CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761054Orig1s000

PHARMACOLOGY REVIEW(S)

Pharmacology and Toxicology Secondary Review for BLA 761054

TO: BLA 761054 (SB2 as a biosimilar to US-licensed Remicade® [infliximab])

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

DATE: December 22, 2016

BLA 761054 was submitted by Samsung Bioepis on March 24, 2016 under section 351(k) of the Public Health Service Act (PHS Act) to support licensure of SB2 as a biosimilar to US-licensed Remicade® (infliximab). US-licensed Remicade is an intravenously administered product, originally developed by Centocor, Inc. (BLA 103772, August 24, 1998), indicated for the treatment of Crohn's disease, Pediatric Crohn's disease, Ulcerative Colitis, Pediatric Ulcerative Colitis[1], Rheumatoid Arthritis (in combination with MTX), Ankylosing Spondylitis, Psoriatic Arthritis, and Plaque Psoriasis. The applicant is seeking approval for all current US-licensed Remicade indications.

Dr. Andrew Goodwin's review dated December 9, 2016 focused on two *in vivo* nonclinical studies submitted in support of a demonstration of biosimilarity of SB2 to US-licensed Remicade: (1) a study assessing the efficacy, pharmacokinetics, and immunogenicity of SB2, EU-approved infliximab, and US-licensed REMICADE in the Tg197 transgenic mouse arthritis model, and (2) a single-dose pharmacokinetic study in Sprague-Dawley rats comparing pharmacokinetics parameters of SB2, EU-approved infliximab, and US-licensed REMICADE.

In the study with Tg197 mice, SB2, US-licensed Remicade, and EU-approved infliximab each demonstrated comparable, dose-dependent increases in body weight gain as well as efficacy measured by Arthritis Score or Histopathological Score. At 10 mg/kg, SB2 exposure in animals receiving SB2 was comparable to that of the EU-approved infliximab and US-licensed REMICADE groups.

The significance of the single-dose pharmacokinetic study in Sprague-Dawley rats was uncertain due to the fact that the rat was not a pharmacologically relevant species for SB2, US-licensed Remicade, or EU-approved infliximab (e.g., no binding to rat TNFα).

Overall, the pharmacology and pharmacokinetic data submitted in BLA 761054 demonstrate the similarity of SB2 and US-licensed REMICADE from the nonclinical pharmacology and toxicology perspective and support a demonstration that SB2 is biosimilar to US-licensed Remicade.

[1] The indication for pediatric ulcerative colitis is protected by orphan drug exclusivity expiring on September 23, 2018. See the Orphan Drug Designations and Approvals database at http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm. Accordingly, FDA will not be able to license SB2 for this indication until the orphan exclusivity expires.

I concur with Dr. Goodwin's review dated December 9, 2016 that recommended approval of SB2 from the nonclinical Pharmacology and Toxicology perspective. Dr. Goodwin's review also contains recommendations for product labeling including compliance with the Pregnancy and Lactation Labeling Rule for Sections 8.1 and 8.2.

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

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/s/

TIMOTHY W ROBISON
12/22/2016

BLA 761054
Nonclinical Memo: Safety Assessment of Extractables and Leachables

Andrew Goodwin, PhD
Pharmacology-Toxicology Reviewer, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Timothy Robison, PhD, DABT
Pharmacology-Toxicology Team Leader, DPARP

Introduction

Samsung Bioepis submitted BLA 761054 on March 24, 2016 under section 351(k) of the Public Health Services Act. The Applicant seeks to register SB2 as a biosimilar to US-licensed REMICADE (infliximab). This memo will focus solely on a safety evaluation of extractables and leachables for the SB2 container-closure system. The overall nonclinical pharmacology and toxicology evaluation, as well as labeling recommendations, was provided in a separate review dated December 9, 2016.

On November 18, 2016, the pharmacology-toxicology reviewer received an informal consult request via email from the assigned drug product reviewer, Timothy Wadkins (Office of Pharmaceutical Quality, Office of Biotechnology Products). Dr. Wadkins requested nonclinical safety assessment of the levels of metals and organic compounds based on results of the extractables and leachables data reported in Section 3.2.P.2.4 of the BLA.

Extractables and Leachables Studies

The primary packaging material for the SB2 drug product is a (b) (4) glass vial, stoppered with a (b) (4) rubber stopper and sealed with an aluminum crimping cap. An extraction study was conducted to identify compounds that may migrate from the vial, stopper, or seal into solvents of interest. The study design is summarized in the Applicant's table below.

Table 3.2.P.2.4–1. Overview of Extractables Study

Analytical Techniques	Extractables	PW	IPA	Acidified Water (pH < 3)	Alkaline Water (pH > 10)
		Reflux for 8 h	50 ± 2°C for 72 ± 2 h		
ICP/MS	(b) (4)	X	X	X	X
GC/MS		X	X	X	X
		X	X	X	X
LC/MS		X	X	X	X
		X	X	X	X

Analytical Techniques	Extractables	PW	IPA	Acidified Water (pH < 3)	Alkaline Water (pH > 10)
		Reflux for 8 h	50 ± 2°C for 72 ± 2 h		
	(b) (4)				
LC/UV		X	X	X	X
IC		X	X	X	X
GC/MS		X	X	N/A	N/A
LC/UV		X	X	N/A	N/A

X: Test was performed

Source: Applicant's table

PW (purified water), IPA (isopropyl alcohol), (b) (4)

Informed by the results of the extraction studies, the sponsor is conducting leachables studies to determine the levels of the extractables in lyophilized SB2 drug product under real-time (2-8 degrees Celsius) and accelerated (25±2 degrees Celsius) storage conditions for a period up to 48 months. Real-time and accelerated storage data for up to 9 and 18 months, respectively, were provided in the BLA. Safety assessment was conservatively based on the highest detected level of each leachable in any of the triplicate samples at any time point and storage condition.

The Applicant calculated the maximum amount of each leachable on a "ug per syringe" basis. The reviewer notes that based on the maximum labeled dose (10 mg/kg) and a 60 kg representative patient weight, a single dose administration would require six 100 mg vials of SB2 drug product. Therefore, the reviewer's safety assessment was based on exposure levels 6 times higher than the analysis conducted by the Applicant in the BLA (likewise, the Applicant's calculated safety margins need to be reduced six-fold). The metals and organic compounds included in the safety assessment, as well as the calculated maximum exposure per dose administration, are summarized in the table below.

