CLINICAL REVIEW

Application Type	351(k) BLA
Application Number(s)	761054
Priority or Standard	Standard
Submit Date(s)	March 21, 2016
Received Date(s)	March 21, 2016
PDUFA Goal Date	April 21, 2017[1]
Division / Office	DPARP – lead division Collaborative review with DGIEP and DDDP
Reviewer Name(s)	Juwaria Waheed, MD
Review Completion Date	January 6, 2017
Nonproprietary Name	SB2 (infliximab-abda)[2]
(Proposed) Trade Name	Renflexis
Therapeutic Class	TNF-inhibitor
Applicant	Samsung Bioepis (Quintiles)
Formulation(s)	Intravenous (IV)
Dosing Regimen	• Rheumatoid Arthritis: In conjunction with methotrexate, 3mg/kg at 0, 2, and 6 weeks, then every 8 weeks increasing up to 10mg/kg or treating every 4 weeks • Ankylosing Spondylitis: 5mg/kg at 0, 2, and 6 weeks, then every 6 weeks • Psoriatic Arthritis, Plaque Psoriasis and Ulcerative Colitis: 5mg/kg at 0, 2, and 6 weeks, then every 8 weeks • Crohn's disease: 5mg/kg at 0, 2, and 6 weeks, then every 8 weeks increasing up

[1] Due to a major amendment from the applicant (pertaining to microbiology review) PDUFA goal date was extended from January 21, 2017 to April 21, 2017

[2] In this document, FDA generally refers to Samsung's proposed product by the Samsung descriptor "SB2."

to 10mg/kg in patients who initially respond but lose their response later

Indications Sought

- Rheumatoid Arthritis in combination with methotrexate,
- Ankylosing Spondylitis
- Psoriatic Arthritis
- Plaque Psoriasis
- Crohn's Disease
- Pediatric Crohn's Disease
- Ulcerative Colitis
- Pediatric Ulcerative Colitis[1]

Intended Population(s)

- Rheumatoid Arthritis: moderate to severe disease
- Ankylosing Spondylitis: active disease
- Psoriatic Arthritis: active disease
- Plaque Psoriasis: chronic, severe disease
- Crohn's Disease: moderate to severe disease
- Pediatric Crohn's Disease: moderate to severe disease
- Ulcerative Colitis: moderate to severe disease
- Pediatric Ulcerative Colitis: moderate to severe disease[1]

[1]We note 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.

Table of Contents

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Recommend approval of BLA 761,054 for SB2 as a biosimilar to US-licensed Remicade, pending completion of microbiology review.

This biologic licensing application (BLA 761,054) seeks approval of the product SB2 (proposed trade name: Renflexis) which is a proposed biosimilar to US-licensed Remicade (also referred to as US-Remicade in this review) with the active ingredient infliximab, a TNFα-inhibitor. The biosimilar licensure pathway under section 351(k) of the Public Health Service Act (PHS Act) requires that the proposed biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between the proposed biosimilar and reference products in terms of safety, purity and potency. Both parts of the statutory definition need to be met to demonstrate biosimilarity, with the foundation being an extensive structural and functional characterization to support a demonstration that the products are highly similar.

The product quality review by OBP (Office of Biotechnology Products) team, of structural and functional characterization, concluded that SB2 is highly similar to US-licensed Remicade notwithstanding minor differences in clinically inactive components. The submitted clinical pharmacology, efficacy, safety, and immunogenicity data from the clinical development program of SB2, support a demonstration of no clinically meaningful differences between SB2 and US-licensed Remicade.

Therefore, SB2 meets both parts of the statutory definition to demonstrate biosimilarity to the reference product in that SB2 is highly similar to the reference product notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between SB2 and the US-licensed Remicade in terms of safety, purity and potency. The applicant has also provided adequate scientific justification to allow for extrapolation of data to support biosimilarity in all indications that US-licensed Remicade is licensed for, and Samsung is seeking licensure of SB2, namely, Ankylosing Spondylitis (AS), Psoriatic Arthritis (PsA), Psoriasis (PsO), adult and pediatric Crohn's Disease (CD), and adult and pediatric Ulcerative Colitis (UC)[1].

[1]We note 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.

1.2 Risk Benefit Assessment

Brief Overview of the Clinical Program

The following two controlled studies provide the primary evidence to support the determination of no clinically meaningful differences between SB2 and US-licensed Remicade:

- Study SB2-G11-NHV, hereon referred to as Study SB2-NHV is a single-dose, 3-way pharmacokinetics (PK) study that assessed the similarity in PK between SB2 and US-Remicade. It also helped in establishing the PK bridge between SB2, US-licensed Remicade, and EU-approved Remicade (EU-Remicade). This bridge is necessary because the reference product of interest for this application is US-Remicade, but the majority of the clinical program utilized EU-Remicade as the comparator. This study therefore provides the PK component of the scientific justification for the relevance of data generated using EU-Remicade to the to the demonstration of biosimilarity of SB2 to US-licensed Remicade. Study SB2-NHV also provides the immunogenicity data comparing SB2 and US-licensed Remicade following single dose administration.
- Study SB2-G31-RA, hereon referred to as Study SB2-RA is the comparative clinical study that provides efficacy, safety and immunogenicity data for SB2 in rheumatoid arthritis (RA) in comparison with EU-Remicade. It was designed as a randomized, double-blind, parallel-group study to compare efficacy, safety and immunogenicity between the two products for 54 weeks. Following the first randomized controlled period, additional long-term safety and immunogenicity data from Week 54 to Week 78 were reported for patients who either continued SB2 or underwent a randomized single transition at week 54 from EU-approved Remicade to SB2 or continued to receive EU-Remicade in a randomized, double-blind fashion.

With the exception of Study SB2-NHV, the majority of the clinical program was conducted with minimal FDA input.

Clinical Efficacy Overview and Conclusions

Study SB2-RA, the comparative clinical study (CCS) in RA patients, met its primary objective of demonstrating that the proportion of patients achieving ACR20 response at Week 30 was similar between the SB2 and EU-Remicade treatment groups [148 (64%), and 163(66%) patients, respectively]. The 95% confidence interval (CI) for the estimate of the treatment difference (-1.88) was contained within the applicant's prespecified similarity margin of -15% to 15% (95% CI: -10.26, 6.51). Of note, as discussed in detail in the FDA statistical review, the Agency has determined that a ±12% similarity margin would be generally expected, based on considerations of the clinical importance of different losses in effect against the feasibility of the comparative clinical study. The results from the primary analysis were supported by consistent sensitivity analyses and

were also within the margin preferred by the Agency. These results support the conclusion of no clinically meaningful differences between SB2 and EU-Remicade in the RA indication.

Analysis of key secondary efficacy endpoints in Study SB2-RA including ACR20 response at Week 54, ACR50 and ACR 70 at Weeks 30 and Week 54, ACR-N at Week 30, individual components of the ACR20 criteria, showed similar results between SB2 and EU-approved Remicade treatment groups.

Supportive of the above findings, the long-term transition-extension period of Study SB2-RA also demonstrated consistent efficacy up to Week 78 with no difference between SB2 maintenance and SB2 transition groups.

Clinical Safety Overview and Conclusions

The safety evaluation plan of SB2 was based on the known safety profile of US-licensed Remicade as described in the USPI and other published data.

The submitted safety and immunogenicity data and analyses using one dosing regimen (3mg/kg IV on the background of MTX) in study SB2-RA, the comparative clinical study in RA are adequate to support the demonstration of no clinically meaningful differences between SB2 and EU-Remicade in patients with RA. Safety and immunogenicity results from the single-dose PK similarity study SB2-NHV (single 5mg/kg IV dose) in healthy subjects provide additional supportive evidence of similarity between SB2, US-licensed Remicade, and EU-approved Remicade. The safety database submitted for SB2 is adequate to provide a reasonable descriptive comparison between the products. The safety risks identified are consistent with the known adverse event profile of US-Remicade. The analysis of the data indicates a safety profile of SB2, similar to that of US-Remicade. No new safety signals were identified in the SB2 group compared to the known adverse event profile of US-Remicade. There were no notable differences between SB2 and US- or EU-Remicade in treatment-emergent adverse events, serious adverse events, adverse events leading to discontinuations, or deaths between the treatment groups. No cases of drug-induced liver injury meeting Hy's law criteria were reported in the SB2 clinical program. Cases of infusion related reactions and anaphylaxis were balanced between the two groups, with 1 case of anaphylaxis in each group (SB2 and EU-Remicade). Rates of infusion-related reactions and anaphylaxis did not increase following transition from EU-Remicade to SB2.

The safety data support the demonstration that there are no clinically meaningful differences between SB2 and EU-Remicade in the populations studied. In addition, transitioning of non-treatment naïve patients, i.e., patients previously treated with EU-Remicade, to SB2 does not appear to result in an increase of clinically significant adverse reactions.

Immunogenicity Overview and Conclusions

Small numerical differences in ADA formation were seen between SB2, EU-Remicade and US-Remicade in the SB2 clinical program. However, in light of the totality of the information discussed in the relevant section on Immunogenicity in this review, these do not represent clinically meaningful differences and do not preclude a demonstration of biosimilarity between SB2 and US-licensed Remicade.

Risk-Benefit Assessment

Overall, the efficacy, safety, and immunogenicity data from the SB2 clinical development program (studies SB2-RA and SB2-NHV) provide evidence of no clinically meaningful differences between SB2 and US-Remicade. Safety and immunogenicity analyses indicate a safety profile of SB2, similar to that of US-Remicade.

Extrapolation to Non-studied Indications

Samsung is seeking licensure for the indication studied in the clinical program, i.e. RA as well as for ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, adult and pediatric Crohn's disease, and adult and pediatric ulcerative colitis[1] which have not been directly studied in SB2 clinical program. To support the use of SB2 for those indications, Samsung has provided adequate scientific justification relying on extrapolation of biosimilarity to those indications. The justification addresses issues for the testing and extrapolating conditions of use outlined in Guidance for Industry: "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009." Also refer to BLA 761054 Division Memos from the collaborating review Divisions, Division of Dermatology and Dental Products (DDDP) and Division of Gastroenterology and Inborn Errors Products (DGIEP), outlining their conclusion that extrapolation of biosimilarity to indications in dermatology and gastroenterology, respectively is scientifically justified.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No clinical postmarket risk evaluation and mitigation strategies are anticipated at this time.

[1]We note 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.

1.4 Recommendations for Postmarket Requirements and Commitments

No postmarket requirements and commitments are anticipated at this time.

