease in each treatment group. Determined by plotting the total clinical score versus time for each animal, integrating the area under the curve (AUC) for each animal, and then calculating the group mean. AUC was calculated from data for Days 8–22.

Significance = determined with ANOVA and post hoc Dunnett's test: ns = not significant, \* =  $P < 0.05$ , \*\* =  $P < 0.01$ , \*\*\* =  $P < 0.001$ , compared to Group 1.

Mean BW Nadir = lowest group mean body weight, as % change from Day 1; --- indicates no decrease in mean body weight was observed; Day = day of nadir.

Responses to treatment based upon composite histopathologic findings:

Hematoxylin and eosin stained sections of the formalin-fixed hindlimb ankle region of each animal were evaluated for five metrics of arthritis progression. Scores ranging from 0 to 5 were assigned for each metric and maximum composite score was 25. 8/10 animals in the control group had composite histopathology scores over 5. The range for the control group was 1-13. In all treatment groups, there were less animals with composite scores above five compared to the control groups. In SB4 treated animals, 5/10 (LD), 3/10 (MD), 4/10 (HD) had clinical scores above 5. In EU-Enbrel treated animals, 1/10 (LD), 2/10 (MD), 3/10 (HD) had clinical scores above 5. In US-Enbrel animals, 2/10 (LD), 1/10 (MD), 5/10 (HD) had clinical scores above 5. Composite clinical scores showed no clear dose-response relationships with the test articles.

## Summary

SB4, EU-Enbrel, and US-Enbrel suppressed development of arthritis based on measurements of reductions in footpad volume, clinical scores, and hindlimb histopathology. There were no significant differences in the test article treatment groups; maximal efficacy appeared to occur at 1 mg/kg. Overall, the effects of SB4 on arthritis development in the CAIA mouse model were similar to US-Enbrel and EU-Enbrel.

## 4.2 Secondary Pharmacology

No secondary pharmacology studies were submitted in support of BLA 761066.

### 4.3 Safety Pharmacology

No safety pharmacology studies were submitted in support of BLA 761066.

## 5 Pharmacokinetics/ADME/Toxicokinetics

### 5.1 PK/ADME

Study Title: Pharmacokinetic Study of SB4 in SD Rats (Study No. RD00407)

Objective: The objective of this study was to investigate the comparability of pharmacokinetic parameters between SB4 and EU-Enbrel following a single subcutaneous administration in Sprague-Dawley rats.

Methods: A single dose of SB4 or EU-Enbrel was administered subcutaneously to male SD rats at a dose of 1 mg/kg, 5/males/group. Pharmacokinetic profiles were then observed up to 96 or 120 hours after dosing. Blood samples (approximately 0.25 mL) were obtained from the jugular vein at approximately 0, 2, 6, 12, 24, 36, 48, 72, 96, and 120 hours after dosing. The blood samples were placed at room temperature for approximately 15 minutes and were centrifuged. Serum samples were obtained and stored in a deep freezer at -50 to -80°C until analysis. Serum concentrations of SB4 and EU-Enbrel were determined by ELISA. The LLOQ for all analytes was 78.13 pg/mL in undiluted serum.

**Table 5: Experimental Groups in PK Study of SB4 in SD Rats**

Group	Test article	No. of animals	Dose level (mg/kg)	Animal ID	Dosing volume <sup>a</sup> (mL/kg)	Dose concentration (mg/mL)
1	SB4	5	1	6-10	2.4	0.409
2	EU Enbrel <sup>®</sup>	5	1	1-5	2.1	0.476

<sup>a</sup> Dosing volumes were adjusted accordingly based on their concentration

#### Results:

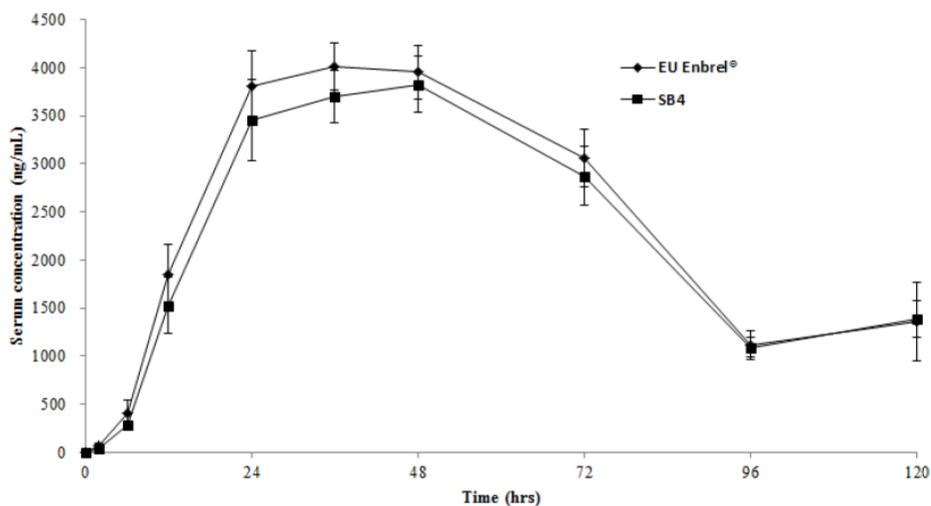
Mean serum concentrations from 0 to 120 hours were plotted in the figure below (Figure 3). The serum concentration at 120 hours was slightly higher than 96 hours in 9/10 samples. The sponsor suggests this may be due normal assay variation. No significant differences were observed between SB4 and EU-Enbrel<sup>®</sup> for C<sub>max</sub>, AUC<sub>last</sub>, T<sub>max</sub>, and T<sub>1/2</sub> (Table 7).

**Table 6: Mean Serum Concentrations of SB4 and EU-Enbrel in male Sprague-Dawley rats**

Time (h)	SB4		EU Enbrel <sup>®</sup>	
	Mean (ng/mL)	SD <sup>b</sup> (ng/mL)	Mean (ng/mL)	SD <sup>b</sup> (ng/mL)
0	0	0	0	0
2	38	13	66	31
6	282	20	410	128
12	1527	294	1845	320
24	3455	425	3806	367
36	3700	275	4011	249
48	3826	296	3952	279
72	2875	307	3054	299
96	1091	106	1112	145
120	1380	191	1360	410

<sup>b</sup> Standard Deviation

**Figure 3: Mean Serum Concentration of SB4 and EU-Enbrel in male Sprague-Dawley rats (0 to 120 hrs)**



**Table 7: Mean Pharmacokinetic Parameters for SB4 and EU-Enbrel in male Sprague-Dawley rats (from 0 to 120 hours)**

Group No.	Test Articles	-	AUC <sub>last</sub> (ng·h/mL)		C <sub>max</sub> (ng/mL)		T <sub>max</sub> (h)	T <sub>1/2</sub> (h)
G1	SB4	Mean	281760	<i>p</i> = 0.2674	3854	<i>p</i> = 0.2730	46.0	45.6
		SD	24230		294		5.4	5.9
G2	EU Enbrel®	Mean	300097		4052		38.0	41.4
		SD	24415		235		10.0	7.5

**Conclusion:**

Following a single dose of 1 mg/kg SB4 or EU-Enbrel® by subcutaneous injection to male SD rats, the observed pharmacokinetic profiles were similar between SB4 and EU-Enbrel. AUC and C<sub>max</sub> values for SB4 were 93.9 and 95.1% of values observed for EU-Enbrel, respectively. There were no notable differences in C<sub>max</sub>, AUC<sub>last</sub>, T<sub>max</sub>, and T<sub>1/2</sub> between SB4 and EU-Enbrel®.