Leachable	CAS #	Maximum potential exposure (ug/dose)
		(b) (4)

Safety Assessment

The available data supporting the safety of the intravenous dose levels of each leachable was reviewed. Data provided by the sponsor was considered, as well as data in published literature and conclusions about threshold exposure levels from various regulatory bodies and guidance documents. The reviewer again notes that the exposures calculated in the table above are conservatively based on the “worst-case” data interpretation from the extractables and leachables studies. In addition, the safety

evaluation was based on the assumption of a daily exposure; however, the fact that infliximab products are administered only every 2-8 weeks provides an additional margin of safety.

(b) (4)

[redacted]

[1] Guidance for industry: ICH Q3D Elemental Impurities. Food and Drug Administration. September 2015.
[2] Impurities: Guideline for residual solvents Q3C(R5). ICH. February 2011.

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Conclusion

The potential exposure to elemental and organic compounds was assessed based on results from the extractables and leachables studies conducted with the SB2 container-closure system. The levels of all identified leachables are considered qualified from the nonclinical perspective.

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/s/

ANDREW C GOODWIN
12/15/2016

TIMOTHY W ROBISON
12/15/2016
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:	761054
Supporting document/s:	Electronic Document Room (EDR) Supporting Document (SD) #1, 11, 31
Applicant's letter date:	March 24, 2016; June 23, 2016; December 2, 2016
CDER stamp date:	March 24, 2016; June 23, 2016; December 2, 2016
Product:	SB2
Indication:	Crohn's Disease, Pediatric Crohn's Disease, Ulcerative Colitis, Pediatric Ulcerative Colitis, Rheumatoid Arthritis, Ankylosing Spondylitis, Psoriatic Arthritis, and Plaque Psoriasis
Applicant:	Samsung Bioepis
Review Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Reviewer:	Andrew Goodwin, PhD
Team Leader:	Timothy Robison, PhD, DABT
Division Director:	Badrul Chowdhury, MD, PhD
Project Manager:	Christine Ford

Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

Samsung Bioepis submitted BLA 761054 on March 24, 2016 under section 351(k) of the Public Health Services Act. The Applicant seeks to register SB2 as a biosimilar to US-licensed REMICADE (infliximab). Infliximab is a chimeric anti-tumor necrosis factor-alpha (TNF-alpha) immunoglobulin G (IgG) with human constant regions and mouse variable regions. The applicant is seeking approval for all current REMICADE indications including Crohn's Disease, Pediatric Crohn's Disease, Ulcerative Colitis, Pediatric Ulcerative Colitis[1], Rheumatoid Arthritis, Ankylosing Spondylitis, Psoriatic Arthritis, and Plaque Psoriasis.

As discussed below, no traditional general toxicology studies were conducted or required with SB2. Nonclinical studies reviewed under the BLA in support of a determination of biosimilarity included a pharmacokinetics study in rats and a pharmacology, pharmacokinetics (PK), and immunogenicity study in transgenic mice. In each study, SB2 was compared to EU- approved infliximab and US-licensed REMICADE.

1.2 Brief Discussion of Nonclinical Findings

Efficacy, pharmacokinetics and immunogenicity of SB2, EU- approved infliximab, and US-licensed REMICADE were assessed in the Tg197 transgenic mouse arthritis model. The test articles were administered as prophylactic treatment at 1, 3, or 10 mg/kg by intraperitoneal (IP) injection twice weekly. Each infliximab product demonstrated comparable, dose-dependent increases in body weight gain as well as efficacy measured by Arthritis Score or Histopathological Score. At 10 mg/kg, infliximab exposure in animals receiving SB2 was comparable to that of the EU-approved infliximab and US-licensed REMICADE groups. Immunogenicity (detection of anti-infliximab antibodies) was observed with all three test articles.

A single-dose PK study was conducted in Sprague-Dawley rats. After a single IV dose at 1, 3, or 10 mg/kg, pharmacokinetics parameters (Tmax, Cmax, and AUClast) were comparable for SB2, EU- approved infliximab, and US-licensed REMICADE. The significance of results from this study is uncertain due to the fact that the rat is not a pharmacologically relevant species for infliximab products (e.g., no binding to rat TNF-alpha).

There is no pharmacologically relevant species in which to conduct a general toxicology assessment of infliximab products such as SB2. Therefore, FDA considered a repeat-

[1] This reflects information for SB2 that Samsung Bioepis submitted on March 24, 2016. The reviewer notes that the indication for pediatric ulcerative colitis is protected by orphan drug exclusivity expiring on September 23, 2018. See the Orphan Drug Designations and Approvals database at http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm.

dose toxicology study in Sprague-Dawley rats to "be of limited value for a demonstration of similarity" (Type B meeting minutes dated March 5, 2012).

Overall, the pharmacology and PK data submitted in BLA 761054 demonstrate the similarity of SB2 and US-licensed REMICADE from the nonclinical pharmacology and toxicology perspective.

1.3 Recommendations

1.3.1 Approvability

SB2 is recommended for approval from the nonclinical pharmacology and toxicology perspective. Recommended labeling is discussed below.

1.3.2 Additional Non Clinical Recommendations

None. There are no outstanding nonclinical issues at this time.

1.3.3 Labeling

The table below compares nonclinical labeling text for 1) the approved REMICADE reference product, 2) the Applicant's proposed labeling submitted to the BLA, and 3) the reviewer's recommended edits to the Applicant's proposed labeling. The reviewer notes that while the product labeling in the current BLA will conform to PLLR format, the reference product label has not yet undergone a PLLR conversion.

Additional recommendations may be forthcoming pending consultation with the Medical Officer and the Division of Pediatric and Maternal Health (DPMH). In particular, the nonclinical reviewer defers any potential edits to the clinical portions of Section 8 to the Medical Officer and DPMH.