2 Introduction and Regulatory Background

Summary

SB2 has been developed as a proposed biosimilar product to US-licensed Remicade (infliximab). The applicant Samsung, submitted a BLA (biologics licensing application) for SB2 under the abbreviated licensure pathway 351(k) of the PHS Act for a proposed biosimilar product. The reference product, US-licensed Remicade (US-Remicade), was approved by the FDA in 1998 on the basis of a complete stand-alone drug development program.

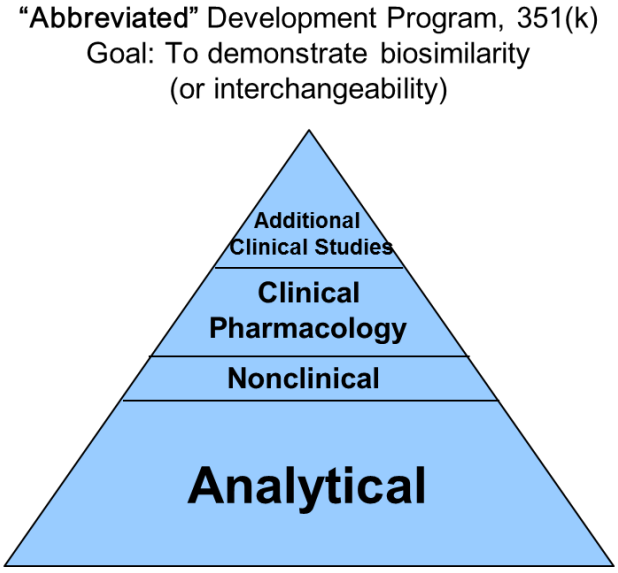
Biosimilar Regulatory Background

The Patient Protection and Affordable Care Act (Affordable Care Act), signed into law in 2010, amended the Public Health Service Act (PHS Act) to create an abbreviated licensure pathway for biological products that are demonstrated to be "biosimilar" to or "interchangeable" with an FDA-licensed biological product. This pathway is provided in the part of the law known as the *Biologics Price Competition and Innovation Act* (BPCI Act). Under the BPCI Act, a biological product may be demonstrated to be "biosimilar" if data show that, among other things, the product is "highly similar" to an already-approved biological product. Of note, SB2 has been developed as a proposed biosimilar to US-Remicade and not as interchangeable product. As such, there will no discussion of interchangeability in this review.

To help clarify definitions surrounding biosimilars, it is important to note that a biosimilar product will utilize the same mechanism of action to the extent the mechanisms are known for the reference product, and has the same route of administration, dosage form and strength as the reference product.

In the abbreviated licensure pathway (under 351(k)), (see Figure 1 below) the goal is to demonstrate biosimilarity between the proposed biosimilar product and the reference product with analytical similarity being the foundation of this assessment. The goal is not to independently establish safety and effectiveness of the proposed product. The abbreviated pathway means that a biosimilar product can be approved based on less than a full complement of product-specific preclinical and clinical data because FDA can rely on certain existing scientific knowledge about the safety and effectiveness of the reference product.

Figure 1. Abbreviated Licensure Pathway for Biosimilar Products under 351(k) Pathway of PHS Act



The biosimilar licensure pathway under section 351(k) of the PHS Act requires that the a) proposed biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components and b) that there are no clinically meaningful differences between the proposed biosimilar and reference products in terms of safety, purity and potency. Both parts of the statutory definition need to be met to demonstrate biosimilarity, but the foundation of the data demonstrating biosimilarity is extensive structural and functional characterization to support a demonstration that the products are highly similar.

The SB2 Story under 351(k) pathway (Product Development Rationale)

The development of SB2 began with demonstration of analytical similarity between SB2 and the reference product, US-Remicade. To demonstrate that SB2 is highly similar to the reference product, the applicant conducted a robust analytical program to compare physico-chemical and biological (structure & functional) characteristics including assessment of primary, secondary and tertiary structure; post-translational profile and in-vitro functional characteristics, purity, stability, potency, including TNF-alpha binding and neutralization to name a few of the key quality attributes. See OBP review for the detailed assessment of analytical similarity. The applicant also conducted a small nonclinical program including in-vitro and in-vivo studies to support the clinical program.

To support that there are no clinically meaningful differences between SB2 and US-Remicade, the applicant conducted two clinical studies. A phase 1 PK study (Study

SB2-NHV) was conducted in healthy subjects to show similarity in PK between the two products. Lastly, a comparative clinical study (Study SB2-RA) in RA patients was conducted to address residual uncertainties or clinically meaningful differences, if any, that remained between SB2 and the reference product. Both these studies assessed safety, efficacy and immunogenicity of SB2 in comparison with Remicade.

Of note, the comparative clinical study compared SB2 with EU-Remicade. To justify the relevance of the data generated using EU-approved Remicade to support a demonstration of biosimilarity between SB2 and US-Remicade, the applicant provided adequate bridging data between SB2, US-Remicade and EU-Remicade. The analytical, and nonclinical studies in addition to the PK study, provided the data to establish a bridge between EU-Remicade and US Remicade.

This review focuses on the clinical program conducted to support a demonstration of no clinically meaningful differences between SB2 and Remicade.

2.1 Product Information

SB2 is a proposed biosimilar biological product to US-licensed Remicade (infliximab). SB2 is a chimeric human murine immunoglobulin G1 (IgG1) monoclonal antibody that binds to the human tumor necrosis factor alpha (TNFα). The active SB2 Drug Product (DP) is 100 mg lyophilized infliximab in a 20 mL vial for injection, for intravenous use, and its strength is 100 mg per vial.

2.2 Currently Available Treatments for Proposed Indications

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

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

Rheumatoid Arthritis
Many effective therapies are approved for the treatment of patients with RA including nonsteroidal anti-inflammatory drugs (NSAIDs) and selective cyclooxygenase-2 (COX-

2) inhibitors, corticosteroids, disease modifying anti rheumatic drugs (DMARDs) and biologics. Currently approved non-biologic and biologic systemic therapies for RA are listed in Table 1 and Table 2, respectively.

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

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

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

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

Product Name (Trade Name) [Applicant] {year}	***Mechanism of Action***	**Approved Indications**					
		RA	**PsA**	**AS**	**pJIA**	**PsO**	**Other**
Sulfasalazine (AZULFIDINE) [Pfizer]{1950}	*Anti-inflammatory and/or immunomodulator*	X			X		UC
Methotrexate sodium (METHOTREXATE SODIUM) [Multiple] {1953}	*Folate anti-metabolite*	X			X	X	Oncology indications
Hydroxychloroquine (PLAQUENIL) [Sanofi-Aventis]{1955}	*Unknown*	X					SLE, Malaria
Prednisone [Multiple sponsors]{1955}	*Anti-inflammatory and other unspecified mechanisms*	X					Many
Azathioprine (IMURAN) [Prometheus Labs]{1968}	*Anti-metabolite*	X					Renal transplant
Penicillamine (CUPRIMINE) [Aton]{1970}	*Unknown*	X					Wilson's Disease, cystinuria
Auranofin (RIDAURA) [Prometheus Labs]{1985}	*Unknown*	X					
Cyclosporine (NEORAL) (SANDIMMUNE) [Novartis]{1990, 1995}	T-cell inhibitor	X				X	Organ rejection, KCS
Acitretin (SORIATANE) (Stiefel){1996}	*Retinoid*					X	
Leflunomide (ARAVA) [Sanofi-Aventis]{1998}	*Anti-metabolite*	X					
Tofacitinib (XELJANZ) [Pfizer] (2012)	*JAK kinase inhibitor*	X					
Tofacitinib (XELJANZ XR) [Pfizer] (2016)	*JAK kinase inhibitor*	X					
Apremilast (Otezla) [Celgene] {2014}	*PDE4 inhibitor*		X			X	
*Year = Year of first approval	UC=Ulcerative Colitis, CD=Crohn's Disease, SLE=Systemic Lupus Erythematosis, KCS=Keratoconjunctivitis sicca						

Table 2. US-Licensed Biologic DMARDs by Indication

Product Name (Trade Name) [Applicant] {year}	Description and *Mechanism of Action*	Approved Indications					
		RA	PsA	AS	pJIA	PsO	Other
Etanercept (ENBREL) [Immunex/Amgen] {1998}	Fusion protein consisting of TNF-R and human IgG1 Fc *TNF inhibitor*	X	X	X	X	X	
Infliximab (REMICADE) [Centocor] {1999}	Chimeric IgG1 k mAb *TNF inhibitor*	X	X	X		X	CD, UC, Pediatric CD/UC
Anakinra (KINERET) [Amgen] {2001}	Recombinant polypeptide *IL-1 receptor antagonist*	X					NOMID
Adalimumab (HUMIRA) [Abbott] {2002}	Human IgG1 k mAb *TNF inhibitor*	X	X	X	X	X	CD, UC, Pediatric CD, HS, Uveitis
Abatacept (ORENCIA) [Bristol Myers Squibb] {2005}	Fusion protein consisting of CTLA-4 and human IGg1 Fc *T cell activation inhibitor*	X			X		
Rituximab (RITUXAN) [Genentech and Biogen] {2006}	Chimeric murine/human IgG1 k mAb *Anti CD20, B cell depletor*	X					GPA, MPA, NHL, CLL
Golimumab (SIMPONI) [Centocor] {2009}	Humanized IgG1 k mAb *TNF inhibitor*	X	X	X			UC
Certolizumab Pegol (CIMZIA) [UCB Inc] {2009}	Humanized Fab fragment *TNF inhibitor*	X	X	X			CD
Ustekinumab (STELARA) [Centocor Ortho Biotech] {2009}	Humanized IgG1 k mAb *IL-12, IL-23 antagonist*		X			X	
Tocilizumab (ACTEMRA) [Genentech/Roche] {2010}	Humanized IgG1 k mAb *IL-6 receptor inhibitor*	X			X		SJIA
Golimumab (SIMPONI ARIA) [Janssen Biotech] {2013}	Humanized IgG1 mAb *TNF inhibitor*	X					
Secukinumab (Cosentyx) [Novartis] {2015}	Humanized IgG1 mAb *IL-17 inhibitor*		X	X		X	
Infliximab-dyyb (INFLECTRA) [Celltrion] {2016}	Chimeric IgG1 k mAb *TNF inhibitor*	X	X	X		X	CD, UC, Pediatric CD
Etanercept-szzs (ERELZI) [Sandoz] {2016}	Fusion protein consisting of TNF-R and human IgG1 Fc *TNF inhibitor*	X	X	X	X	X	
Adalimumab-atto (AMJEVITA) [Amgen] {2016}	Human IgG1 k mAb *TNF inhibitor*	X	X	X	X	X	CD, UC
*Year = Year of first approval	CD=Crohn's Disease, UC=Ulcerative Colitis, NOMID=Neonatal Onset Multisystem Inflammatory Disease, GPA=Granulomatosis with Polyangiitis, MPA=Microscopic Polyangiitis, NHL=Non-Hodgkin's Lymphoma, CLL=Chronic Lymphocytic Leukemia, SJIA= Systemic Juvenile Idiopathic Arthritis, HS=Hidradenitis Suppurativa						