## 6 General Toxicology

### 6.2 Repeat-Dose Toxicity

**Study title: A 4- Week Repeat Dose Toxicity Study of SB4 in Cynomolgus Monkeys**

Study no.:	2064-004
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	July 17, 2012
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SB4/BIIB602, PDR-112-12-137, 98.8% EU-Enbrel, F27600, Reduced: 96.8%; Non-reduced 99.1% US-Enbrel, 1026343, Reduced: 96.1%; Non-reduced 99.3%

**Key Study Findings**

- In a 28-day toxicology study, Cynomolgus monkeys (3/sex/group) received subcutaneous injections of 0 mg/kg (SB4 vehicle), 1 mg/kg SB4, 15 mg/kg SB4, 1 mg/kg EU-Enbrel, 15 mg/kg EU-Enbrel, 1 mg/kg US-Enbrel, or 15 mg/kg US-Enbrel twice per week on Days 1, 4, 8, 11, 15, 18, 22, and 25.

- There was one unscheduled death of a male monkey (No. 439) on Day 17, in the 15 mg/kg US-Enbrel group. There were microscopic findings in the thoracic cavity of pericardial adhesion/inflammation/fibrosis, inflammation of the epicardium, thrombus of the ventricle of the heart, and thrombus of the lung. The presence of bacterial colonies in the heart and pericardium were identified by H & E and Giemsa staining. The cause of death was likely due to preexisting bacterial infection that was exacerbated by the immunosuppressive effects of etanercept.
- Changes in clinical chemistry included increased globulin levels in all male treatment groups and in the EU-Enbrel female groups. Consequently, the A/G ratio generally decreased in these groups.
- Microscopic findings in SB4, EU-Enbrel and US-Enbrel treated animals were generally comparable.
- Expected treatment-related immunosuppressive microscopic findings included atrophy of the mandibular LN and decreased follicular lymphocytes of the mesenteric LB and spleen.
- Male #409 that received 15 mg/kg SB4 had findings consistent with macrophage activation syndrome in multiple tissues that were considered test article related.
- Sinusoidal leukocytosis of the liver was observed for one 1 mg/kg EU-Enbrel female, two 15 mg/kg EU-Enbrel females, one 1 mg/kg US-Enbrel female, and one 15 mg/kg US-Enbrel female. This finding may have been a weak signal of macrophage activation syndrome.
- Toxicokinetic analysis showed that systemic exposure (AUC,  $C_{max}$ ,  $T_{1/2}$ ) of SB4 was generally comparable to US-Enbrel, and EU-Enbrel on Study Days 1 and 25.
- The toxicity and toxicokinetic profiles of SB4, EU-Enbrel, and US-Enbrel in *Cynomolgus* monkeys were judged to be similar.

## Methods

**Table 8: Study Design**

Group	Treatment	Dose level (mg/kg/dose)	Number of animals	
			Males	Females
1	SB4 vehicle	0	3	3
2	SB4	1	3	3
3	SB4	15	3	3
4	EU Enbrel®	1	3	3
5	EU Enbrel®	15	3	3
6	US Enbrel®	1	3	3
7	US Enbrel®	15	3	3

Doses: 0 (SB4 vehicle), 1, or 15 mg/kg of SB4, US-Enbrel, or EU-Enbrel

Frequency of dosing: Twice weekly (Day 1, 4, 8, 11, 15, 18, 22, 25)

Route of administration: Subcutaneous injection

Dose volume: 2-2.22 mg/mL

Formulation/Vehicle: SB4 Vehicle: (b) (4) Sucrose, (b) (4) Sodium chloride, and (b) (4) Sodium phosphate, pH 6.2  
 Enbrel® vehicle: (1% sucrose, 100 mM sodium chloride, 25 mM L-Arginine hydrochloride, and 25 mM sodium phosphate, pH 6.3±0.2)

Species/Strain: Cynomolgus Monkey

Number/Sex/Group: 3/sex/group

Age: 3- 4.25 years

Weight: Males: 2.65 to 3.45 kg; Female: 2.5 to 3.9 kg

Satellite groups: None

Unique study design: None

Deviation from study protocol: Protocol deviations were reviewed and judged to not affect the quality or integrity of study data.

**Observations and Results****Mortality**

All animals were observed for mortality twice daily.

On Day 16, Male No. 439 in the 1 mg/kg US-Enbrel® group, presented as hunched in the cage with low body temperature. On Day 17, the animal was euthanized due to the following additional observations: weak, pale, lethargic, and difficulty breathing. Gross pathology examinations indicated there was approximately 15 mL of clear fluid accumulation in the abdominal cavity. Gross pathology examination indicated severe

inflammation/adhesions between the heart, pericardium and lungs, which correlated with microscopic findings in the thoracic cavity of pericardial adhesion/inflammation/fibrosis, inflammation of the epicardium, thrombus of the ventricle of the heart, and thrombus of the lung. The presence of bacterial colonies in the heart and pericardium were identified by H & E and Giemsa staining. Bacterial infection may have been a pre-existing condition which was exacerbated by the immune suppressive properties of US-Enbrel.

## Clinical Signs

Detailed clinical examinations of each animal were performed two times per day during the study. Occasionally, clinical observations were recorded at unscheduled intervals. Observations included, but were not limited to, evaluation of the skin, fur, eyes, nose, oral cavity, thorax, abdomen, external genitalia, limbs and feet, respiratory and circulatory effects, autonomic effects such as salivation, and nervous system effects including tremors, convulsions, reactivity to handling, and unusual behavior.

Soft and watery feces were noted in SB4, EU-Enbrel<sup>®</sup>, and US-Enbrel<sup>®</sup>-treated animals on multiple days during the study period. The incidence increased in relationship to the dose for SB4 and US-Enbrel treated males, and SB4 and EU-Enbrel treated females. These observations might be attributed to the immunosuppressive effects of etanercept.

**Table 9: Clinical Observations during treatment period**

Observation	MALES							FEMALES							
	Vehicle	SB4		EU Enbrel		US Enbrel		Vehicle	SB4		EU Enbrel		US Enbrel		
		mg/kg/dose		mg/kg/dose		mg/kg/dose			mg/kg/dose		mg/kg/dose		mg/kg/dose		
	1	15	1	15	1	15	1	15	1	15	1	15	1	15	
Excretion															
Feces discolored, red	0/0	0/0	0/0	6/3	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Feces soft	0/0	9/3	43/3	53/3	38/3	1/1	42/3	0/0	31/3	52/3	11/2	36/3	73/3	21/3	
Feces watery	0/0	10/2	47/3	31/3	10/3	10/3	20/3	0/0	9/3	21/3	9/2	65/3	9/3	2/1	

## Body Weights

Body weights for all animals were measured and recorded at transfer, twice prior to randomization (Days -7 and -1), and weekly during the study.