Table 1. Summary of recommended nonclinical labeling

REMICADE reference product labeling[a]	Applicant's proposed SB2 labeling[b]	Reviewer's recommended labeling[c]
Section 8. Use in Specific Populations		
8.1 Pregnancy **Pregnancy Category B.** It is not known whether REMICADE can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. REMICADE should be given to a pregnant woman only if clearly needed. Because infliximab does not cross-react with TNFα in species other than	**8.1 Pregnancy** (b) (4)	**8.1 Pregnancy** Risk Summary Limited published data on use of infliximab in pregnant women are insufficient to inform a drug associated risk. Published studies with infliximab use during pregnancy have not reported a clear association with infliximab and pregnancy outcome. A moderate number (approximately

REMICADE reference product labeling[a]	Applicant's proposed SB2 labeling[b]	Reviewer's recommended labeling[c]
humans and chimpanzees, animal reproduction studies have not been conducted with REMICADE. No evidence of maternal toxicity, embryotoxicity or teratogenicity was observed in a developmental toxicity study conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse TNFα. Doses of 10 to 15 mg/kg in pharmacodynamic animal models with the anti-TNF analogous antibody produced maximal pharmacologic effectiveness. Doses up to 40 mg/kg were shown to produce no adverse effects in animal reproduction studies. As with other IgG antibodies, infliximab crosses the placenta. Infliximab has been detected in the serum of infants up to 6 months following birth. Consequently, these infants may be at increased risk of infection, including disseminated infection which can become fatal. At least a six month waiting period following birth is recommended before the administration of live vaccines (e.g., BCG vaccine or other live vaccines, such as the rotavirus vaccine) to these infants [see Warnings and Precautions (5.14)].	(b) (4)	450) of prospectively collected pregnancies exposed to infliximab with known outcomes did not indicate unexpected effects on pregnancy outcome *[see Data]*. In an embryofetal development study conducted in mice using an analogous antibody, there was no evidence of embryotoxicity or teratogenicity *[see Data]*. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. *Reviewer's comment: Clinical aspects of the Risk Summary, as well as the Clinical Considerations and Human Data sections, are deferred to the Medical Officer and DPMH. The final sentence was deleted as this language is not used according to division standard PLLR labeling practices.* Clinical Considerations *Fetal/Neonatal adverse reactions* As with other IgG antibodies, infliximab crosses the placenta. Infliximab has been detected in the serum of infants up to 6 months following birth. Consequently, these infants may be at increased risk of infection, including disseminated infection which can become fatal. At least a six month waiting period following birth is recommended before the administration of live vaccines (e.g., BCG vaccine or other live vaccines, such as the rotavirus vaccine) to these infants *[see Warnings and Precautions (5.14)]*. Data *Human Data* The moderate number

REMICADE reference product labeling[a]	Applicant's proposed SB2 labeling[b]	Reviewer's recommended labeling[c]
	(b) (4)	(approximately 450) of prospectively collected pregnancies exposed to infliximab with known outcomes, including a limited number (approximately 230) exposed during the first trimester, does not indicate unexpected effects on pregnancy outcome. Due to its inhibition of TNFα, infliximab administered during pregnancy could affect normal immune responses in the newborn. The available clinical experience is too limited to exclude a risk, and administration of infliximab is therefore not recommended during pregnancy. *Animal Data* Because infliximab products do not cross-react with TNFα in species other than humans and chimpanzees, animal reproduction studies have not been conducted with infliximab products. An embryofetal development study was conducted in pregnant mice using an analogous antibody that selectively inhibits the functional activity of mouse TNFα. This antibody, administered during the period of organogenesis on gestation days 6 and 12 at IV doses up to 40 mg/kg produced no evidence of maternal toxicity, embryotoxicity, or teratogenicity. Doses of 10 to 15 mg/kg in pharmacodynamic animal models with the anti-TNF analogous antibody produced maximal pharmacologic effectiveness. *Reviewer's comment: Additional details were provided regarding the embryofetal development study in mice. References to 'infliximab' were revised to 'infliximab products' to conform to division standard labeling practices. Associated grammatical edits were made to*

REMICADE reference product labeling[a]	Applicant's proposed SB2 labeling[b]	Reviewer's recommended labeling[c]
		reflect the change from singular to plural references.
8.3 Nursing Mothers It is not known whether REMICADE is excreted in human milk or absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for adverse reactions in nursing infants from REMICADE, women should not breast-feed their infants while taking REMICADE. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.	**8.2 Lactation** (b) (4)	*Reviewer's comment: No nonclinical data. Defer to Medical Officer and DPMH.*
	8.3 Females and Males of Reproductive Potential (b) (4)	*Reviewer's comment: The reviewer notes that there is no nonclinical basis for the sponsor's language* (b) (4) *and that this language is not present in the REMICADE label. Therefore, the nonclinical reviewer recommends that this sentence be deleted but defers to the Medical Officer and DPMH.* *Reviewer's comment: There is no need to report the negative nonclinical data in section 8.3,*
8.4 Pediatric Use The safety and effectiveness of REMICADE have been established in pediatric patients 6 to 17 years of age for induction and maintenance treatment of Crohn's disease or ulcerative	**8.4 Pediatric Use** The safety and effectiveness of infliximab have been established in pediatric patients 6 to 17 years of age for induction and maintenance treatment of Crohn's disease or ulcerative	*Reviewer's comment: No nonclinical data. Defer to Medical Officer and DPMH.*

REMICADE reference product labeling[a]	Applicant's proposed SB2 labeling[b]	Reviewer's recommended labeling[c]
colitis. However, REMICADE has not been studied in children with Crohn's disease or ulcerative colitis <6 years of age.	colitis. However, infliximab has not been studied in children with Crohn's disease or ulcerative colitis <6 years of age.	
Section 12. Clinical Pharmacology		
12.1 Mechanism of Action Infliximab neutralizes the biological activity of TNFα by binding with high affinity to the soluble and transmembrane forms of TNFα and inhibits binding of TNFα with its receptors. Infliximab does not neutralize TNFβ (lymphotoxin-α), a related cytokine that utilizes the same receptors as TNFα. Biological activities attributed to TNFα include: induction of pro-inflammatory cytokines such as interleukins (IL) 1 and 6, enhancement of leukocyte migration by increasing endothelial layer permeability and expression of adhesion molecules by endothelial cells and leukocytes, activation of neutrophil and eosinophil functional activity, induction of acute phase reactants and other liver proteins, as well as tissue degrading enzymes produced by synoviocytes and/or chondrocytes. Cells expressing transmembrane TNFα bound by infliximab can be lysed in vitro or in vivo. Infliximab inhibits the functional activity of TNFα in a wide variety of in vitro bioassays utilizing human fibroblasts, endothelial cells, neutrophils, B and T-lymphocytes and epithelial cells. The relationship of these biological response markers to the mechanism(s) by which REMICADE exerts its clinical effects is unknown. Anti-TNFα antibodies reduce disease activity in the cotton-top tamarin colitis model, and decrease synovitis and joint erosions in a murine model of collagen-	**12.1 Mechanism of Action** (b) (4)	**12.1 Mechanism of Action** Infliximab products neutralize the biological activity of TNFα by binding with high affinity to the soluble and transmembrane forms of TNFα and inhibits binding of TNFα with its receptors. Infliximab products do not neutralize TNFβ (lymphotoxin-α), a related cytokine that utilizes the same receptors as TNFα. Biological activities attributed to TNFα include: induction of pro-inflammatory cytokines such as interleukins (IL) 1 and 6, enhancement of leukocyte migration by increasing endothelial layer permeability and expression of adhesion molecules by endothelial cells and leukocytes, activation of neutrophil and eosinophil functional activity, induction of acute phase reactants and other liver proteins, as well as tissue degrading enzymes produced by synoviocytes and/or chondrocytes. Cells expressing transmembrane TNFα bound by infliximab products can be lysed *in vitro* or *in vivo*. Infliximab products inhibit the functional activity of TNFα in a wide variety of *in vitro* bioassays utilizing human fibroblasts, endothelial cells, neutrophils, B and T-lymphocytes and epithelial cells. The relationship of these biological response markers to the mechanism(s) by which infliximab products exert their clinical effects is unknown. Anti-TNFα antibodies reduce disease activity in the cotton-top tamarin colitis model, and decrease