2.3 Availability of Proposed Active Ingredient in the United States

SB2 is not currently marketed in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

The safety program for SB2 was designed based on the well-known safety profile of US-licensed Remicade. Potential risks based on class of drug (TNFα) and of the drug substance (foreign protein) were considered. Potential risks associated with immunomodulating biologic therapies may include infections, cardiovascular safety, malignancies and autoimmune disorders. Potential risks of a foreign protein may include administration or immune reactions, such as hypersensitivity, infusion reactions and immunogenicity.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

SB2 was developed globally with regulatory input from the FDA and European Medicines Agency (EMA). The major clinical regulatory activity with the FDA was as follows:

- Feb 2012
  - Pre-IND meeting to discuss meeting to discuss the development program for SB2 as a proposed biosimilar to US-licensed Remicade
- December 2012
  - BPD (Biological Product Development) meeting to discuss the clinical development program of SB2 including study design and endpoint selection for the clinical studies.
- March 2014
  - BPD Type 3 meeting to discuss the development program of SB2 including analytical assessment, immunogenicity assessment, and selection of equivalence margins.
- July 2015
  - BPD Type 2 teleconference meeting to discuss assessment of analytical similarity and planned statistical approach
- December 2015
  - BDP Type 4 meeting to discuss analytical similarity data, statistical analysis and the structure, format, and content of a proposed BLA

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The data quality and integrity of the studies were considered reliable. The amount of missing data was small and did not significantly impact the assessment of the clinical data.

OSI Inspection

The BLA submission was in electronic common technical document (eCTD) format and was adequately organized. The Office of Scientific Investigations (OSI) was consulted to conduct routine clinical site and applicant/monitor inspection for SB2, a proposed biosimilar to US-licensed Remicade.

The inspection audited both clinical studies SB2-RA and SB2-NHV. Two clinical sites (one in Bosnia & Herzegovina, and one in Poland), which were among the highest enrollers of patients were selected for inspection. The CRO monitoring site (Quintiles in North Carolina) was also inspected.

Per OSI, the final CDER classification of the CRO monitoring site (Quintiles) and the clinical site in Bosnia & Herzegovina is no action indicated. The final CDER classification of the clinical site in Poland is pending at the time of this review.

OSI's collaboration with an international regulatory agency revealed a potential error in the inclusion/eligibility criteria applied at one particular site (this site was not inspected by the FDA). The error occurred around potential misclassification of the ESR values for less than 10 patients at this site. Overall, the international agency inspection summary indicated (b) (4) .

OSI inspection of the applicant did not identify major deficiencies in data quality and integrity. The study appears to have been conducted and monitored adequately and that the data reported by the applicant is reliable. Based on review of inspectional findings for the clinical investigators and the applicant, the study data collected appear generally reliable in support of the BLA.

3.2 Compliance with Good Clinical Practices

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

Written informed consent was obtained prior to the subject entering the studies (before initiation of protocol-specified procedures). The investigators explained the nature, purpose, and risks of the study to each subject. Each subject was informed that he/she could withdraw from the study at any time and for any reason. Each subject was given sufficient time to consider the implications of the study before deciding whether to participate. Subjects who chose to participate signed an informed consent document.

3.3 Financial Disclosures

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

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

SB2 is a proposed similar biological product to US-licensed Remicade (infliximab). SB2 is a chimeric human/mouse monoclonal antibody (mAb), typically a "Y"-shaped large glycoprotein consisting of four polypeptide chains, two identical heavy chains (HC) and two identical light chains (LC), with a total of 1328 amino acids, whereby the four chains are cross-linked by disulphide bonds with a molecular weight (MW) of approximately 149 kDa.

Studies to Support Biosimilarity

To support a determination that SB2 is highly similar to the reference product, Samsung submitted an extensive analytical similarity package consisting of multiple orthogonal physicochemical and biological assays.

Further, the clinical development program was conducted using EU-approved Remicade. To obtain licensure of SB2 under section 351(k) of the PHS Act, the Samsung had to demonstrate that SB2 is biosimilar to a single reference product that previously has been licensed by FDA, i.e. US-licensed Remicade. As outlined in the draft FDA Guidance for Industry "*Scientific Considerations in Demonstrating Biosimilarity to a Reference Product - February 2012*", Samsung had to provide adequate data or information to scientifically justify the relevance of these comparative data to an assessment of biosimilarity and to establish an acceptable bridge to the US-licensed reference product. To that extent, Samsung submitted a 3-way analytical similarity assessment comparing SB2 to both EU- approved and US-licensed Remicade to establish an acceptable bridge to US-licensed Remicade. These analyses were intended to demonstrate:

- Identical primary structure
- Highly similar secondary and higher order structure
- Highly similar disulfide bonding
- Highly similar glycosylation profile with very minor differences in core fucose content
- Highly similar critical quality attributes such as TNF binding and neutralization and other functional characteristics, including, Fc receptor binding, induction of cell-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), Induction of regulatory macrophages and mucosal healing.

The Product Quality review team concluded that the sponsor provided a sufficiently robust analysis for the purposes of establishing the analytical component of the scientific bridge among the three products to justify the relevance of comparative data generated from clinical studies that used EU-approved Remicade, to support a demonstration of biosimilarity of SB2 to US-licensed Remicade.

The SB2 product has been evaluated and compared to US-licensed Remicade and EU-approved Remicade in a variety of structural, physicochemical, and functional assays as noted above. The assessment also included assays that addressed each potential mechanism of action, either directly or indirectly. The evidence submitted supports a demonstration that SB2 is highly similar to US-licensed Remicade.

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

4.2 Clinical Microbiology

Microbiology data is currently under review.

4.3 Preclinical Pharmacology/Toxicology

Adapted from BLA761054 FDA pharmacology/toxicology review.

The nonclinical program for SB2 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 Remicade, 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 Remicade, and US-licensed Remicade. The significance of the single-dose pharmacokinetic study in Sprague-Dawley rats was uncertain as the rat was not a pharmacologically relevant species for SB2, US-licensed Remicade, or EU-approved Remicade (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.

Please refer to the review by Dr. Goodwin, Ph.D. for detailed analysis of the pharmacology/toxicology findings.

4.4 Clinical Pharmacology

Adapted from BLA 761054, Dr. Lei's clinical-pharmacology review.

The objectives of clinical pharmacology program were to evaluate the pharmacokinetic similarity between SB2 and US-licensed Remicade and to establish the scientific bridge between SB2, US-licensed Remicade, and EU-approved Remicade in order to justify the relevance of comparative data generated using EU-approved Remicade (in the comparative clinical efficacy study SB2-RA) to support a demonstration of the biosimilarity of SB2 to US-licensed Remicade.

Pharmacokinetic (PK) similarity between SB2 and US-Remicade was evaluated in a pivotal three-way PK similarity study to compare the PK, safety, tolerability, and immunogenicity of SB2, EU-approved Remicade and US-licensed Remicade in 159 healthy subjects (53/treatment arm) (Study SB2-NHV). The study was required by the FDA to provide needed PK bridging data, in addition to the analytical bridging, to

scientifically justify the relevance of the comparative clinical data from SB2 clinical development program which exclusively used EU-approved Remicade.

In Study SB2-NHV, the primary endpoints were Cmax, AUClast and AUCinf. Secondary PK endpoints included but were not limited to time to Cmax (Tmax), volume of distribution during the terminal phase (Vz), and terminal half-life (T1/2). In Study SB2-NHV, healthy subjects were given a single 5 mg/kg dose of SB2, EU-approved Remicade or US-licensed Remicade.

Analysis of the results showed that the 90% confidence intervals (CIs) for the geometric mean ratios (GMR) of SB2 to EU-approved Remicade, SB2 to US-licensed Remicade, and EU-approved Remicade to US-licensed Remicade for the tested PK parameters (i.e., AUC0- inf, AUC0-t, and Cmax) were all within the PK similarity acceptance interval of 80-125%. These pairwise comparisons met the pre-specified criteria for PK similarity between SB2, US-licensed Remicade and EU-approved Remicade, thus a scientific PK bridge was established to support the relevance of the data generated using EU-approved Remicade in the comparative clinical efficacy trial (Study SB2-RA). The PK study SB2-NHV met its primary endpoint supporting the conclusion that SB2, US-licensed Remicade and EU-approved Remicade are similar in regards to PK.

In addition, the applicant collected PK data (as one of the secondary endpoints) in the comparative clinical study, SB2-RA. However, PK data from this study is limited. Serum trough concentrations (Ctrough) were collected in a subset of patients (the first 50% of the enrolled subjects) at baseline and prior to dosing at Weeks 2, 6, 14, 22 and 30. However, due to the relatively short half-life of infliximab products and limited pre-dose Ctrough sampling, the PK data from this study is limited.

Overall, the submitted clinical pharmacology data support the demonstration of PK similarity between SB2 and US-licensed Remicade. Further, these data did not raise any new uncertainties in the assessment of biosimilarity of SB2 to US-licensed Remicade. The PK results support a demonstration of no clinically meaningful differences between SB2 and US-Remicade.

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

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

To support that there are no clinically meaningful differences between SB2 and US-Remicade, the applicant conducted two clinical studies. A phase 1 PK study (Study SB2-NHV) was conducted in healthy subjects to show similarity in PK between SB2, US-Remicade and EU-Remicade. Subsequently, a comparative clinical study (Study SB2-RA) in RA patients was conducted to assess similarity in efficacy between SB2 and EU-Remicade. Both these studies also evaluated safety, tolerability and immunogenicity of SB2 in comparison with Remicade.