No treatment-related changes in body weight were observed following administration of SB4, US-Enbrel or EU-Enbrel.

## Feed Consumption

A daily qualitative assessment of food intake was conducted for all animals as part of the twice daily cageside observations.

No treatment-related changes in food consumption were observed following administration of SB4, US-Enbrel or EU-Enbrel

### **Ophthalmoscopy**

Ophthalmoscopic examinations were conducted on all animals pretest, during Week 2, and prior to the terminal necropsy.

No treatment-related changes in Ophthalmoscopic findings were observed following administration of SB4, US-Enbrel or EU-Enbrel.

### **ECG**

ECG exams were performed for all animals prior to initiation of dosing, predose, and 1-2 hours postdose during week 2 of dosing and the last week of dosing. RR, PR, and QT intervals, and QRS duration were measured and recorded using an appropriate lead. HR was calculated from the average of 5 RR intervals and QTc was calculated using Bazett's correction.

No treatment-related changes in ECG parameters were observed following administration of SB4, US-Enbrel or EU-Enbrel.

### **Hematology**

Hematology evaluations were conducted on all animals at pretest and on surviving animals prior to terminal necropsy (Day 28). The animals had access to drinking water but were fasted overnight prior to scheduled sample collection. Blood samples (approximately 4.8- to 5.8 mL) were collected from the femoral vein. The samples were collected into tubes containing K<sub>3</sub>EDTA for evaluation of hematology parameters.

There were no test article-related findings in hematology parameters following administration of SB4, US-Enbrel or EU-Enbrel.

### **Clinical Chemistry**

Clinical chemistry evaluations were conducted on all animals at pretest and surviving animals prior to terminal necropsy. The animals had access to drinking water but were fasted overnight prior to scheduled sample collection. Blood samples (approximately 4.8- to 5.8 mL) were collected from the femoral vein. The samples were collected into tubes containing serum separators with no anticoagulant for the clinical chemistry samples.

In males at Day 28, elevated globulin levels were noted in the 1 mg/kg SB4 group (+28.5%), 15 mg/kg SB4 group (+34.8%), 1 mg/kg EU-Enbrel (+11.2%), 15 mg/kg EU-Enbrel (27.3%), 1 mg/kg US-Enbrel (+12.4%), 15 mg/kg US-Enbrel (13.5%), relative to vehicle controls. Reduced Albumin/Globulin Ratio was observed in all treatment groups ranging from 13.2 to 38.3% reduction, relative to vehicle controls. This result could be due to the presence of the test article, a genetically engineered chimeric IgG1 homodimer, in the plasma.

In females at Day 28, elevated globulin levels were noted in the 1 mg/kg EU-Enbrel group (+8.6%) and 15 mg/kg EU-Enbrel (18.2%) group, relative to vehicle controls. Reduced Albumin/Globulin Ratios were noted in the SB4 treatment groups. A decreased Albumin/Globulin ratio was also noted in the 15 mg/kg EU-Enbrel group.

### **Urinalysis**

No treatment-related changes in urinalysis parameters were observed following administration of SB4, US-Enbrel or EU-Enbrel.

### **Gross Pathology**

Necropsy examinations were performed under procedures approved by a veterinary pathologist on one animal euthanized in extremis and all animals euthanized at the scheduled necropsy. The animals were euthanized by sedation with ketamine, followed by an intravenous overdose of sodium pentobarbital solution and exsanguination by severing the femoral vessels. The animals were examined carefully for external abnormalities including palpable masses. The skin was reflected from a ventral midline incision and any subcutaneous masses were identified and correlated with antemortem findings. The abdominal, thoracic, and cranial cavities were examined for abnormalities. The organs were removed, examined, and, where required, placed in fixative. All designated tissues were fixed in neutral buffered formalin, except for the eye (including the optic nerve) and testes, which were fixed using a modified Davidson's fixative. Formalin was infused into the lung. A full complement of tissues and organs was collected from all animals.

No test article related gross pathologic findings were noted for following administration of SB4, US-Enbrel or EU-Enbrel.

### **Organ Weights**

Body weights and protocol-designated organ weights were recorded for all animals at the scheduled necropsy and appropriate organ weight ratios were calculated (relative to body and brain weights). Paired organs were weighed together. A combined weight for the thyroid and parathyroid glands was collected. Only the right mandibular salivary gland was weighed.

Males and females in the study were generally sexually immature leading to high variability in reproductive organ weights. No treatment-related changes in organ weights were observed following administration of SB4, US-Enbrel or EU-Enbrel.

### **Histopathology**

Adequate Battery

Yes. A complete battery of organs and tissue was examined.

**Table 10: Battery of organs evaluated in histopathologic analysis**

- Adrenal (2)*	- Larynx
- Aorta	- Liver [3 sections collected; 2 examined]*
- Bone with marrow [femur]	- Lung with bronchi [collected whole; 2 sections examined]*
- Bone with marrow [rib]	- Lymph nodes: mandibular [2 collected; 1 examined] and mesenteric
- Bone with marrow [sternum]	- Mammary gland [only process females]
- Bone marrow smear [2 collected]*	- Pancreas*
- Brain [cerebrum, midbrain, cerebellum, medulla/pons]*	- Pituitary
- Epididymis (2)*	- Prostate* and seminal vesicle (2)
- Eye including optic nerve (2)	- Salivary gland, mandibular [2 collected; 1 examined]* <sup>b</sup>
- Gallbladder	- Salivary gland, parotid [2 collected; 1 examined]
- GALT [Gut Associated Lymphoid Tissue]	- Salivary gland, sublingual [2 collected; 1 examined]
- Gastrointestinal tract:	- Sciatic nerve
esophagus	- Skeletal muscle, rectus femoris
stomach [cardia, fundus, and pylorus]	- Skin
duodenum	- Spinal cord [cervical, thoracic, and lumbar]
jejunum	- Spleen*
ileum	- Thymus*
cecum	- Thyroid/parathyroid (2)*
colon	- Tongue
rectum	- Trachea
- Gonads:	- Ureter (2)
ovary (2)* with oviduct (2)	- Urinary bladder
testis (2)*	- Uterus/Cervix*
- Gross lesions	- Vagina
- Heart*	
- Injection site [1-4]	
- Joint, tibiofemoral	
- Kidney (2)*	

<sup>a</sup>Bone marrow smears were collected at necropsy and held.  
<sup>b</sup>Only the weight of the right mandibular salivary gland was obtained.