REMICADE reference product labeling[a]	Applicant's proposed SB2 labeling[b]	Reviewer's recommended labeling[c]
induced arthritis. Infliximab prevents disease in transgenic mice that develop polyarthritis as a result of constitutive expression of human TNFα, and when administered after disease onset, allows eroded joints to heal.	(b) (4)	synovitis and joint erosions in a murine model of collagen-induced arthritis. Infliximab products prevent disease in transgenic mice that develop polyarthritis as a result of constitutive expression of human TNFα, and when administered after disease onset, allows eroded joints to heal. *Reviewer's comment:* *References to 'infliximab' were revised to 'infliximab products' to conform to division standard labeling practices. Associated grammatical edits were made to reflect the change from singular to plural references.*
	Section 13. Nonclinical Toxicology	
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility The significance of the results of nonclinical studies for human risk is unknown. A repeat dose toxicity study was conducted with mice given cV1q anti-mouse TNFα to evaluate tumorigenicity. CV1q is an analogous antibody that inhibits the function of TNFα in mice. Animals were assigned to 1 of 3 dose groups: control, 10 mg/kg or 40 mg/kg cV1q given weekly for 6 months. The weekly doses of 10 mg/kg and 40 mg/kg are 2 and 8 times, respectively, the human dose of 5 mg/kg for Crohn's disease. Results indicated that cV1q did not cause tumorigenicity in mice. No clastogenic or mutagenic effects of infliximab were observed in the in vivo mouse micronucleus test or the Salmonella-Escherichia coli (Ames) assay, respectively. Chromosomal aberrations were not observed in an assay performed using human lymphocytes. It is not known whether infliximab can impair fertility in humans. No impairment	**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** (b) (4)	**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** The significance of the results of nonclinical studies for human risk is unknown. A repeat dose toxicity study was conducted with mice given cV1q anti-mouse TNFα to evaluate tumorigenicity. CV1q is an analogous antibody that inhibits the function of TNFα in mice. Animals were assigned to 1 of 3 dose groups: control, 10 mg/kg or 40 mg/kg cV1q given weekly for 6 months. The weekly doses of 10 mg/kg and 40 mg/kg are 2 and 8 times, respectively, the human dose of 5 mg/kg for Crohn's disease. Results indicated that cV1q did not cause tumorigenicity in mice. No clastogenic or mutagenic effects of infliximab products were observed in the *in vivo* mouse micronucleus test or the *Salmonella-Escherichia coli* (Ames) assay, respectively. Chromosomal aberrations were not observed in an assay performed using human lymphocytes. It is not known whether infliximab products can

REMICADE reference product labeling[a]	Applicant's proposed SB2 labeling[b]	Reviewer's recommended labeling[c]
of fertility was observed in a fertility and general reproduction toxicity study with the analogous mouse antibody used in the 6-month chronic toxicity study.	(b) (4)	impair fertility in humans. No impairment of fertility was observed in a fertility and general reproduction toxicity study with the analogous mouse antibody used in the 6-month chronic toxicity study. *Reviewer's comment: References to 'infliximab' were revised to 'infliximab products' to conform to division standard labeling practices*

a. BLA 103772, most recent label with action date October 2, 2015 (source: Drugs@FDA website)
b. BLA 761054, SD 31 received December 2, 2016
c. Tracked changes indicate differences compared to Applicant's proposed labeling.

2 Drug Information

2.1 Drug

CAS number: 170277-31-3

Code Name: SB2 (proposed infliximab biosimilar)

Chemical Name: Anti-tumor necrosis factor alpha (TNF-alpha) immunoglobulin G with human [constant region] –mouse [variable region] monoclonal cA2 heavy and light chains (two each) connected by disulfide bonds

Molecular Formula / Molecular Weight: $C_{6462}H_{9964}N_{1728}O_{2038}S_{44}$ / Approximately 149 kDa (1328 amino acids)

Structure or Biochemical Description

Figure 1. Amino Acid Sequence of SB2

```
  1 EVKLEESGGG LVQPGGSMKL SCVASGFIFS NHWMNWVRQS PEKGLEWVAE
 51 IRSKSINSAT HYAESVKGRF TISRDDSKSA VYLQMTDLRT EDTGVYYCSR
101 NYYGSTYDYW GQGTTLTVSS ASTKGPSVFP LAPSSKSTSG GTAALGCLVK
151 DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTQT
201 YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP
251 KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
301 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ
351 VYTLPPSRDE LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV
401 LDSDGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK
```

Figure 3.2.S.1.2–1. Amino Acid Sequence of SB2 Heavy Chain
Variable region: Normal letters
Constant region: **Bold letters**
N-linked glycosylation site: *Boxed letter*
Cysteine residue: Underlined letters

```
  1 DILLTQSPAI LSVSPGERVS FSCRASQFVG SSIHWYQQRT NGSPRLLIKY
 51 ASESMSGIPS RFSGSGSGTD FTLSINTVES EDIADYYCQQ SHSWPFTFGS
101 GTNLEVKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV
151 DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG
201 LSSPVTKSFN RGEC
```

Figure 3.2.S.1.2–2. Amino Acid Sequence of SB2 Light Chain
Variable region: Normal letters
Constant region (*kappa* chain): **Bold letters**
Cysteine residue: Underlined letters

Source: Applicant's figure (3.2.S.1.2)

Pharmacologic Class: Tumor necrosis factor (TNF) blocker

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 113461

2.3 Drug Formulation

SB2 is formulated as a lyophilized powder in single-use glass vials. Each vial contains 100 mg SB2 and is to be reconstituted in 10 mL sterile water for injection to obtain a 10 mg/mL infliximab solution at pH 6.2. The reconstituted product is further diluted in 0.9% sodium chloride (saline) for administration via intravenous (IV) infusion. The quantitative composition of the SB2 drug product is shown in the table below.