Protocol	Patient Population	Design/ Objectives	Duration	Sample size/ Randomization	Treatment arms
SB2-G11-NHV	HV	R, SB, PG, SD 3-way PK bridging	Single dose	N=159 (53/arm) 1:1:1	• SB2 • EU-Remicade • US-Remicade
SB2-G31-RA	RA (MTX-IR)	R, DB, PG Comparative Clinical Study	54 weeks	N=584 1:1	• SB2 + MTX (n=291) • EU-Remicade + MTX (n=293)
	Transition-Extension Period				
	RA, MTX-IR, rolled over from part 1 of the study (weeks 0-54)	R, DB Safety & Immunogenicity	24 weeks (Week 54-78)	N=396 1:1	• SB2 Maintenance (SB2→SB2) (n=201) • EU-Remicade Maintenance (EU-Remi→ EU-Remi) (n=101) • Transition group (EU-Remi → SB2) (n=94)

Source: FDA Analysis of SB2 351(k) application
R–Randomized, SB-Single blind, DB-Double blind, HV-Healthy Volunteers, PG-Parallel-group, PK-Pharmacokinetics, SD-Single dose, MTX– Methotrexate, IR-Inadequate Responders, EU-Remi-EU-Remicade

Key design features of the SB2 clinical studies are summarized in Table 3.

Table 3. SB2 Clinical Development Program

5.2 Review Strategy

The clinical development program SB2 consists of two controlled clinical studies, listed in Table 3. These two studies provide the primary evidence to support the determination of no clinically meaningful differences between SB2 and US-licensed Remicade.

- Study SB2- NHV is a single-dose, 3-way PK-bridging study in healthy subjects with the primary objective of comparing PK profiles between SB2, US-licensed Remicade and EU-approved Remicade
- Study SB2- RA is the comparative clinical study with the primary objective of comparing and assessing similarity of efficacy between SB2 and EU-Remicade in RA patients on background methotrexate

Study SB2-NHV provided a 3-way comparison of SB2, US-Remicade, and EU-Remicade intended to support PK similarity of SB2 and US-Remicade as well as to provide a PK bridge to support the relevance of the comparative data generated using EU-Remicade to support a demonstration of the biosimilarity of SB2 to US-Remicade. It also provided supportive evidence of clinical safety and immunogenicity comparisons between the three products.

Study SB2-RA provided an assessment of comparative clinical efficacy, safety, and immunogenicity between SB2 and EU-Remicade. Additional long-term safety and immunogenicity data for patients who either continued SB2 or underwent a randomized single transition from EU-approved Remicade to SB2 or continued to receive EU-Remicade were provided in the transition extension period of SB2-RA, the comparative clinical study.

The safety analysis included in this review includes data from both clinical studies and represents the Agency's primary safety analysis. The efficacy analysis presented in this review here will concentrate on the results of the multiple repeat dose Study SB2-RA in RA patients as it represents the bulk of the safety data and a relevant clinical setting. For detailed efficacy analysis, refer to Dr. Ginto's Statistical Review of Study SB2-RA. Detailed review of the PK analyses from Study-NHV can be found in Dr. Lei's review from the clinical pharmacology review team.

All endpoints used are validated endpoints used in the approval of other drugs in RA and represent clinically meaningful endpoints. The overall clinical program is adequate to provide the evidence to support the determination of no clinically meaningful differences in the studied indication of RA.

5.3 Discussion of Individual Studies/Clinical Trials

Clinical Development Program

Study SB2-NHV: PK Similarity Study

Title: A Randomized, Single-blind, Three-arm, Parallel Group, Single-dose Study to Compare the Pharmacokinetics, Safety, Tolerability, and Immunogenicity of Three Formulations of Infliximab (SB2, EU-approved Remicade, and US-licensed Remicade) in Healthy Subjects

The study was conducted at one center in one country (Germany) from July 13, 2013 to Oct 14, 2013.

Study Objectives

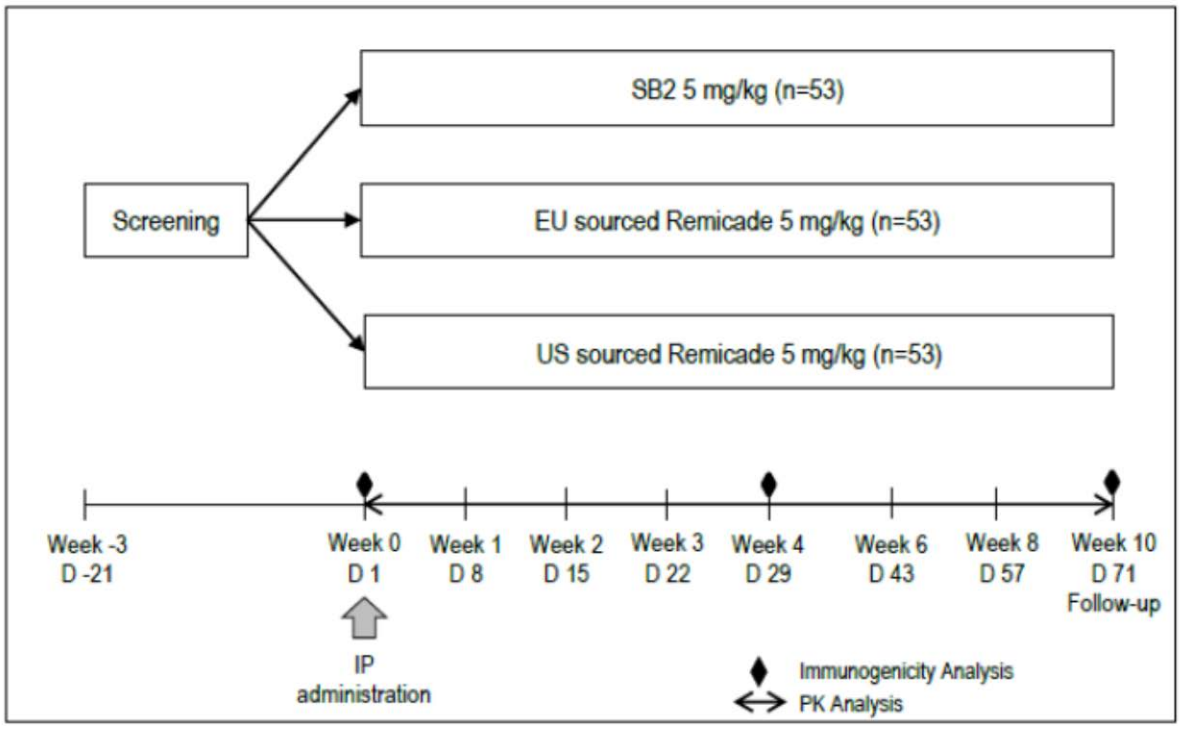
Primary objective
The primary objective was to investigate and compare the PK profiles of SB2, EU-approved Remicade, and US-licensed Remicade in healthy subjects (SB2 to US-Remicade, EU-Remicade to US-Remicade and SB2 to EU-Remicade)

- The primary PK endpoints evaluated in the study included AUC_{inf}, $AUC_{0\text{-}last}$, and C_{max}

Secondary objectives
The secondary objectives were to investigate the safety, tolerability, and immunogenicity of SB2, US-Remicade and EU-Remicade in healthy subjects

Study Design
This was a single-blind, 3-arm, parallel group, single-dose study. A total of 159 healthy subjects aged 18-55 years (inclusive) were enrolled; 53 subjects in each of the 3 arms of the clinical study. In each arm, all subjects received a single dose of either SB2, EU-Remicade, or US-Remicade by intravenous (IV) infusion for 120 minutes on Day 1 and then followed for 10 weeks, during which the pharmacokinetic, safety, tolerability and immunogenicity measurements were made. To avoid infusion-related reactions, premedication with IV hydrocortisone (100 mg), oral acetaminophen (1000 mg) and oral loratadine (10 mg) were administered 30 to 60 minutes prior to the infusion of SB2, EU-approved Remicade, or US-licensed Remicade.

Figure 2. Study SB2-NHV Schematic Diagram



Source: Study SB2-NHV CSR Figure 9-1
IP-Investigational Product

Treatment Groups and Regimen:
A total of 159 patients were randomized (1:1:1) to receive 1 dose (IV infusion) at a dose of 5mg/kg of:

- SB2
- EU-approved Remicade
- US-licensed Remicade

Patient Population
Healthy male and female subjects.

Major inclusion and exclusion criteria are as follows:

- **Key Inclusion Criteria**
  - Male or female subjects aged 18 to 55 years
  - Body mass index (BMI) between 20 and 29.9 kg/m^2
  - Normal or clinically acceptable physical examination, clinical laboratory values, ECG, and vital signs at screening and baseline.
  - Females of child-bearing potential were required to use a medically-reliable method of contraception throughout their participation in the study

- **Key Exclusion Criteria**
  - History or evidence of a clinically significant disorder, condition, or disease that would have posed a risk to subject safety or would have interfered with the study evaluation, procedures, or study completion in the opinion of the investigator.
  - Evidence of any bacterial, viral, parasitic, systemic fungal infections, or infections due to other opportunistic pathogens within the 30 days prior to investigational product administration
  - Evidence of a recent (≤ 6 months) infection requiring in-patient hospitalization or intravenous antibiotics
  - Evidence of either active or latent tuberculosis (TB) or had a history of TB
  - History of malignancy of any type, other than surgically excised non-melanomatous skin cancers, within 5 years prior to investigational product administration
  - Positive test for hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV) antibodies at screening
  - Received live vaccines within 30 days prior to Screening
  - Women who were pregnant or nursing
  - Use of any protocol-prohibited medications

Concomitant Medications

Concomitant medications and doses include**:**

- Hydrocortisone 100 mg IV, oral paracetamol (1000 mg) and oral loratidine (10 mg) used as premedication
- Occasional use of 1000 mg paracetamol per single dose

Prohibited and restricted treatments

- Any medicinal product, except in an emergency situation after approval from the investigator

Statistical Analysis Plan

Primary endpoint (PK) analysis

The statistical analysis of the $\log_e$-transformed primary endpoint was based on an analysis of variance (ANOVA) model. Equivalence of systemic exposure (Cmax, AUCinf and AUClast) was determined for the following pairwise comparisons:

- SB2 vs EU-approved Remicade
- SB2 vs US–licensed Remicade
- EU-approved Remicade vs US-licensed Remicade

The difference in least squares means (LSMeans) $\log_e$-transformed AUC_{inf}, AUC_{last}, and C_{max} between the SB2 and EU-Remicade, SB2 and US-Remicade, and between EU-Remicade and US-Remicade and the associated 90% confidence intervals (CIs) were estimated. Back transformation provided the ratio of geometric means and 90% CIs for these ratios. Equivalence was concluded between SB2 and EU-Remicade, SB2 and

US-Remicade, and EU-Remicade and US-Remicade if the 90% CIs for the ratio of geometric LSMeans for the primary endpoints were completely within the acceptance interval of 0.8 to 1.25.

Secondary endpoint (safety & immunogenicity) analyses:
Descriptive analyses of the secondary endpoints were provided.

Protocol Amendments:
Minor amendments were made to the protocol which did not affect PK, safety & immunogenicity results.