Peer Review

No

Histological Findings

Animal No. 409 that received 15 mg/kg SB4 had findings consistent with macrophage activation in multiple tissues that were considered test article related. Increased

numbers of enlarged macrophages with granular cytoplasm and cell debris and/or intact RBC or leukocytes, were observed in the spleen of this animal. Lymphoid cellularity was decreased in the spleen. In the liver, sinusoidal cells (presumed to be macrophages), were also enlarged with granular cytoplasm and cell debris and/or intact RBC or leukocytes. Atrophy of the mesenteric and mandibular LNs was associated with decreased lymphocyte cellularity. The subcapsular sinuses and sinusoids contained macrophages that were enlarged with granular cytoplasm. Decreased lymphoid cellularity in the spleen and mesenteric and mandibular LNs might be attributed to the immunosuppressive findings of SB4.

At termination, Animal #409 in the 15 mg/kg SB4 group had significant decreases in peripheral blood leukocytes count (most significantly in NK cells and lymphocytes including mature T cells and CD4+ cells population) compared to pretest and other animals in the study, indicative of immunosuppression. This animal also had a very robust anti-drug antibody (ADA) response. On Day 22, Animal #409 had a mean ADA signal that was almost 7 times higher than the mean peak signal for all the other animals in the study that had positive responses. The findings in Animal #409 may have been triggered by pre-existing infectious pathogens, although it is not identified whether this animal had an endemic disease or pathogen during the study, which was exacerbated by coincident pharmacologically-mediated immune suppression by TNF $\alpha$  inhibition.

Sinusoidal leukocytosis of the liver was observed in one 15 mg/kg SB4 male (Male No. 409), with clear evidence of macrophage activation syndrome, as well as one 1 mg/kg EU-Enbrel female, two 15 mg/kg EU-Enbrel females, one 1 mg/kg US-Enbrel female, and one 15 mg/kg US-Enbrel female. This finding in the 4 females treated with reference products may have been a weak signal of macrophage activation syndrome.

Atrophy of the mandibular LN was observed for one female in each of the 1 mg/kg and 15 mg/kg US-Enbrel groups. Decreased follicular lymphocytes of the mesenteric LN were observed for 1 of 3 male or female monkeys in each of the 15 mg/kg treatment groups except for the 15 mg/kg US-Enbrel group. Decreased follicular lymphocytes of the spleen were observed for two females in the 15 mg/kg SB4 group and one male and one female in the 15 mg/kg US-Enbrel groups.

Perivascular lymphoid infiltration was noted in the brain; however, this is generally a common background finding (mean of 2.5% with a range of 0-50%; Toxicologic Pathology 38: 642-657, 2010). The incidence for SB4 treated animals was within the historical range. Incidences in the 15 mg/kg US-Enbrel male group and 1 and 15 mg/kg EU-Enbrel female groups were 2 of 3 (66%) animals, which slightly exceeded the historical control range (0-50%).

Perivascular inflammation and fibrosis of the heart was observed in one 15 mg/kg US-Enbrel female.

**Table 11: Histopathological findings in 4-week monkey study with SB4, EU-Enbrel, and US-Enbrel**

Tissue	Severity	MALES								FEMALES							
		Vehicle	SB4		EU Enbrel		US Enbrel		Vehicle	SB4		EU Enbrel		US Enbrel			
			mg/kg/dose		mg/kg/dose		mg/kg/dose			mg/kg/dose		mg/kg/dose		mg/kg/dose			
Observation	N=3	N=3	N=3	N=3	N=3	N=3	N=3	N=3	N=3	N=3	N=3	N=3	N=3	N=3	N=3		
<b>lymph node mandibular</b>																	
atrophy		0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	
	minimal	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	
decreased lymphocytes, follicular		0	0	1**	0	0	0	0	0	0	0	0	0	0	0	0	
	minimal	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	
hyperplasia/hypertrophy/cell phagocytosis, macrophages		0	0	1**	0	0	0	0	0	0	0	0	0	0	0	0	
	minimal	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	
<b>lymph node mesenteric</b>																	
decreased lymphocytes, follicular		0	0	1**	0	1	0	1	1	0	0	1	0	1	1	0	
	minimal	0	0	1	0	1	0	1	1	0	0	1	0	1	1	0	
hyperplasia/hypertrophy/cell phagocytosis, macrophages		0	0	1**	0	0	0	0	0	0	0	0	0	0	0	0	
	minimal	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	
<b>Spleen</b>																	
decreased lymphocytes, follicular		0	0	1**	0	0	0	1	1	0	0	2	0	0	0	1	
	minimal	0	0	1	0	0	0	0	0	0	0	2	0	0	0	0	
decreased lymphocytes, generalized		0	0	1**	0	0	0	0	0	0	0	0	0	0	0	0	
	minimal	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	
hyperplasia/hypertrophy/cell phagocytosis, macrophages		0	0	1**	0	0	0	0	0	0	0	0	0	0	0	0	
	moderate	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	
<b>Thymus</b>																	
decreased lymphocytes		2	0	1**	0	1	2	1	1	1	0	1	1	2	1	2	
	minimal	1	0	0	0	1	1	1	1	0	0	1	0	0	1	1	
	moderate	1	0	1	0	0	1	0	0	1	0	2	1	2	0	1	
<b>Heart</b>																	
adhesion/inflammation/fibrosis, epicardium		0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	
	minimal	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	
thrombus		0	0	0	0	0	1*	0	0	0	0	0	0	0	0	0	
	mild	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	
<b>Liver</b>																	
leukocytosis, sinusoidal		0	0	1**	0	0	0	0	0	0	0	0	1	2	1	1	
	minimal	0	0	1	0	0	0	0	0	0	0	0	0	2	1	1	
	mild	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	
<b>Brain</b>																	
infiltration, lymphoid, perivascular		0	1	1	1	0	1	2	2	0	0	1	2	2	0	1	
	minimal	0	1	1	1	0	1	2	2	0	0	1	2	1	0	0	
	mild	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	

\* Male No. 439, euthanized on Day 17 due to bacterial infection around the heart

\*\* Male No. 409 15 mg/kg SB4 with signals of macrophage activation syndrome

## Special Evaluation

### Peripheral Blood Leukocyte Analysis

To assess the potential effects of the test article and reference articles on the lymphocyte subtypes, a 0.3 mL blood sample was collected from each animal at pretest and surviving animals prior to termination. Blood samples were collected via the femoral vein and placed into tubes with sodium heparin as an anticoagulant. Lymphocytes including B cells, helper T cells, cytotoxic T cells and mature T cells, monocytes and natural killer (NK) cells were analyzed by flow cytometry.