Table 2. Quantitative composition of SB2 drug product

Component	Function	Quality Standard	Nominal quantity per vial	
			SB2	REMICADE
Infliximab	Active substance	In-house	100 mg	100 mg
Monobasic sodium phosphate	(b) (4)	USP-NF	5.55 mg (monohydrate)	2.2 mg (monohydrate)
Dibasic sodium phosphate		USP-NF	2.60 mg (heptahydrate)	6.1 mg (dihydrate)
Sucrose		PhEur / USP-NF	500 mg	500 mg

Polysorbate 80	Surfactant	PhEur / USP-NF	0.5 mg	0.5 mg
Water for injection	(b) (4)	PhEur / USP-NF	q.s. (b) (4)	

SB2 source: Applicant's table (3.2.P.1)
REMICADE source: Product label accessed via Drugs@FDA website (dated October 2, 2015)

2.4 Comments on Novel Excipients

There are no novel excipients in SB2. The quantities of sucrose and polysorbate 80 are identical between SB2 and REMICADE. As noted in Table 2, the quantities of monobasic and dibasic sodium phosphate differ between the two products. In addition, SB2 contains the heptahydrate salt of dibasic sodium phosphate, while REMICADE contains the dihydrate salt. The differences in these excipients between the REMICADE and SB2 drug product do not represent a nonclinical safety concern.

2.5 Comments on Impurities/Degradants of Concern

Toxicological assessment of extractables and leachables will be provided in a separate review.

2.6 Proposed Clinical Population and Dosing Regimen

The Applicant is seeking approval for SB2 in all indications for which REMICADE is currently approved. Dosing regimens vary by indication, but the maximum indicated dose is 10 mg/kg IV every 4 weeks.

2.7 Regulatory Background

Pre-IND communications took place under IND 113461, but there was no IND submission and no clinical trials with SB2 have been conducted under IND.

At the Type B pre-IND meeting held February 14, 2012 (meeting minutes dated March 5, 2012), the following nonclinical advice and agreements were discussed.

- Study design elements and dose levels for the Tg197 mouse study
- There are no pharmacologically relevant species available for toxicity studies with infliximab products
- Repeat-dose toxicology study in rats would be of limited value

3 Studies Submitted

3.1 Studies Reviewed

The following nonclinical studies were submitted in the BLA 761054 submission (SD 1; March 21, 2016) and are reviewed in this memo:

- Evaluation of the efficacy of SB2 in the TG197 transgenic mouse model of arthritis (RD_06590 – *Primary Pharmacology*)
- Pharmacokinetics study of SB2 and REMICADE in SD rats (NC_00014 – *Pharmacokinetics*)
- Pharmacokinetics and immunogenicity study report of SB2 and REMICADE in human TNF-a transgenic mice (RD_00691 – *Pharmacokinetics*)

3.2 Studies Not Reviewed

The following nonclinical studies were submitted in the BLA 761054 submission (SD 1; March 21, 2016) but are not reviewed in this memo as they were not pivotal to the nonclinical assessment:

- Assay method for the quantification of infliximab in rat serum (LP_01033)
- Validation of a ligand-ligand binding method to detect infliximab in mouse plasma (RD_00752)
- Validation of a ligand-ligand binding method to detect anti-infliximab antibodies in mouse serum (RD_00753)

4 Pharmacology

4.1 Primary Pharmacology

Evaluation of the efficacy of SB2 in the Tg197 transgenic mouse model of arthritis
Study #RD_06590
July 1, 2014 (in-life phase October-November 2012)
(b) (4)
Non-GLP

Pharmacokinetics and immunogenicity study report of SB2 and REMICADE in human TNF-a transgenic mice
Study #RD_00691
September 3, 2015
Samsung Bioepis (Incheon, Korea)

Key Study Findings

Efficacy, pharmacokinetics and immunogenicity of 1, 3, or 10 mg/kg SB2 by IP injection twice weekly was compared to US-licensed REMICADE (infliximab) as a prophylactic treatment in the Tg197 transgenic mouse arthritis model. As measured by Arthritis Score and Histopathological Score, there were no statistically significant differences in efficacy between SB2 and US-licensed REMICADE.

Methods

The study consisted of 10 treatment groups, as shown in the table below. Each group had 4 animals per sex for the efficacy study and an additional 3 males per group were

allocated for a supplemental toxicokinetics time point. All animals were treated twice weekly via intraperitoneal injection for 7 weeks, beginning at 3 weeks of age (prophylactic administration; e.g., before onset of arthritis). A supplemental control group (2 animals per sex) was sacrificed at 3 weeks of age to benchmark the histopathological disease scores at the initiation of treatment.

Table 3. Tg197 mouse study design

Group No	Test article	Dose (mg/kg)	Dose frequency *	Dose volume (mL/kg)	Route of adm.	Animal number **	Age at sacrifice ***
1-A	SB2	1	Twice per week	10	IP	7M/4F	≥10 wks
2-B	SB2	3					
3-C	SB2	10					
4-D	EU Remicade®	1					
5-E	EU Remicade®	3					
6-F	EU Remicade®	10					
7-G	US Remicade®	1					
8-H	US Remicade®	3					
9-J	US Remicade®	10					
10-K	vehicle	-				4M/4F	10 wks
3 week controls	-	-	-	-	-	2M/2F	3 wks

Source: Applicant's table

Test, reference, and control articles were supplied at 0.1, 0.3, or 1.0 mg/mL:

- SB2 Lot PUR-R12-06-V
- EU- approved infliximab Lot 1RMA62101 (not considered relevant to the nonclinical review of BLA 761054)
- US-licensed REMICADE Lot 11F104P1
- SB2 vehicle formulation

Clinical signs (week days only) and body weights (weekly, on days of scoring) were recorded for all animals. Arthritis scores were evaluated on Days 1, 8, 15, 22, 29, 36, 43, and 50 based on the following scale:

- 0.0: no arthritis, (normal appearance, mouse can support upside its weight, whole body flexibility/evasiveness normal, grip strength maximum.)
- 0.5: onset of arthritis (mild joint swelling above paw, all other parameters as above)
- 1.0: mild arthritis (joint distortion by swelling, paw inflamed, all other parameters as above)
- 1.5: mild to moderate arthritis (joint-paw swelling, distortion + last finger inward deformation
- brief support upside its weight borderline yes/no, whole body flexibility reduced, less grip strength)

- 2.0: moderate arthritis (severe joint, paw and finger swelling, joint –leg deformation, no support upside its weight falls off, no whole body flexibility, no grip strength, climbing/feeding affected)
- 2.5: moderate to heavy arthritis (as above 2 + finger deformation in paws, mouse movement impaired)
- 3.0: heavy arthritis (ankylosis detected on flexion and severely impaired movement, mouse moribund).
- Addition of 0.25 to score indicated that at least one, but not all, criteria met the next highest score level.