All AEs recorded during the study were coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA), Version 15.0, and presented by subject in the data listings. Adverse events leading to study discontinuation, serious AEs (SAEs), and deaths were listed separately.

A treatment-emergent AE was defined as an AE that was not present prior to treatment with investigational product, but appeared following treatment or was present at treatment initiation but worsened during treatment. An AE that was present at treatment initiation but resolved and then reappeared while the subject was on treatment was a TEAE. The overall incidence of TEAEs, AEs, and SAEs as well as the number of events, was summarized by treatment.

For the incidence at the subject level by SOC and PT, if a subject experienced ≥1 event within the same SOC and PT, only one occurrence was included. For the incidence at the subject level by SOC, PT, and severity, if a subject experienced more than 1 event within the same SOC and PT, only the most severe occurrence was included.

Observed and change from baseline vital signs data were listed and summarized descriptively by treatment and scheduled time point. Observed and change from baseline 12-lead ECG data were listed with all associated comments and summarized descriptively by treatment and scheduled time point. Antidrug antibody results were listed and summarized by treatment.

A total of 159 subjects were enrolled and completed the study. No subjects discontinued from the study.

All randomized subjects were included in the Safety and Intent-to-Treat populations and no data were excluded.

There were a total of 45 protocol deviations reported with 24 (15%) related to deviations in the timing of PK blood draws. Two subjects (both in the SB2 treatment group) had major protocol deviations reported (i.e., they received PK influencing concomitant medication for treatment of AEs) and were therefore not included in the PK population.

One patient received Doxycycline and other medications for a hospitalization related to Borrelia infection. The other patient received Metamizole for a concussion, considered unrelated to the drug. These protocol deviations are not expected to impact the analysis and interpretation of the results for Study SB2-NHV.

Overall, the baseline demographics were similar between treatment arms with the average patient being approximately 40 years of age, white (>95%), male (>95%) with an average BMI of 25 kg/m^2.

Study SB2-RA: Comparative Clinical Study in RA

Study SB2-RA

Title: A Randomized, Double-blind, Parallel Group, Multicenter Clinical Study to Evaluate the Efficacy, Safety, Pharmacokinetics and Immunogenicity of SB2 Compared to Remicade in Subjects with Moderate to Severe Rheumatoid Arthritis despite Methotrexate Therapy

The study was conducted between Aug 12, 2013 and Aug 25, 2015 at 73 centers in 11 countries.

Study Objectives:
Primary objective
The primary objective of this study was to demonstrate the therapeutic equivalence of SB2 to EU-Remicade at Week 30, in terms of efficacy as determined by clinical response according to American College of Rheumatology (ACR) 20% response criteria (ACR20) response rate in subjects with moderate to severe rheumatoid arthritis (RA) despite methotrexate (MTX) therapy.

Secondary objectives
Key secondary objectives include

- comparisons of SB2 and EU-Remicade for efficacy other than ACR20, long-term efficacy, safety, tolerability, pharmacokinetics and immunogenicity
- evaluation of safety, tolerability, immunogenicity and efficacy in the transition extension period i.e. subjects with RA who transitioned to SB2 from EU-Remicade compared to subjects who maintained Remicade from the 54-week randomized, double-blind period

Study Design:
<u>For the randomized, double-blind period:</u>
This period was conducted from Week 0 to Week 54.

This was a randomized, double-blind, parallel group, multicenter clinical study. The study design, as shown in Figure 3, consisted of 6 weeks of Screening period and 54 weeks of active treatment. At randomization, a total of 584 subjects with moderate to severe RA who have had an inadequate response to MTX were randomized in a 1:1 ratio to receive either SB2 3 mg/kg (n = 291) or European Union (EU) sourced Remicade (EU-Remicade) 3 mg/kg (n = 293). Dosing occurred via 2 hours (h) intravenous (IV) infusion, at Week 0, 2, 6 and then every 8 weeks with last dose at Week 46. From Week 30 the dose level could be increased step-wise by 1.5 mg/kg, up to a maximum of 7.5 mg/kg, every 8 weeks if the subject's RA symptoms were not well controlled by the existing dose. The primary endpoint (ACR20 response at Week 30) was assessed in all subjects who completed 30 weeks of study treatment. Secondary endpoints included other relevant efficacy parameters, safety, pharmacokinetics and immunogenicity parameters.

An independent Data Safety Monitoring Board (DSMB) acted in an advisory capacity to monitor subject safety and tolerability data from the study.

For the transition-extension period:
The transition-extension period was conducted from Week 54 to Week 78.

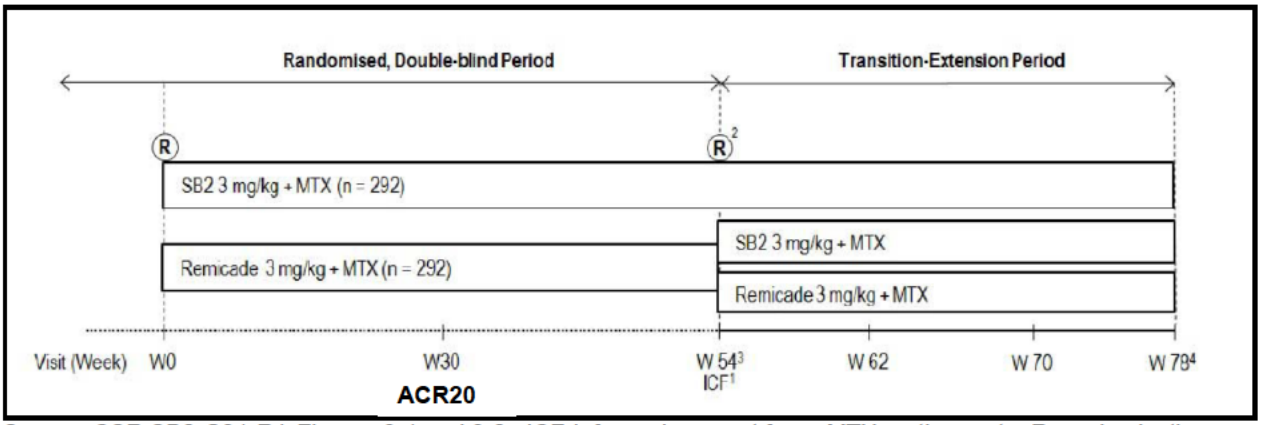
This was a randomized, double-blind, transition-extension period to investigate the safety, tolerability, immunogenicity, and efficacy of SB2 in subjects with RA who underwent a randomized single transition from the EU-Remicade treatment group to SB2, compared with subjects who maintained EU-Remicade treatment after Week 54 from the randomized, double-blind period of the study. In addition, the long-term safety, tolerability, immunogenicity, and efficacy of SB2 in subjects with RA who continued in the SB2 treatment group after Week 54, compared with the EU-Remicade treatment group from the randomized, double-blind period of the SB2- RA study was investigated.

The study design, as shown in Figure 3, consisted of 24 weeks of active treatment. Subjects were enrolled in the transition-extension period for up to 24 weeks after Week 54 of the randomized, double-blind period. Subjects received 3 to 7.5 mg/kg of either SB2 or EU-Remicade every 8 weeks at Weeks 54, 62 and 70 via IV infusion for 2 h. The dose level could be increased step-wise by 1.5 mg/kg, up to a maximum of 7.5 mg/kg, every 8 weeks if the subject's RA symptoms were not well controlled by the existing dose. The dosing schedule continued from the randomized, double-blind period of the SB2-RA study, and dose increments could occur at Week 54.

At Week 54, subjects receiving EU-Remicade from the randomized, double-blind period of the SB2- RA study were randomized again in a 1:1 ratio to either continue on EU-Remicade (EU-Remicade/EU-Remicade) or be transitioned to SB2 (EU-Remicade/SB2) up to Week 70. Subjects receiving SB2 from the randomized, double-blind period of the SB2-RA study continued to receive extended treatment of SB2 up to Week 70 but they also followed the randomization procedure to maintain blinding.

See Figure 3 for a schematic representation of the study design.

Figure 3. Study SB2-RA (Study Schematic)



Source: CSR SB2-G31-RA Figures 9-1 and 9-2. ICF-Informed consent form; MTX-methorexate, R-randomization, W-week

Treatment Groups and Regimen:

In the randomized, double-blind period up to week 54, patients were randomized (1:1) to the following treatment groups:

- SB2 + MTX
- EU-approved Remicade + MTX

Dosing occurred via 2 hours (h) intravenous (IV) infusion, at Week 0, 2, 6 and then every 8 weeks with last dose at Week 46. From Week 30 the dose level could be increased step-wise by 1.5 mg/kg, up to a maximum of 7.5 mg/kg, every 8 weeks if the subject's RA symptoms were not well controlled by the existing dose.

Patients from the randomized, double-blind period (weeks 0-54) who agreed to continue onto the transition-extension period were enrolled into the transition-extension period

In the transition-extension period (weeks 54-78), patients previously in the EU-Remicade group were randomized to continue to EU-Remicade or switch to SB2 in a 1:1 manner. Patients in the SB2 treatment group were also randomized to maintain the blind. The following treatment groups resulted:

- SB2 + MTX maintenance (SB2→SB2)
- EU-Remicade + MTX maintenance (EU-Remicade→EU-Remicade)
- EU-Remicade to SB2 transition group (EU-Remicade→SB2)

Patient Population

A total of 584 male and female patients with active rheumatoid arthritis (RA) with inadequate response to methotrexate (MTX) were enrolled in a 1:1 ratio to receive SB2 or EU-Remicade.