**Table 12: Peripheral Blood Lymphocyte subtypes evaluated**

Peripheral Blood Leukocyte Parameters	
Antigen Determinants	Cell Type
CD45 <sup>+</sup> CD20 <sup>+</sup>	B Cell
CD45 <sup>+</sup> CD3 <sup>+</sup> CD4 <sup>+</sup>	CD4 <sup>+</sup> T Cell
CD45 <sup>+</sup> CD3 <sup>+</sup> CD8 <sup>+</sup>	CD8 <sup>+</sup> T Cell
CD45 <sup>+</sup> CD14 <sup>+</sup>	Monocyte
CD45 <sup>+</sup> CD3 <sup>+</sup>	Mature T Cell
CD45 <sup>+</sup> CD16 <sup>+</sup>	Natural Killer Cell

**Table 13: Peripheral Blood Lymphocyte and NK cell counts and percentages for Animal # 409 (male, SB4 15 mg/kg)**

SB4 15 mg/kg Male No. 409	Lymphocytes		Natural Killer Cells	
	Cells/ $\mu$ L	% of gated	Cells/ $\mu$ L	% of gated
Pretest	4909	44.1	260	5.2
Terminal	941	34.95	20	2.33

In general, no test article related effects on mean counts or percentages of lymphocyte subtypes were noted for SB4, EU-Enbrel, or US-Enbrel. However, reduced lymphocytes and NK cells (percentage and absolute counts) was noted relative to pretest levels in male No. 409 in the SB4 15 mg/kg group. This animal was noted with macrophage activation as discussed in the Histopathology section. There were no comparable changes for other males and females in the SB4 15 mg/kg group or monkeys in reference product groups.

### Immunogenicity Studies

Blood samples (approximately 0.5 to 1 mL) were collected via the femoral vein from all surviving animals prior to initiation of dosing, and from all surviving animals on Day 22 (predose), and at termination for determination of etanercept anti-drug antibody (ADA) levels in the blood.

At study termination, most animals treated with 1 mg/kg (LD) SB4, EU-Enbrel<sup>®</sup>, or US-Enbrel<sup>®</sup> were positive for ADA responses. The ADA response was less prevalent in the 15 mg/kg (HD) groups, ranging from 0/3 to 2/3 positive responses per group. The immunosuppressive action of the test articles might suppress the ADA response at the higher dose of 15 mg/kg relative to the lower dose of 1 mg/kg. The ADA positive profile of SB4 was similar to EU-Enbrel and US-Enbrel.

**Table 14: Incidence of Anti-Drug Antibody Response in monkeys treated with SB4, EU-Enbrel, and US-Enbrel at 1 mg/kg and 15 mg/kg**

Incidence Table of Antibody Response (animals with positive antibody response / total number of animals)														
Collection interval	SB4 vehicle		SB4				EU Enbrel®				US Enbrel®			
			1 mg/kg		15 mg/kg		1 mg/kg		15 mg/kg		1 mg/kg		15 mg/kg	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Day 22	0/3	0/3	2/3	3/3	1/3	0/3	2/3	3/3	1/3	2/3	2/2	3/3	0/3	2/3
Termination	0/3	0/3	3/3	3/3	1/3	0/3	3/3	3/3	1/3	2/3	2/2	3/3	1/3	2/3

### Toxicokinetics

Monkeys were administered subcutaneous injections of SB4, EU-Enbrel or US-Enbrel twice per week on Days 1, 4, 8, 11, 15, 18, 22 and 25. Blood samples were obtained from each monkey at predose and at 2, 6, 12, 24, 48 and 72 hours after the dose on Days 1 and 25.

Reduced systemic exposure,  $C_{max}$ , and  $T_{max}$  was observed in the 1 mg/kg SB4 treated animals from Day 1 to Day 25 in males and females. Reduced systemic exposure appeared to correlate with positive anti-etanercept antibody results. Further, exposure was significantly lower in 1 mg/kg SB4 treated females than males on day 25. Similar PK parameters were observed for 1 mg/kg animals treated with EU-Enbrel or US-Enbrel, compared to 1 mg/kg SB4.

In the 15 mg/kg SB4 treated animals AUC was similar for males and females on Day 25. Generally, no significant sex-related differences in the TK parameters were observed with the exception of 1 mg/kg/dose groups of all treatments on day 25.

**Table 15: Toxicokinetic Parameters in SB4, EU-Enbrel, and US-Enbrel Treated Groups (includes both ADA positive and negative animals)**

Treatment	Day	Dose (mg/kg/dose)	Sex	AUC <sub>0-72</sub> (hr*ng/mL)	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (hr)
SB4	1	1	Male	755000	12700	40.0
			Female	620600	11000	48.0
		15	Male	10200000	173000	32.0
			Female	9080000	148000	32.0
	25	1	Male	271000	5070	18.0
			Female	17500	662	14.0
		15	Male	13400000	229000	20.0

Treatment	Day	Dose (mg/kg/dose)	Sex	AUC <sub>0-72</sub> (hr*ng/mL)	Cmax (ng/mL)	Tmax (hr)
EU-Enbrel®	1	1	Male	639000	11700	48.0
			Female	719000*	13000	48.0
		15	Male	7170000**	125000	48.0
			Female	9570000	152000	40.0
	25	1	Male	83600	2490	14.0
			Female	11000	303	30.0
		15	Male	11700000	213000	24.0
			Female	1940000	44600	20.0
Treatment	Day	Dose (mg/kg/dose)	Sex	AUC <sub>0-72</sub> (hr*ng/mL)	Cmax (ng/mL)	Tmax (hr)
US-Enbrel®	1	1	Male	649000	11100	56.0
			Female	739000	12300	56.0
		15	Male	11300000	179000	40.0
			Female	8780000	148000	48.0
	25	1	Male	61400	2000	6.0
			Female	14900	494	14.0
		15	Male	12500000	15500	24.0
			Female	6020000	8160	18.0

\*Animal 412 (female) Omitted

\*\*Animal 415 (male) Omitted

### Dosing Solution Analysis

Concentration analyses of SB4, EU-Enbrel, and US-Enbrel dosing formulations were performed on Days 1 and 25. Duplicate samples from the middle stratum of the 0.50 mg/mL and 7.50 mg/mL concentrations were analyzed by UV absorbance. All SB4, EU-Enbrel, and US-Enbrel samples were within the  $\pm 10\%$  of the nominal concentration and  $\leq 5\%$  RSD.

## 10 Special Toxicology Studies

No special toxicology studies were submitted in the application.

## 11 Integrated Summary and Safety Evaluation

BLA 761066 was submitted by Samsung Bioepis Co on May 25, 2017 to support registration of SB4 as a biosimilar to US-licensed Enbrel® (etanercept). Etanercept is a monoclonal antibody that targets the TNF receptor. Enbrel® was originally approved in

1998 under BLA 103795 by Immunex Corporation. Enbrel® is approved for the following indications: rheumatoid arthritis, polyarticular juvenile idiopathic arthritis in patients aged 2 years or older, psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis in patients 4 years or older. The Sponsor intends to obtain indications for SB4 identical to the indications of the reference product that are not subject to orphan exclusivity and are supported by the current presentations of SB4: rheumatoid arthritis, juvenile idiopathic arthritis in patients that weigh over 63 kg (138 lbs.) from ages 2 and older, psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis in patients that weigh over 63 kg (138 lbs.) from ages 4 and older.