Doses were administered on Days 3, 7, 10, 14, 17, 21, 24, 28, 31, 35, 38, 42, 45, and 49 in a volume of 10 mL/kg. The main study animals from each group were sacrificed on Day 51, 48 hours after the final dose.

Ankle joints were removed and 4 uM sections were prepared at 3 depths (surface, -30 um, -70 um) for histopathological assessment according to the following scale:

- 0.0: no detectable pathology (synovial membrane = cell monolayer, clear bone cavity and periarticular space)
- 1.0: hyperplasia of the synovial membrane (thickness clearly not due to folding and presence of polymorphonuclear infiltrates in bone cavity and/or periarticular space) Mild tendonitis may be present
- 2.0: pannus and fibrous tissue formation and focal subchondrial bone erosion
- 3.0: cartilage destruction and bone erosion
- 4.0: extensive cartilage destruction and bone erosion with bone outline structure lost.
- Additional 0.5 points were added to score if some, but not all, of the criteria for the next highest level were met.
- Maximum score from all available sections is the score for the joint

Statistical analysis was performed using non-parametric Kruskal-Wallis multiple comparison test with Dunn’s pair-wise testing.

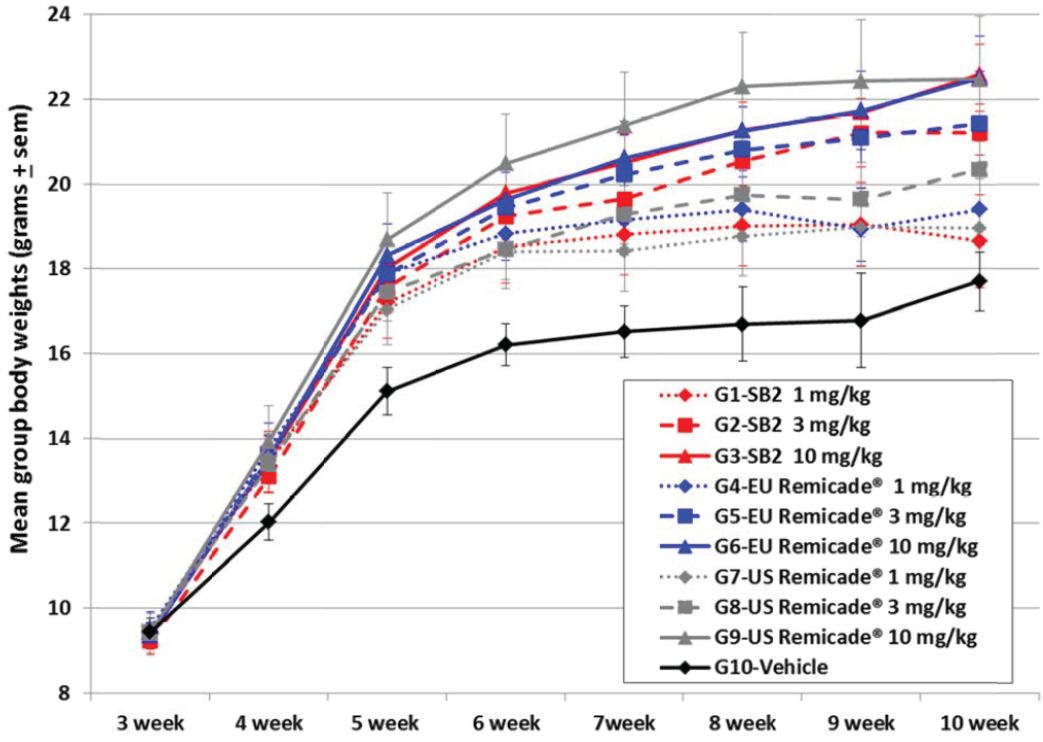
At sacrifice, blood was drawn from efficacy study animals by cardiac puncture and serum isolated for PK analysis. Blood samples from TK animals were collected at 0, 2, 6, 24, and 72 hours after the final dose. Plasma samples were analyzed for infliximab content by Samsung Bioepis using a validated analytical method with LLOQ 25 ng/mL.

The TK animals were sacrificed (and a final blood sample collected) on Day 52, 72 hours after the final dose. Serum samples were analyzed for anti-infliximab antibodies using a validated ELISA method.

Results

Body weight gain was greater in all treated groups compared to the vehicle control, in a dose-dependent manner, but differences were not statistically significant. There were no consistent differences in the body weight curves between groups receiving SB2 and US-licensed REMICADE at the same dose levels. See figure below (males and females combined).

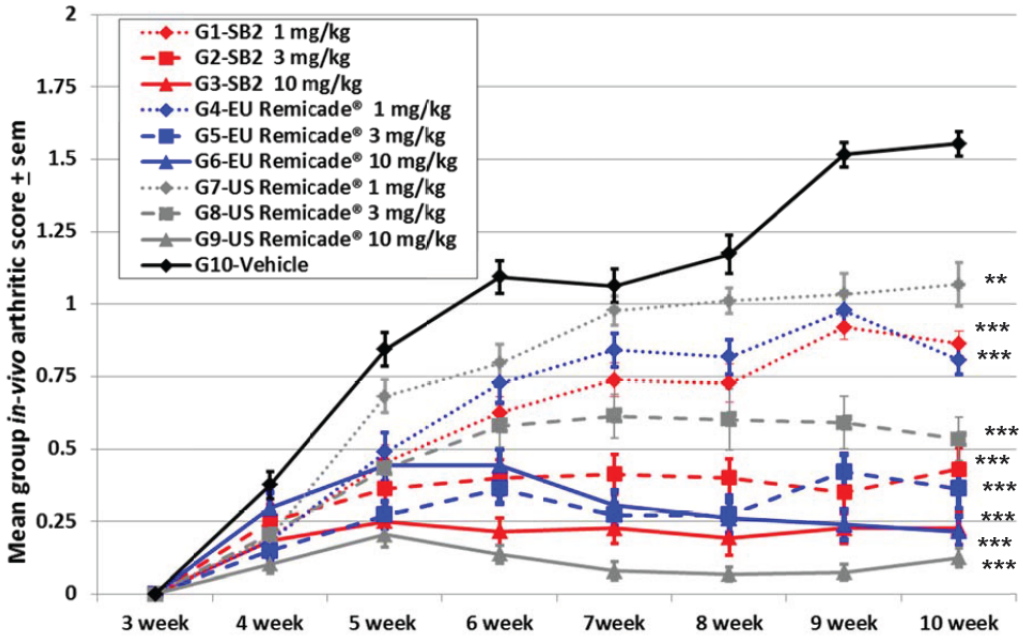
Figure 2. Tg197 mouse study: Body weights



Source: Applicant's figure

Arthritis scores (AS) increased continually in vehicle control animals from Week 3 to Week 10. Dose-dependent decreases in AS were observed in all groups receiving SB2, EU- approved infliximab or US-licensed REMICADE. There were no statistically significant differences in AS between groups receiving SB2 vs. US-licensed REMICADE at equal dose levels.