Major inclusion and exclusion criteria were as follows:

- Key Inclusion Criteria
  - Male or female subjects aged 18 to 75 years
  - Diagnosed with RA as determined by meeting revised 1987 ACR classification criteria for RA for at least 6 months prior to screening
  - Had moderate to severe active disease despite MTX therapy defined as:
    a) ≥6 swollen joints and ≥6 tender joints (based on 66/68 joint count excluding distal interphalangeal joints) at screening and randomization
    b) Either erythrocyte sedimentation rate (ESR; Westergren) ≥ 28mm/hr or serum CRP > 1.0 mg/dL at screening
  - Subjects must be taking MTX for at least 6 months prior to randomization and be on a stable dose of 10 to 25 mg/week for at least 4 weeks prior to screening
  - Stable doses of NSAIDs or low potency analgesics for at least 4 weeks prior to randomization
  - Stable doses of oral corticosteroids, (≤10 mg prednisone or equivalent) for at least 4 weeks prior to randomization
  - Sexually active subjects of child-bearing potential were required to use a medically-reliable method of contraception throughout their participation in the study

- Key Exclusion Criteria
  - Active infection or history of infection
  - Known history of HIV, HbsAg, or HCV antibody positivity
  - Uncontrolled, clinically significant systemic disease such as diabetes mellitus, cardiovascular disease including moderate to severe heart failure, renal disease, liver disease or hypertension
  - Malignancy within 5 years except completely excised and cured squamous carcinoma of the uterine cervix, cutaneous basal cell carcinoma, or cutaneous squamous cell carcinoma
  - Major chronic inflammatory disease or connective tissue disease other than RA
  - Had a current diagnosis of active tuberculosis (TB)
  - Had been recently exposed to a person with active TB, or were considered to have latent TB from the screening tests (QuantiFERON® Gold test and chest X-ray). If such subjects completed at least 30 days of

isoniazid prophylaxis or other anti-TB therapy according to country-specific guidelines and were willing to complete the entire course of recommended anti-TB therapy they may have been enrolled into the study following re-screening

- Laboratory abnormalities at screening, including any of the following:
  a) hemoglobin < 8 g/dL
  b) platelet count < 100,000/mm^3
  c) white blood cell count < 3,500 cells/mm^3
  d) AST and/or ALT ≥2.0 x the upper limit of normal
  e) Serum creatinine ≥2.0 x the upper limit of normal
- Any of the following within 28 days prior to first dose of study drug:
  a) IA, intramuscular (IM), or IV corticosteroids, including oral corticosteroids ≥10mg
  b) Non-biologic DMARDs other than MTX within 28 days prior to first dose of study drug except as noted in protocol
- Prior use of any biologic therapies for RA
- Live vaccines within 8 weeks prior to randomization
- Women who were pregnant or breast feeding

Concomitant Medications

Concomitant Medications for the Treatment of RA

In addition to Methotrexate (MTX) 10-25 mg/week of oral or parenteral MTX and folic acid 5-10mg/week, Figure 4 lists additional permitted medications in the study.

Figure 4. Permitted Concomitant Medications

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

Source: CSR SB2-RA Table 9-2

The dose and the type of NSAIDs could be changed after Week 30 of the study. Intra-articular injections were allowed in exceptional circumstances after Week 30 of the study; however, the number of intra-articular injections was limited to 2 during the randomized, double-blind period. In the analysis of tender and swollen joints, the joint

receiving the intra-articular injection was considered as swollen and tender from the time of the first injection onward.

Low potency topical, otic and ophthalmic glucocorticoid preparations were permitted. Subjects requiring oral, IV, intramuscular or inhaled corticosteroids for the prevention or treatment of IP-related infusion reaction, asthma, chronic obstructive pulmonary disease, allergic conditions or any condition other than RA were allowed to receive limited corticosteroid therapy while participating in the study.
Approval from the Investigator was sought prior to the subject taking other medication during the course of the study except in emergency situations. If treatment was required in an emergency then the Investigator was notified as soon as possible.

Medications listed in Figure 5 could interfere with the evaluation of efficacy, they were prohibited prior to and throughout the study. Intra-articular injections were allowed in exceptional circumstances after Week 30.

Figure 5. Prohibited Medications for the Treatment of RA

Medication	Time prohibited prior to Randomisation
Oral glucocorticoids equivalent to > 10 mg prednisolone daily	4 weeks
DMARDs/systemic immunosuppressive agents excluding methotrexate	4 weeks
Leflunomide with chelation with 8 g cholestyramine 3 times daily for 11 days	4 weeks
Injections of corticosteroids	4 weeks
Leflunomide without chelation	12 weeks
Investigational product from another study	5 half-lives of that product
Alkylating agents	12 months

Source: CSR SB2-RA Table 9-3

Endpoints/Outcome Measures

Primary endpoint

- The primary efficacy endpoint was proportion of patients achieving ACR20 response at Week 30

Key Secondary endpoints

1) Efficacy

- ACR20 response at Week 54
- ACR50 and ACR70 at Weeks 14, 30, and 54
- The numeric index of the ACR response (ACR-N) at Week 30 and Week 54
- The area under the curve (AUC) of ACR-N up to Week 30
- The disease activity score based on a 28 joint count (DAS28 score) at Week 30 and Week 54

- The European League Against Rheumatism response at Week 30 and Week 54
- The AUC of the change in DAS28 from Baseline up to Week 30

2) Safety, PK and Immunogenicity

- Incidence of adverse events (AEs), graded as mild, moderate and severe)
- Incidence of serious AEs (SAEs)
- Incidence of clinical laboratory abnormalities
- Vital signs abnormalities
- Concentration of infliximab at Baseline and prior to dosing at Weeks 2, 6, 14, 22 and 30 (Ctrough)
- Incidence of anti-drug antibodies (ADA)
- Incidence of neutralizing antibodies (NAb)

Statistical Analysis Plan

ACR20 response rate was the primary endpoint of the study. In order to demonstrate the similarity between SB2 and EU-Remicade, the applicant compared ACR20 response rates between the two treatment arms. The null hypothesis of the study was defined as either 1) SB2 is inferior to EU-Remicade or 2) SB2 is superior to EU-Remicade based on a pre-specified similarity margin. According to the statistical analysis plan, the biosimilarity between the two treatments would be concluded if the two-sided 95% confidence interval of the difference in ACR20 response rate was contained within the similarity margin of [-15%,15%]. The applicant also carried out an analysis using a 90% confidence interval with a similarity margin of [-12%, 12%] based on FDA recommendations.

The 95% CI of the difference between the two treatment groups in relation to the percentage of subjects achieving an ACR20 response at Week 30 was estimated for the PPS1 using the non-parametric analysis of covariance (ANCOVA) model stratified by study center (or pooled centers) and adjusting for the Baseline CRP.

Efficacy analysis set

The full analysis set (FAS) consisted of all subjects who were randomized at the Randomization Visit. Following the intent-to-treat principle, subjects were analyzed according to the treatment they were assigned at Randomization.

The per-protocol set 1 (PPS1) consisted of all FAS subjects who completed the Week 30 visit and had an adherence (from Baseline to Week 30) within the range 80-120% of both the expected number of IP administrations and the expected sum of MTX doses without any major protocol deviations that affected the efficacy assessment. The PPS1 was the primary analysis set. Major protocol deviations that led to exclusion from this set were pre-specified prior to unblinding the treatment codes for analyses.

The per-protocol set (PPS2) consisted of all FAS subjects who completed the Week 54 visit and had an adherence within the range 80-120%, through Week 54, of both the expected number of IP administrations and the expected sum of MTX doses without any major protocol deviations that affect the efficacy assessment.

Protocol Amendments:
Minor amendments were made to the protocol which did not affect safety or efficacy results.

6 Review of Efficacy

Efficacy Summary

Similarity of efficacy of SB2 compared to Remicade was assessed in Study SB2-RA, the comparative clinical study (CCS), comparing SB2 with EU-approved Remicade in patients with RA. Efficacy was not assessed in the PK-similarity study, SB2-NHV in healthy subjects. The FDA evaluation of efficacy focused on the single, randomized, double-blind controlled study SB2-RA in RA patients. The transition-extension study period of the same study in which patients underwent a single transition from EU-approved Remicade to SB2 provided descriptive assessment of efficacy with longer administration of SB2

Study SB2-RA met its primary objective of demonstrating that the proportion of patients achieving ACR20 response at week 30 was similar between the SB2 and EU-approved Remicade treatment groups, 64% and 66% patients, respectively. The 95% CI for the estimate of treatment difference was contained within applicant-prespecified similarity margin of -15% to 15% (95% CI: -10.3, 6.5). Of note, as discussed in detail in the FDA statistical review, the Agency has determined that a ±12% similarity margin would be generally expected, based on considerations of the clinical importance of different losses in effect against the feasibility of the comparative clinical study. The results from the primary analysis were supported by consistent sensitivity analyses and were also within the margin preferred by the Agency. These results support the conclusion of no clinically meaningful differences between SB2 and EU-approved Remicade in RA.

Analysis of key secondary efficacy endpoints in Study SB2-RA including ACR20 response at week 54, ACR50 and ACR70 at weeks 30 and 54, disease activity score based on 28 joint counts (DAS28) at week 30 and week 54, showed similar results between SB2 and EU-approved Remicade treatment groups.

The transition-extension period of study SB2-RA had a single transition from EU-approved Remicade to SB2 at week 54. ACR20 response rates over time up to week 78 were comparable between the different treatment arms. Efficacy endpoint analysis

demonstrated consistent efficacy up to week 78 in each treatment group, SB2 maintenance, EU-Remicade maintenance and EU-Remicade→ SB2 transition group.

FDA's analysis of the key primary and secondary endpoints was consistent with the Applicant's.

6.1 Indication

The proposed therapeutic indications, dosage and route of administration (intravenous infusion over a period of not less than 2 hours) for SB2 are listed below:

Rheumatoid Arthritis (RA):
Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis. To be administered in conjunction with methotrexate (MTX) at doses of 3 mg/kg at 0, 2 and 6 weeks, then every 8 weeks; for patients who have an incomplete response, consideration may be given to adjusting the dose up to 10 mg/kg or treating as often as every 4 weeks.

Ankylosing Spondylitis (AS):
Reducing signs and symptoms in patients with active ankylosing spondylitis. Recommended dosing is 5 mg/kg at 0, 2 and 6 weeks, then every 6 weeks.

Psoriatic Arthritis (PsA):
Reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in patients with psoriatic arthritis. Recommended dosing is 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks with or without MTX.

Plaque Psoriasis(Ps):
Treatment of adult patients with chronic severe (i.e., extensive and /or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate. Recommended dosing is 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.

Crohn's Disease (CD):

- Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely Crohn's active disease who have had an inadequate response to conventional therapy.
- Reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing Crohn's disease.
- Recommended dosing is 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. Some adult patients who initially respond to treatment may benefit from increasing the dose to 10 mg/kg if they later lose their response. Patients who do

not respond by Week 14 are unlikely to respond with continued dosing and consideration should be given to discontinue.

Pediatric Crohn's Disease:
Reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. Recommended dosing is 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.

Ulcerative Colitis (UC):
Reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy. Recommended dosing is 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.

Pediatric Ulcerative Colitis:[1]
Reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy. Recommended dosing is 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.

6.1.1 Methods

In the context of a biosimilar development program, the objective of the clinical development program of a proposed biosimilar is to help resolve any residual uncertainties that arise after a robust analytical similarity is established between the proposed biosimilar and the reference product. As such, the clinical development program of SB2 was designed to assess efficacy and safety SB2 in a limited number of clinical studies, namely Study SB2-RA, the comparative clinical study.