The FDA approved the expanded use of Enbrel® for pediatric patients from ages 4 to 17 with the chronic moderate-to-severe plaque psoriasis in November 2016. (b) (4)

it was determined that the Sponsor needs to develop their pediatric presentation with clinical studies under PREA.

The nonclinical development program for SB4 included: 1) a primary pharmacology study evaluating efficacy in a CAIA-mouse model comparing SB4 vs US-licensed Enbrel and EU-approved Enbrel (Study # CAIA-e007), 2) a single-dose PK study conducted in SD rats comparing SB4 vs. EU-approved Enbrel (Study # RD00407), and 3) a 4-week repeat-dose toxicity study in monkeys comparing SB4 vs US-licensed Enbrel and EU-approved Enbrel (Study # 264-004).

In the comparative efficacy study with SB4 in the CAIA mouse model, no differences in efficacy were observed between SB4, EU-Enbrel, or US-Enbrel compared for vehicle treated mice.

In the single-dose subcutaneous PK study in male Sprague-Dawley rats, PK profiles were demonstrated to be comparable between SB4 and EU-Enbrel at a dose of 1 mg/kg.

The pivotal 28-day comparative repeat-dose toxicology study of SB4, EU-Enbrel, and US-Enbrel was conducted in cynomolgus monkeys (3/sex/group) that received subcutaneous doses of 1 and 15 mg/kg administered twice per week. There was one unscheduled death of a male monkey (No. 439) on Day 17, in the 15 mg/kg US-Enbrel group. There were microscopic findings in the thoracic cavity of pericardial adhesion/inflammation/fibrosis, inflammation of the epicardium, thrombus of the ventricle of the heart, and thrombus of the lung. The presence of bacterial colonies in the heart and pericardium were identified by H & E and Giemsa staining. The cause of death was likely due to preexisting bacterial infection that was exacerbated by the immunosuppressive effects of etanercept.

Microscopic findings in SB4, EU-Enbrel and US-Enbrel treated animals were generally comparable. Expected treatment-related immunosuppressive microscopic findings included atrophy of the mandibular LN and decreased follicular lymphocytes of the mesenteric LB and spleen. Male #409 that received 15 mg/kg SB4 had findings

consistent with macrophage activation syndrome in multiple tissues that were considered test article related. Sinusoidal leukocytosis of the liver was observed for one 1 mg/kg EU-Enbrel female, two 15 mg/kg EU-Enbrel females, one 1 mg/kg US-Enbrel female, and one 15 mg/kg US-Enbrel female. This finding may have been a weak signal of macrophage activation syndrome.

In general, systemic exposures (AUC<sub>0-72</sub> and C<sub>max</sub>) in the SB4 treated animals were comparable to those for EU-Enbrel and US-Enbrel treated monkeys. The decreased systemic exposures in 1 mg/kg-treated animals Day 25 were likely due to the development of ADAs. The development of ADAs in 1 mg/kg/dose SB4 treated animals on Day 22 and at study termination, were generally comparable to those observed in EU-Enbrel and US-Enbrel treated monkeys. However, In the 15 mg/kg SB4 treated females, 0/3 were positive for ADA on Day 22 or at study termination.

The nonclinical pharmacology study in mice, single dose pharmacokinetic study in male rats, and repeat-dose toxicology study in monkeys (3/sex/group) submitted in support of this BLA demonstrated comparable efficacy in the CIAA mouse model, achieved systemic exposures in rats, and safety profiles in monkeys, indicating similarity between SB4, EU-Enbrel, and US-Enbrel.

The BLA is recommended for approval from the nonclinical perspective. No additional animal studies are recommended. There are no outstanding issues from the nonclinical Pharmacology and Toxicology perspective.

Table 16 provides a side-by-side comparison of the language in Sections 8.1 (Pregnancy), 8.2 (Lactation), 12.1 (Mechanism of Action), and 13 (Nonclinical Toxicology) for (1) the reference product Enbrel (BLA 103975, approved 07-11-2017), (2) Samsung’s proposed labeling for SB4, and (3) the Division’s recommended labeling. Additions were denoted as underlined text. Deletions were denoted with ~~text~~. The labeling format complies with the Pregnancy and Lactation Labeling Rule (PLLR). Labeling closely follows that for ENBREL® (BLA 103795) and ERELZI® (an approved Etanercept biosimilar, BLA 761042).

**Table 16: Comparison and Edits of Proposed Labeling for SB4 vs Reference Product**

Enbrel (reference product) labeling BLA 103795	Samsung proposed SB4 labeling	DPARP recommended SB4 labeling
<b>Section 8. USE IN SPECIFIC POPULATIONS</b>		
8.1 Pregnancy <u>Risk Summary</u> Available studies with use of etanercept during pregnancy do not reliably support an association between etanercept and major birth defects. Clinical	8.1 Pregnancy <u>Risk Summary</u> Available studies with use of etanercept during pregnancy do not reliably support an association between etanercept and major birth defects. Clinical	8.1 Pregnancy <u>Risk Summary</u> Available studies with use of etanercept during pregnancy do not reliably support an association between etanercept <u>products</u> and major birth