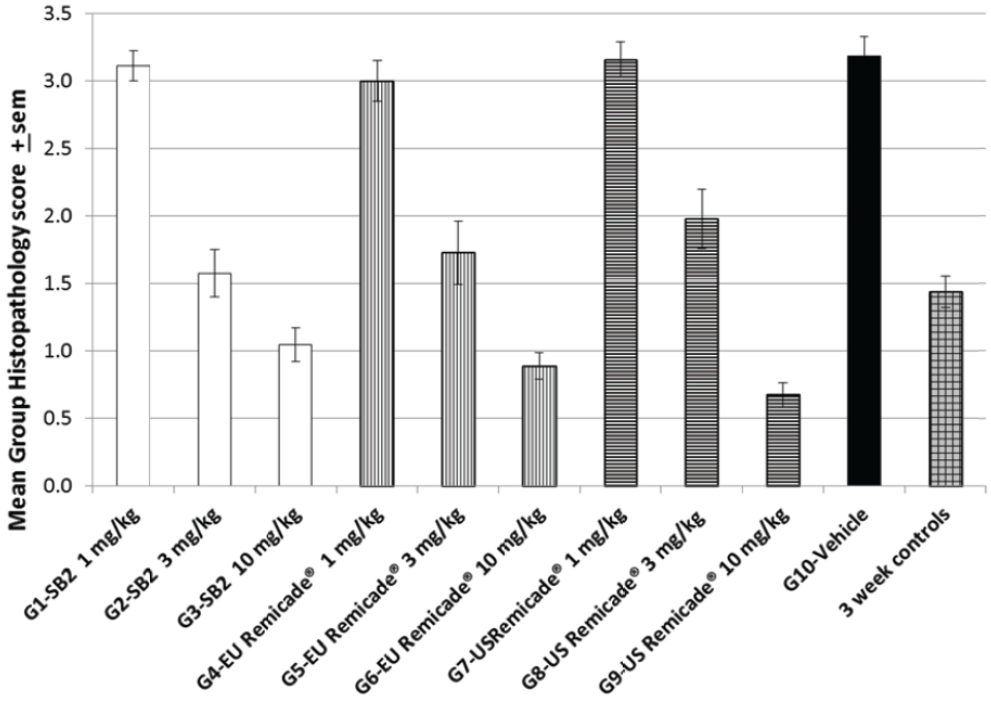
Figure 3. Tg197 mouse study: Arthritis scores



Source: Applicant's figure

Likewise, histopathological scores increased in control animals from Week 3 to Week 10. In contrast to the AS, no improvement was noted in groups treated with the lowest dose of 1 mg/kg SB2, EU- approved infliximab, or US-licensed REMICADE. Dose-dependent decreases in scores were noted at 3 and 10 mg/kg. No statistically significant differences in scores were observed between the SB2 and US-licensed REMICADE groups.

Figure 4. Tg197 mouse study: Histopathology scores



Source: Applicant's figure

All satellite animals in the 1 mg/kg groups (3/3 each for SB2, EU- approved infliximab, and US-licensed REMICADE) developed ADA. At the 3 mg/kg dose level, 4/9 animals (2/3 SB2, 1/3 EU- approved infliximab, 1/3 US-licensed REMICADE) developed ADA. Animals noted with ADA showed a loss of exposure at most or all time points. ADA were not observed in the high-dose (10 mg/kg) groups, a result which could be attributable to interference from high infliximab levels in these samples.

The ADA-negative animal (M5) in the 3 mg/kg SB2 group died prematurely due to the repeated blood sampling. As a result, the immunogenicity assessment was at 24 hours rather than 72 hours post-dose, increasing the possibility of interference resulting in a false negative result. Given slight imbalance observed, combined with the circumstances of this animal, the reviewer cannot rule out SB2 being more immunogenic that the reference product in this study. Any interpretation is limited by the very small animal numbers evaluated.

Based on the ADA observed and resulting loss of exposure, detailed PK comparisons were only conducted at the 10 mg/kg dose level. At that dose, AUClast and Cmax for the SB2 group were 88% and 82%, respectively, of that for the US-REMICADE group.

Table 4. Tg197 mouse study: Pharmacokinetics

Group No.	Treatment	-	AUC_{last} (ng•hr/mL)		C_{max} (ng/mL)		T_{max} (h)[d]
G3	SB2	Mean	31081667	$p = 0.760$	540504	$p = 0.345$	2
		SD	6700408		126292		N/A
G6	EU Remicade®	Mean	30751614		507225		2
		SD	10123799		116119		N/A
G9	US Remicade®	Mean	35129608		661234		2
		SD	6256618		129974		N/A

[d] T_{max}: Median T_{max} presented

Source: Applicant's table

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Pharmacokinetics Study of SB2 and REMICADE in SD Rats
Document NC_00014
December 17, 2014

Key Study Findings
After a single IV dose at 1, 3, or 10 mg/kg, pharmacokinetics parameters (Tmax, Cmax, and AUClast) were comparable for SB2, EU- approved infliximab, and US-licensed REMICADE. The significance of results from this study is uncertain due to the fact that the rat is not a pharmacologically relevant species for infliximab products (e.g., no binding to rat TNF-alpha).

Methods

The following test articles were used in the study:

- SB2 (Batch/Lot P49204A)
- EU- approved infliximab (Batch/Lot 1RMA64901)
- US-licensed Remicade (Batch/Lot 11F104P1)

Sprague-Dawley rats were obtained from (b) (4) at 8 weeks of age and initial body weights of 241-280 grams. The test articles were diluted in 0.9% saline for tail vein IV administration according to the design outlined in the table below.