To demonstrate therapeutic similarity between SB2 and US-licensed Remicade, the applicant chose the indication of RA in the pivotal comparative clinical study as RA has been well-studied among the anti-TNF indications. Further, use of infliximab has been well-characterized including PK profiles, safety and efficacy in the RA population. The Agency agrees with the applicant's rationale that the study population is a sensitive population to use in the assessment of no clinically meaningful differences in the context of a proposed biosimilar development.

6.1.2 Demographics

Study SB2-NHV

[1] We note 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.

Patient Disposition, Demographic and Baseline Characteristics

A total of 159 subjects were enrolled and completed the study. No subjects discontinued from the study.

All randomized subjects were included in the Safety and Intent-to-Treat populations and no data were excluded.

Overall, the baseline demographics were similar between treatment arms with the average patient being approximately 40 years of age, White (>95%), male (>95%) with an average BMI of 25 kg/m^2. See Table 4.

Table 4. Baseline Demographic Characteristics (PK Study)

Treatment	SB2 (N=53)	EU Remicade® (N=53)	US Remicade® (N=53)
Age (years)			
Mean	40.7	40.3	39.4
SD	9.67	9.72	9.87
Median	42	42	41
Min	19	19	23
Max	55	55	55
Gender, n (%)			
Male	49 (92.5)	51 (96.2)	50 (94.3)
Female	4 (7.5)	2 (3.8)	3 (5.7)
Race, n (%)			
White	51 (96.2)	52 (98.1)	52 (98.1)
Asian	1 (1.9)	0 (0.0)	1 (1.9)
Black or African American	1 (1.9)	0 (0.0)	0 (0.0)
Other	0 (0.0)	1 (1.9)	0 (0.0)
Ethnicity, n (%)			
Not Hispanic or Latino	53 (100.0)	52 (98.1)	53 (100.0)
Hispanic or Latino	0 (0.0)	1 (1.9)	0 (0.0)
Height (cm)			
Mean	178.5	178.1	178.6
SD	7.65	6.04	7.20
Median	179	179	178
Min	158	164	163
Max	191	188	194
Weight (kg)			
Mean	78.38	80.48	79.10
SD	8.709	7.506	8.304
Median	79.2	80.1	79.6
Min	60.2	63.9	62.9
Max	93.2	94.3	94.2
BMI (kg/m^2)			
Mean	24.56	25.39	24.79
SD	2.078	2.092	2.058
Median	24.6	25.0	24.8
Min	20.8	20.9	20.8
Max	29.1	29.8	30.0

Source: CSR SB2-G11-NHV, Table 11-2, Summary of Clinical Safety Table 2.7.4.1-7

Study SB2-RA

Patient Disposition, Demographic and Baseline Characteristics

A total of 584 RA subjects were enrolled in the study, 291 in the SB2 treatment group and 293 in the EU-Remicade treatment group. One subject in the SB2 treatment group who did not meet the inclusion/exclusion criteria was withdrawn prior to administration of the first dose; and therefore excluded from the Full Analysis Set (FAS). A total of 583 (99.8%) subjects were included in the FAS, 478 (81.8%) subjects satisfied the criteria for the PPS1, and 410 (70.2%) subjects satisfied the criteria for the PPS2. Missing ACR responses were treated as non-responders in the FAS and no missing data were imputed in the PPS1 and PPS2.

For reference, FAS is the full analysis set, PPS1 and PPS2 are per protocol sets 1 and 2, respectively. For definitions, see Statistical Analysis Plan in Section 5, Study SB2-RA: Comparative Clinical Study in RA.

Prior to Week 30, 79 (13.5%) subjects withdrew from the study, which included 45 subjects (15.5%) from the SB2 treatment group and 34 subjects (11.6%) from the EU Remicade treatment group. In both treatment groups, the most common reasons for withdrawal among the randomized subjects were adverse events (AEs) in 31 subjects (5.3%) and withdrawal of consent for 29 (5.0%) subjects. The proportions of withdrawals were balanced between the two treatment groups.

For the transition-extension period, 396 RA subjects (201 subjects in the SB2 treatment group and 195 subjects in the Remicade treatment group) were re-randomized to receive either SB2 or EU-Remicade. Of the subjects who received EU-Remicade during the randomized, double-blind period (Weeks 0 – 54), 195 were re-randomized transitioned to SB2 (EU-Remicade → SB2 treatment group, n=94) or continue on EU-Remicade (EU-Remicade → EU-Remicade treatment group, n=101). The 201 subjects who received SB2 during the randomized, double-blind period continued to receive SB2 (SB2 → SB2 treatment group).

For the randomized, double-blind period, the demographic and baseline characteristics were comparable between the two treatment groups. The average age was 52.1 years, and the proportion of subjects aged over 65 was 13.7% in the SB2 and 15.4% in the EU EU-Remicade treatment groups. The majority of subjects were female (80.1%) and white (86.6%). The mean disease duration was 6.6 years in the SB2 and 6.3 years in the EU-Remicade treatment groups. The mean weekly dose of MTX at baseline was 14.7 mg in the SB2 and 14.7 mg in the EU-Remicade treatment groups. Baseline

disease characteristics for RA measures were also well balanced between the treatment groups. See Table 5 and Table 6.

For the transition-extension period, the baseline demographic and disease characteristics were also comparable between the treatment groups. See Table 7 and Table 8.

Table 5. Baseline Demographic Characteristics (Study SB2-RA)

	SB2		Remicade®		Total	
	N=291		N=293		N=584	
Age (years)						
Mean (SD)	51.6	(11.92)	52.6	(11.74)	52.1	(11.83)
Age group n (%)						
< 65 years	251	(86.3)	248	(84.6)	499	(85.4)
≥ 65 years	40	(13.7)	45	(15.4)	85	(14.6)
Gender n (%)						
Male	59	(20.3)	57	(19.5)	116	(19.9)
Female	232	(79.7)	236	(80.5)	468	(80.1)
Race, n (%)						
White	252	(86.6)	254	(86.7)	506	(86.6)
American Indian or Alaskan Native	0	(0.0)	0	(0.0)	0	(0.0)
Asian	37	(12.7)	39	(13.3)	76	(13.0)
Black or African American	0	(0.0)	0	(0.0)	0	(0.0)
Native Hawaiian or other Pacific Islander	0	(0.0)	0	(0.0)	0	(0.0)
Other	2	(0.7)	0	(0.0)	2	(0.3)
Ethnicity n (%)						
Hispanic or Latino	5	(1.7)	3	(1.0)	8	(1.4)
Chinese	0	(0.0)	0	(0.0)	0	(0.0)
Indian (Indian subcontinent)	1	(0.3)	1	(0.3)	2	(0.3)
Japanese	0	(0.0)	0	(0.0)	0	(0.0)
Mixed ethnicity	1	(0.3)	0	(0.0)	1	(0.2)
Other	284	(97.6)	289	(98.6)	573	(98.1)
Height (cm)						
Mean (SD)	164.58	(9.278)	164.79	(8.569)	164.69	(8.922)
Weight (kg)						
Mean (SD)	72.27	(15.812)	71.92	(16.513)	72.10	(16.155)
BMI (kg/m^2)						
Mean (SD)	26.62	(5.252)	26.49	(5.973)	26.56	(5.621)

Source: SB-CSR Table 11-2

Table 6. Baseline Disease Characteristics (SB2-RA)

		SB2	Remicade	Total
Baseline Disease	**N**	290	293	583
HAQ-DI (0-3)	**Mean**	1.5	1.5	1.5
	SD	0.6	0.6	0.6
Physician Global Assessment	**Mean**	61.7	61.8	61.8
	SD	15.6	15.8	15.7
Subject global Assessment	**Mean**	62.9	62.7	62.8
	SD	17.5	18.7	18.1
Swollen joint count (0-66)	**Mean**	14.6	14.9	14.8
	SD	7.8	7.7	7.8
Subject Pain Assessment	**Mean**	61.2	63.3	62.3
	SD	18.6	20.0	19.3
Tender Joint Count	**Mean**	23.6	23.9	23.8
	SD	12.3	12.2	12.2
Duration of RA (years)	**Mean**	6.6	6.3	6.4
	SD	6.0	5.9	5.9
Duration of methotrexate used (months)	**Mean**	48.4	53.1	50.7
	SD	45.6	49.5	47.6
Weekly dose of MTX (mg) at baseline	**Mean**	14.7	14.7	14.7
	SD	4.1	4.2	4.2
Erythrocyte Sedimentation Rate - Baselin	**Mean**	46.7	44.5	45.6
	SD	22.3	19.2	20.9
CRP- Baseline (mg/L)	**Mean**	13.7	12.5	13.1
	SD	19.2	18.8	19.0

Source: BLA 761054 FDA Statistics Review

Table 7. Baseline Demographic Characteristics (Transition-Extension Period)

N	SB2 ⇒ SB2 N=201		EU-Remicade ⇒ SB2 N=94		EU-Remicade ⇒ Remicade N=101		Total N=396	
Age	51.8	12.13	52.9	10.9	51.4	11.2	52	11.6
Age group								
< 65 years	171	85.1	80	85.11	90	89.11	341	86.11
>= 65 years	30	14.9	14	14.89	11	10.89	55	13.89
Sex								
Male	43	21.3	17	18.09	22	21.78	82	20.71
Female	158	78.6	77	81.91	79	78.22	314	79.29
Race								
White	183	91.0	87	92.55	88	87.13	358	90.40
Other	1	0.5	.	.	.	.	1	0.25
Asian	17	8.4	7	7.45	13	12.8	37	9.34
Weight (kg)	72.72	14.6	72.2	14.9	73.1	17.3	72.7	(15.4)
Height (cm)	165.18	9.0	165.6	8.0	165.4	7.5	165.4	(7.5)
BMI (kg/m^2)	26.64	5.0	26.3	5.1	26.8	6.4	26.6	(5.4)

Source: BLA 761054 FDA Statistics Review Cell contents are mean (standard deviation) or frequency (percent), CSR SB2-RA 78week, Table 11-3

Table 8. Baseline Disease Characteristics (Transition-Extension Period)

		EU-Remicade ⇒EU-Remicade	EU-Remicade⇒SB2	SB2⇒SB2
HAQ-DI (0-3)	N	101	94	201
	Mean	1.0	1.0	1.0
	Std	0.7	0.6	0.7
Physician Global Assessment	Mean	25.0	24.5	25.1
	Std	17.1	18.1	18.0
Subject global Assessment	Mean	35.8	35.5	34.8
	Std	21.9	22.6	23.3
Swollen joint count (0-66)	Mean	4.0	2.7	3.5
	Std	6.1	4.4	5.2
Subject Pain Assessment	Mean	36.0	35.9	35.6
	Std	22.6	23.4	23.8
Tender Joint Count	Mean	8.2	6.1	7.2
	Std	10.5	7.0	9.2
Duration of RA (years)	Mean	6.7	6.3	6.3
	Std	6.1	5.4	6.2
Duration of methotrexate used (mons)	Mean	52.1	49.7	51.1
	Std	50.6	45.4	46.8
Weekly dose of MTX (mg) at baseline	Mean	15.2	14.3	14.7
	Std	4.0	3.9	4.1
Erythrocyte Sedimentation Rate - Baseline	Mean	45.3	45.7	43.0
	Std	19.7	23.0	17.5
CRP- Baseline (mg/L)	Mean	13.7	13.8	12.0
	Std	18.8	21.9	19.1

Source: BLA 761054 FDA Statistics Review

6.1.3 Subject Disposition

Study SB2-NHV

A total of 159 subjects were enrolled and completed the study. 53 subjects were randomized to each treatment arm, SB2, EU-Remicade, and US-Remicade

respectively. No subjects discontinued from the study. All subjects were included in the safety dataset.