<p>data are available from the Organization of Teratology Information Specialists (OTIS) Enbrel Pregnancy Registry in women with rheumatic diseases or psoriasis and a Scandinavian study in pregnant women with chronic inflammatory disease. Both the OTIS Registry and the Scandinavian study showed the proportion of liveborn infants with major birth defects was higher for women exposed to etanercept compared to diseased etanercept unexposed women. However, the lack of pattern of major birth defects is reassuring and differences between exposure groups (e.g. disease severity) may have impacted the occurrence of birth defects (see Data). In animal reproduction studies with pregnant rats and rabbits, no fetal harm or malformations were observed with subcutaneous administration of etanercept during the period of organogenesis at doses that achieved systemic exposures 48 to 58 times the exposure in patients treated with 50 mg Enbrel once weekly (see Data).</p>	<p>data are available from the Organization of Teratology Information Specialists (OTIS) etanercept Pregnancy Registry in women with rheumatic diseases or psoriasis and a Scandinavian study in pregnant women with chronic inflammatory disease. Both the OTIS Registry and the Scandinavian study showed the proportion of liveborn infants with major birth defects was higher for women exposed to diseased etanercept unexposed women. However, the lack of pattern of major birth defects is reassuring and differences between exposure groups (eg. disease severity) may have impacted the occurrence of birth defects (see Data). In animal reproduction studies with pregnant rats and rabbits, no fetal harm or malformations were observed with subcutaneous administration of etanercept during the period of organogenesis at doses that achieved systemic exposures 48 to 58 times the exposure in patients treated with 50 mg etanercept once weekly (see Data).</p>	<p>defects. Clinical data are available from the Organization of Teratology Information Specialists (OTIS) <del>etanercept</del> Pregnancy Registry in women with rheumatic diseases or psoriasis and a Scandinavian study in pregnant women with chronic inflammatory disease. Both the OTIS Registry and the Scandinavian study showed the proportion of liveborn infants with major birth defects was higher for women exposed to diseased etanercept unexposed women. However, the lack of pattern of major birth defects is reassuring and differences between exposure groups (eg. disease severity) may have impacted the occurrence of birth defects (see Data). In animal reproduction studies with pregnant rats and rabbits, no fetal harm or malformations were observed with subcutaneous administration of etanercept during the period of organogenesis at doses that achieved systemic exposures 48 to 58 times the exposure in patients treated with 50 mg etanercept <u>products</u> once weekly (see Data).</p>
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<p>All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the United States, about 2-4% of liveborn babies have a major birth defect and about 15-20% of pregnancies end in miscarriage, regardless of drug exposure.</p> <p><u>Clinical Considerations</u>  <i>Fetal/Neonatal adverse reactions</i>                  The risk of fetal/neonatal adverse reactions with in utero exposure to Enbrel is unknown. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to Enbrel in utero [see Use in Specific Populations (8.4)].</p> <p><u>Data</u>  <i>Human Data</i>                  A prospective cohort pregnancy registry conducted by OTIS in the US and Canada between 2000 and 2012 compared the risk of major birth defects in liveborn infants of women with rheumatic diseases or psoriasis exposed to etanercept in</p>	<p>All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the United States, about 2-4% of liveborn babies have a major birth defect and about 15-20% of pregnancies end in miscarriage, regardless of drug exposure.</p> <p><u>Clinical Considerations</u>  <i>Fetal/Neonatal adverse reactions</i>                  The risk of fetal/neonatal adverse reactions with in utero exposure to etanercept is unknown. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to etanercept in utero [see Use in Specific Populations (8.4)].</p> <p><u>Data</u>  <i>Human Data</i>                  A prospective cohort pregnancy registry conducted by OTIS in the US and Canada between 2000 and 2012 compared the risk of major birth defects in liveborn infants of women with rheumatic diseases or psoriasis exposed to etanercept in</p>	<p>All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the United States, about 2-4% of liveborn babies have a major birth defect and about 15-20% of pregnancies end in miscarriage, regardless of drug exposure.</p> <p><u>Clinical Considerations</u>  <i>Fetal/Neonatal adverse reactions</i>                  The risk of fetal/neonatal adverse reactions with in utero exposure to etanercept <u>products</u> is unknown. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to etanercept <u>products</u> in utero [see Use in Specific Populations (8.4)].</p> <p><u>Data</u>  <i>Human Data</i>                  A prospective cohort pregnancy registry conducted by OTIS in the US and Canada between 2000 and 2012 compared the risk of major birth defects in liveborn infants of women with rheumatic diseases or psoriasis exposed to etanercept in</p>
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<p>the first trimester. The proportion of major birth defects among liveborn infants in the etanercept-exposed (N = 319) and diseased etanercept unexposed cohorts (N = 144) was 9.4% and 3.5%, respectively. The findings showed no statistically significant increased risk of minor birth defects and no pattern of major or minor birth defects.</p>	<p>the first trimester. The proportion of major birth defects among liveborn infants in the etanercept-exposed (N = 319) and diseased etanercept unexposed cohorts (N = 144) was 9.4% and 3.5%, respectively. The findings showed no statistically significant increased risk of minor birth defects and no pattern of major or minor birth defects.</p>	<p>the first trimester. The proportion of major birth defects among liveborn infants in the etanercept-exposed (N = 319) and diseased etanercept unexposed cohorts (N = 144) was 9.4% and 3.5%, respectively. The findings showed no statistically significant increased risk of minor birth defects and no pattern of major or minor birth defects.</p>
<p>A Scandinavian study compared the risk of major birth defects in liveborn infants of women with chronic inflammatory disease (CID) exposed to TNF-inhibitors during early pregnancy. Women were identified from the Danish (2004-2012) and Swedish (2006-2012) population based health registers. The proportion of major birth defects among liveborn infants in the etanercept-exposed (N=344) and CID etanercept unexposed cohorts (N = 21,549) was 7.0% and 4.7%, respectively.</p>	<p>A Scandinavian study compared the risk of major birth defects in liveborn infants of women with chronic inflammatory disease (CID) exposed to TNF-inhibitors during early pregnancy. Women were identified from the Danish (2004-2012) and Swedish (2006-2012) population based health registers. The proportion of major birth defects among liveborn infants in the etanercept-exposed (N=344) and CID etanercept unexposed cohorts (N = 21,549) was 7.0% and 4.7%, respectively.</p>	<p>A Scandinavian study compared the risk of major birth defects in liveborn infants of women with chronic inflammatory disease (CID) exposed to TNF-inhibitors during early pregnancy. Women were identified from the Danish (2004-2012) and Swedish (2006-2012) population based health registers. The proportion of major birth defects among liveborn infants in the etanercept-exposed (N=344) and CID etanercept unexposed cohorts (N = 21,549) was 7.0% and 4.7%, respectively.</p>
<p>Overall, while both the OTIS Registry and Scandinavian study show a higher proportion of major birth defects in etanercept-exposed patients compared to diseased etanercept unexposed patients, the</p>	<p>Overall, while both the OTIS Registry and Scandinavian study show a higher proportion of major birth defects in etanercept-exposed patients compared to diseased etanercept unexposed patients, the</p>	<p>Overall, while both the OTIS Registry and Scandinavian study show a higher proportion of major birth defects in etanercept-exposed patients compared to diseased etanercept unexposed patients, the</p>

<p>lack of pattern of birth defects is reassuring and differences between exposure groups (e.g. disease severity) may have impacted the occurrence of birth defects.</p>	<p>lack of pattern of birth defects is reassuring and differences between exposure groups (e.g. disease severity) may have impacted the occurrence of birth defects.</p>	<p>lack of pattern of birth defects is reassuring and differences between exposure groups (e.g. disease severity) may have impacted the occurrence of birth defects.</p>
<p>Three case reports from the literature showed that cord blood levels of etanercept at delivery, in infants born to women administered etanercept during pregnancy, were between 3% and 32% of the maternal serum level.</p>	<p>Three case reports from the literature showed that cord blood levels of etanercept at delivery, in infants born to women administered etanercept during pregnancy, were between 3% and 32% of the maternal serum level.</p>	<p>Three case reports from the literature showed that cord blood levels of etanercept at delivery, in infants born to women administered etanercept during pregnancy, were between 3% and 32% of the maternal serum level.</p>
<p><i>Animal Data</i> In embryofetal development studies with etanercept administered during the period of organogenesis to pregnant rats from gestation day (GD) 6 through 20 or pregnant rabbits from GD 6 through 18, there was no evidence of fetal malformations or embryotoxicity in rats or rabbits at respective doses that achieved systemic exposures 48 to 58 times the exposure in patients treated with 50 mg Enbrel once weekly (on an AUC basis with maternal subcutaneous doses up to 30 mg/kg/day in rats and 40 mg/kg/day in rabbits). In a peri-and post-natal development study with pregnant rats that received etanercept during</p>	<p><i>Animal Data</i> In embryofetal development studies with etanercept administered during the period of organogenesis to pregnant rats from gestation day (GD) 6 through 20 or pregnant rabbits from GD 6 through 18, there was no evidence of fetal malformations or embryotoxicity in rats or rabbits at respective doses that achieved systemic exposures 48 to 58 times the exposure in patients treated with 50 mg etanercept once weekly (on an AUC basis with maternal subcutaneous doses up to 30 mg/kg/day in rats and 40 mg/kg/day in rabbits). In a peri-and post-natal development study with pregnant rats that received etanercept during</p>	<p><i>Animal Data</i> In embryofetal development studies with etanercept administered during the period of organogenesis to pregnant rats from gestation day (GD) 6 through 20 or pregnant rabbits from GD 6 through 18, there was no evidence of fetal malformations or embryotoxicity in rats or rabbits at respective doses that achieved systemic exposures 48 to 58 times the exposure in patients treated with 50 mg etanercept <u>products</u> once weekly (on an AUC basis with maternal subcutaneous doses up to 30 mg/kg/day in rats and 40 mg/kg/day in rabbits). In a peri-and post-natal development study with pregnant rats that received</p>