Table 5. SD Rat PK Study Design

Group	Treatment	No. of Animals	Animal ID	Dose Level (mg/kg)	Dosing Volume (mL/kg)	Dose Concentration (mg/mL)
1	SB2	6	1-6	1	5	0.2
2	EU Remicade®	6	7-12	1	5	0.2
3	US Remicade®	6	13-18	1	5	0.2
4	SB2	6	19-24	3	5	0.6
5	EU Remicade®	6	25-30	3	5	0.6
6	US Remicade®	6	31-36	3	5	0.6
7	SB2	6	37-42	10	5	2
8	EU Remicade®	6	43-48	10	5	2
9	US Remicade®	6	49-54	10	5	2

Source: Applicant's table

Blood samples (0.2-0.3 mL) for pharmacokinetics (PK) evaluation were collected at 0, 0.08, 0.5, 2, 6, 24, 48, 72, 120, 168, 336, and 504 hours post-dose. Serum was isolated and analyzed for infliximab content using goat anti-human IgG Fc and goat anti-human IgG (Fab-specific)-peroxidase antibody. The range of quantification was 25-500 ng/mL in undiluted serum.

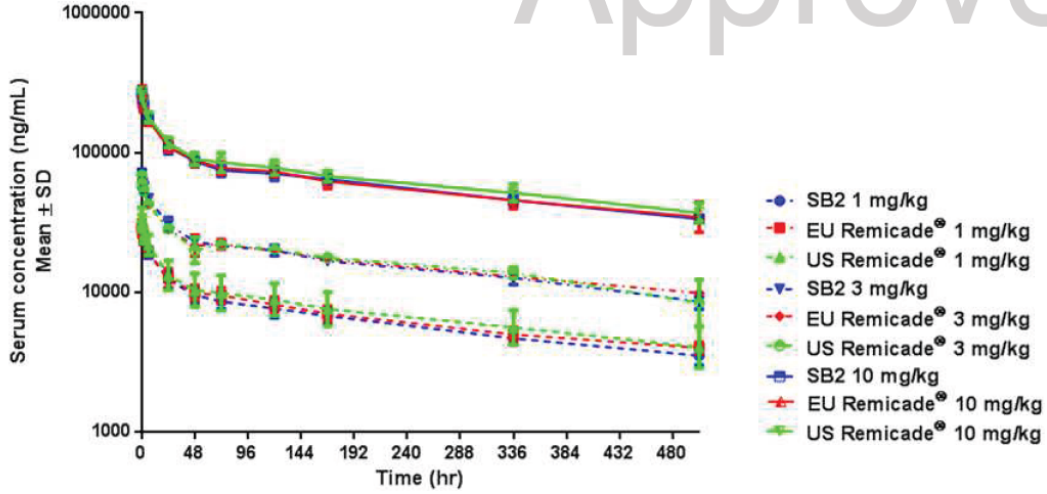
No post-dose evaluations of clinical signs, body weights, or other parameters were described in the protocol or study report.

Results

Serum concentration-time plots after a single IV injection of 1, 3, or 10 mg/kg SB2, EU REMICADE, and US REMICADE are shown in the figure below.

Figure 5. SD Rat PK Study: Serum concentration-time relationship

Appears this way on original



Source: Applicant's figure

Pharmacokinetic parameters for each test article are shown in the table below. Tmax was uniformly observed at 0.08 hr (first time point assessment) after the IV injection. AUClast and Cmax values were comparable for all three test articles at each dose levels. Infliximab exposure increased roughly dose proportionally after administration of each test article over the range of 1-10 mg/kg IV.

Table 6. SD Rat PK Study: Comparison of Pharmacokinetic Parameters

Dose	Parameter	SB2	EU Remicade	US Remicade	SB2 vs. EU	SB2 vs. US
1 mg/kg	AUClast (ng*hr/mL)	3280148	3476193	3753149	0.94	0.87
	Cmax (ng/mL)	29803	29232	34484	1.02	0.86
3 mg/kg	AUClast (ng*hr/mL)	8317074	8422871	8463806	0.99	0.98

	Cmax (ng/mL)	69722	69858	68984	1.00	1.01
10 mg/kg	AUClast (ng*hr/mL)	30693252	30867300	33434032	0.99	0.92
	Cmax (ng/mL)	269111	280924	274701	0.96	0.98

Table constructed by reviewer from Applicant's data

11 Integrated Summary and Safety Evaluation

Samsung Bioepis submitted BLA 761054 seeking approval of SB2 as a biosimilar to US-licensed REMICADE (infliximab). There are no pharmacologically relevant species available for toxicology studies with infliximab products. Therefore, the nonclinical assessment of similarity between SB2 and US-licensed REMICADE was based on pharmacology and pharmacokinetics data only.

Efficacy, pharmacokinetics and immunogenicity of SB2, EU- approved infliximab, and US-licensed REMICADE were assessed in the Tg197 transgenic mouse arthritis model. The test articles were administered as prophylactic treatment at 1, 3, or 10 mg/kg by intraperitoneal (IP) injection twice weekly. The effect of the infliximab products on disease progression in this mouse model was assessed via body weight gain, Arthritis Score (clinical examination / physical function), and Histopathology Score (microscopic examination of ankle joint). Each infliximab product demonstrated comparable, dose-dependent increases in body weight gain as well as improvements in Arthritis Score (all doses) and Histopathological Score (mid- and high-dose groups). At 10 mg/kg, infliximab exposure in animals receiving SB2 was comparable to that of the EU-approved infliximab and US-licensed REMICADE groups. Mean AUC and Cmax in the SB2 group were 88% and 82%, respectively, of the mean values in the US-licensed REMICADE group. Immunogenicity (detection of anti-infliximab antibodies) was observed with all three test articles.

A single-dose PK study was conducted in Sprague-Dawley rats. After a single IV dose at 1, 3, or 10 mg/kg, pharmacokinetics parameters (Tmax, Cmax, and AUClast) were comparable for SB2, EU- approved infliximab, and US-licensed REMICADE. Mean AUC and Cmax values in the SB2 groups were 87-98% and 86-101%, of the mean values in the US-licensed REMICADE groups, respectively. The significance of results from this study is uncertain due to the fact that the rat is not a pharmacologically relevant species for infliximab products (e.g., no binding to rat TNF-alpha).

The nonclinical pharmacology and pharmacokinetics data provided in the BLA support a demonstration of similarity between SB2 and US-licensed REMICADE from the nonclinical pharmacology and toxicology perspective. There are no outstanding nonclinical issues and BLA 761054 is recommended for approval from the nonclinical pharmacology and toxicology perspective.

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/s/

ANDREW C GOODWIN
12/09/2016

TIMOTHY W ROBISON
12/09/2016
I concur