<p>organogenesis and the later gestational period from GD 6 through 21, development of pups through post-natal day 4 was unaffected at doses that achieved exposures 48 times the exposure in patients treated with 50 mg Enbrel once weekly (on an AUC basis with maternal subcutaneous doses up to 30 mg/kg/day).</p>	<p>organogenesis and the later gestational period from GD 6 through 21, development of pups through post-natal day 4 was unaffected at doses that achieved exposures 48 times the exposure in patients treated with 50 mg etanercept once weekly (on an AUC basis with maternal subcutaneous doses up to 30 mg/kg/day).</p>	<p>etanercept during organogenesis and the later gestational period from GD 6 through 21, development of pups through post-natal day 4 was unaffected at doses that achieved exposures 48 times the exposure in patients treated with 50 mg etanercept <u>products</u> once weekly (on an AUC basis with maternal subcutaneous doses up to 30 mg/kg/day).</p>
<p><b>8.2 Lactation</b> <u>Risk Summary</u> Limited data from published literature show that etanercept is present in low levels in human milk and minimally absorbed by a breastfed infant. No data are available on the effects of etanercept on the breastfed child or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for Enbrel and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.</p>	<p><b>8.2 Lactation</b> <i>Risk Summary</i> Limited data from published literature show that etanercept is present in low levels in human milk and minimally absorbed by a breastfed infant. No data are available on the effects of etanercept on the breastfed child or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for SB4 and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.</p>	<p><b>8.2 Lactation</b> <u>Risk Summary</u> Limited data from published literature show that etanercept is present in low levels in human milk and minimally absorbed by a breastfed infant. No data are available on the effects of etanercept <u>products</u> on the breastfed child or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for SB4 and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.</p>
<p><b>Section 12.1 Mechanism of Action</b></p>		
<p>TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. It plays an important role in the inflammatory processes of</p>	<p>TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. It plays an important role in the inflammatory processes of</p>	<p>TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. It plays an important role in the inflammatory processes of</p>

<p>RA, polyarticular JIA, PsA, and AS and the resulting joint pathology. In addition, TNF plays a role in the inflammatory process of PsO. Elevated levels of TNF are found in involved tissues and fluids of patients with RA, JIA, PsA, AS, and PsO.</p>	<p>RA, polyarticular JIA, PsA, and AS and the resulting joint pathology. In addition, TNF plays a role in the inflammatory process of PsO. Elevated levels of TNF are found in involved tissues and fluids of patients with RA, JIA, PsA, AS, and PsO.</p>	<p>RA, polyarticular JIA, PsA, and AS and the resulting joint pathology. In addition, TNF plays a role in the inflammatory process of PsO. Elevated levels of TNF are found in involved tissues and fluids of patients with RA, JIA, PsA, AS, and PsO.</p>
<p>Two distinct receptors for TNF (TNFRs), a 55 kilodalton protein (p55) and a 75 kilodalton protein (p75), exist naturally as monomeric molecules on cell surfaces and in soluble forms. Biological activity of TNF is dependent upon binding to either cell surface TNFR.</p>	<p>Two distinct receptors for TNF (TNFRs), a 55 kilodalton protein (p55) and a 75 kilodalton protein (p75), exist naturally as monomeric molecules on cell surfaces and in soluble forms. Biological activity of TNF is dependent upon binding to either cell surface TNFR.</p>	<p>Two distinct receptors for TNF (TNFRs), a 55 kilodalton protein (p55) and a 75 kilodalton protein (p75), exist naturally as monomeric molecules on cell surfaces and in soluble forms. Biological activity of TNF is dependent upon binding to either cell surface TNFR.</p>
<p>Etanercept is a dimeric soluble form of the p75 TNF receptor that can bind TNF molecules. Etanercept inhibits binding of TNF-<math>\alpha</math> and TNF-<math>\beta</math> (lymphotoxin alpha [LT-<math>\alpha</math>]) to cell surface TNFRs, rendering TNF biologically inactive. In in vitro studies, large complexes of etanercept with TNF-<math>\alpha</math> were not detected and cells expressing transmembrane TNF (that binds Enbrel) are not lysed in the presence or absence of complement.</p>	<p>Etanercept products are a dimeric soluble form of the p75 TNF receptor that can bind TNF molecules. Etanercept products inhibit binding of TNF-<math>\alpha</math> and TNF-<math>\beta</math> (lymphotoxin alpha [LT-<math>\alpha</math>]) to cell surface TNFRs, rendering TNF biologically inactive. In in vitro studies, large complexes of etanercept with TNF- <math>\beta</math> were not detected and cells expressing transmembrane TNF (that binds etanercept products) are not lysed in the presence or absence of complement.</p>	<p>Etanercept products are dimeric soluble forms of the p75 TNF receptor that can bind TNF molecules. Etanercept products inhibit binding of TNF-<math>\alpha</math> and TNF-<math>\beta</math> (lymphotoxin alpha [LT-<math>\alpha</math>]) to cell surface TNFRs, rendering TNF biologically inactive. In in vitro studies, large complexes of etanercept with TNF-<math>\alpha</math> were not detected and cells expressing transmembrane TNF (that binds etanercept products) are not lysed in the presence or absence of complement.</p>
<p><b>13.1 Carcinogenicity, Mutagenesis, Impairment of Fertility</b></p>		
<p>Long-term animal studies have not been conducted to evaluate the</p>	<p>Long-term animal studies have not been conducted to evaluate the</p>	<p>Long-term animal studies have not been conducted to evaluate the</p>

carcinogenic potential of etanercept or its effect on fertility.	carcinogenic potential of etanercept or its effect on fertility.	carcinogenic potential of etanercept <u>products</u> or <u>their</u> <del>its</del> effect on fertility
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## 12 Appendix/Attachments

None

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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IJEOMA K UZOMA  
02/13/2018

TIMOTHY W ROBISON  
02/13/2018  
I concur