Study SB-RA

Subject disposition was similar between treatment groups in each study as shown in Table 9. There were 291 subjects in the SB2 and 293 subjects in the EU-Remicade treatment groups, respectively. In the enrolled set, 505 (86.5%) subjects completed 30 weeks of the study, i.e. the time point for the primary efficacy assessment, and 452 (77.4%) subjects completed 54 weeks of the study, i.e. the double-blind controlled period. The overall reasons for withdrawal, primarily due to adverse events and withdrawal of consent, were similar between the two treatment groups. Prior to Week 30, 79 (13.5%) subjects withdrew from the study, which included 45 subjects (15.5%) from the SB2 treatment group and 34 subjects (11.6%) from the EU-Remicade treatment group. In both treatment groups, the most common reasons for withdrawal among the randomized subjects were adverse events (AEs) in 31 subjects (5.3%) and withdrawal of consent for 29 (5.0%) subjects. Similar trend was observed up to Week 54. A numerical imbalance was observed in the number of patients withdrawing due to adverse events. The pattern of these adverse events however, was similar between the two groups and together with the small number of events, does not indicate a clinically meaningful difference in safety between SB2 and EU-Remicade.

Table 9. Subject Disposition (Study SB2-RA)

	SB2	Remicade®	Total
	n (%)	n (%)	n (%)
Screened			805
Screening failures			221
Reasons for screening failures			
Does not meet inclusion criteria			43 (19.5)
Does meet exclusion criteria			140 (63.3)
Withdrew consent			35 (15.8)
Other			15 (6.8)
Randomised	291	293	584
Completed Week 30 of treatment	246 (84.5)	259 (88.4)	505 (86.5)
Withdrew before Week 30	45 (15.5)	34 (11.6)	79 (13.5)
Reason for withdrawal			
Adverse event	21 (7.2)	10 (3.4)	31 (5.3)
Protocol deviation	1 (0.3)	3 (1.0)	4 (0.7)
Lack of efficacy	5 (1.7)	5 (1.7)	10 (1.7)
Subject lost to follow-up	0 (0.0)	1 (0.3)	1 (0.2)
Investigator Discretion	1 (0.3)	3 (1.0)	4 (0.7)
Withdrew consent	17 (5.8)	12 (4.1)	29 (5.0)
Completed Week 54 of treatment	227 (78.0)	225 (76.8)	452 (77.4)
Withdrew before Week 54	60 (20.6)	64 (21.8)	124 (21.2)
Reason for withdrawal			
Adverse event	27 (9.3)	21 (7.2)	48 (8.2)
Protocol deviation	1 (0.3)	5 (1.7)	6 (1.0)
Lack of efficacy	5 (1.7)	6 (2.0)	11 (1.9)
Subject lost to follow-up	0 (0.0)	1 (0.3)	1 (0.2)
Pregnancy	0 (0.0)	1 (0.3)	1 (0.2)
Investigator Discretion	4 (1.4)	4 (1.4)	8 (1.4)
Withdrew consent	23 (7.9)	26 (8.9)	49 (8.4)
Subjects from Eastern Ukraine sites without disposition information available*	4 (1.4)	4 (1.4)	8 (1.4)

Source: SB2-RA CSR Table 10-1
Percentages were based on the number of randomized subjects.
Percentages for the screening failure reason were based on the number of screening failures. Multiple screening failure reasons were possible.
* Data collected or updated for these Eastern Ukrainian sites after the first database lock (30-week CSR) were excluded from the analysis due to regional issues.

Of the 396 subjects who enrolled in the transition-extension period, 370 (93.4%) subjects completed 78 weeks of the study. Up to Week 78, 26 (6.6%) subjects withdrew from the study including 15 (7.5%) subjects from the SB2/SB2 treatment group, 6 (6.4%) subjects from the EU-Remicade/SB2 treatment group, and 5 (5.0%) subjects from the EU-Remicade/EU-Remicade treatment group. Overall, the reasons for withdrawal were withdrawal of consent (2.5%), AEs (1.8%), lost to follow-up (1.5%) and investigator discretion (0.8%). Overall, the frequency of and reasons for withdrawal were comparable between the 3 treatment groups up to Week 78.

Dosing of SB2 and EU-Remicade

Study SB2-NHV

In study SB2-NHV, a single dose of 5mg/kg was administered across all treatment groups, SB2, EU- and US-Remicade, respectively.

Study SB2-RA

Infliximab is approved in the US for the treatment of RA at a dose of 3 mg/kg given as an *i.v.* infusion followed by additional 3 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter increasing up to 10mg/kg or treating every 4 weeks. In study SB2-RA, dosing followed the approved dosing of infliximab; dosing at 3mg/kg occurred via 2 hours (h) intravenous (IV) infusion, at Week 0, 2, 6 and then every 8 weeks with last dose at Week 46. From Week 30, i.e. the time point of primary efficacy assessment, the dose level could be increased step-wise by 1.5 mg/kg, up to a maximum of 7.5 mg/kg, every 8 weeks if the subject's RA symptoms were not well controlled by the existing dose. Table 10 lists the distribution of doses given to patients at Weeks 30, 38 and 46. 5 patients in the EU-Remicade required the highest allowed dose of 7.5mg/kg and none in SB2 treatment group. Overall, the increment pattern in treatment dosing in the SB2 and EU-Remicade treatment groups was similar throughout the 54-week randomized period of the study.

Table 10. Dosage Increment by Treatment Group (SB2-RA)

Study Week - Dose	SB2 N=290 n (%)		EU Remicade® N=293 n (%)		Total N=583 n (%)	
Week 30						
3.0 mg/kg	189	(65.2)	192	(65.5)	381	(65.4)
4.5 mg/kg	57	(19.7)	67	(22.9)	124	(21.3)
6.0 mg/kg	0	(0.0)	0	(0.0)	0	(0.0)
7.5 mg/kg	0	(0.0)	0	(0.0)	0	(0.0)
Week 38						
3.0 mg/kg	161	(55.5)	162	(55.3)	323	(55.4)
4.5 mg/kg	66	(22.8)	71	(24.2)	137	(23.5)
6.0 mg/kg	11	(3.8)	12	(4.1)	23	(3.9)
7.5 mg/kg	0	(0.0)	0	(0.0)	0	(0.0)
Week 46						
3.0 mg/kg	147	(50.7)	147	(50.2)	294	(50.4)
4.5 mg/kg	50	(17.2)	62	(21.2)	112	(19.2)
6.0 mg/kg	31	(10.7)	17	(5.8)	48	(8.2)
7.5 mg/kg	0	(0.0)	5	(1.7)	5	(0.9)

Source: SB2-RA CSR Table 12-2

The doses of treatment drug (3.0 to 7.5 mg/kg) given to subjects in the transition-extension period are presented by treatment group in Table 11. The increment pattern in treatment dosing in the 3 treatment groups (SB2/SB2, EU-Remicade/SB2 and EU-Remicade/EU-Remicade) was comparable at all time points from Week 54 to Week 70 indicating that similar proportions of patients required dose escalation, including following a single transition from EU-Remicade to SB2, supporting a demonstration of no clinically meaningful differences between the products.

Table 11. Treatment Dosage Increment in the Transition-extension Period

Study Week - Dose	SB2	Remicade®			Total
		Overall	SB2	Remicade®	
	N=201	N=195	N=94	N=101	N=396
	n/n' (%)	n/n' (%)	n/n' (%)	n/n' (%)	n/n' (%)
Week 54					
3.0 mg/kg	126/201 (62.7)	121/195 (62.1)	58/94 (61.7)	63/101 (62.4)	247/396 (62.4)
4.5 mg/kg	42/201 (20.9)	48/195 (24.6)	26/94 (27.7)	22/101 (21.8)	90/396 (22.7)
6.0 mg/kg	27/201 (13.4)	16/195 (8.2)	7/94 (7.4)	9/101 (8.9)	43/396 (10.9)
7.5 mg/kg	6/201 (3.0)	10/195 (5.1)	3/94 (3.2)	7/101 (6.9)	16/396 (4.0)
Week 62					
3.0 mg/kg	113/191 (59.2)	117/194 (60.3)	57/94 (60.6)	60/100 (60.0)	230/385 (59.7)
4.5 mg/kg	43/191 (22.5)	46/194 (23.7)	22/94 (23.4)	24/100 (24.0)	89/385 (23.1)
6.0 mg/kg	27/191 (14.1)	17/194 (8.8)	10/94 (10.6)	7/100 (7.0)	44/385 (11.4)
7.5 mg/kg	8/191 (4.2)	14/194 (7.2)	5/94 (5.3)	9/100 (9.0)	22/385 (5.7)
Week 70					
3.0 mg/kg	109/186 (58.6)	108/184 (58.7)	53/89 (59.6)	55/95 (57.9)	217/370 (58.6)
4.5 mg/kg	37/186 (19.9)	44/184 (23.9)	20/89 (22.5)	24/95 (25.3)	81/370 (21.9)
6.0 mg/kg	32/186 (17.2)	16/184 (8.7)	9/89 (10.1)	7/95 (7.4)	48/370 (13.0)
7.5 mg/kg	8/186 (4.3)	16/184 (8.7)	7/89 (7.9)	9/95 (9.5)	24/370 (6.5)

Source: SB2-RA (78 week)CSR Table 12-3

6.1.4 Analysis of Primary Endpoint(s)

6.1.4.1 Study SB2-RA : Comparative Clinical Study in RA

Primary Endpoint: ACR20 response

The primary efficacy endpoint was to demonstrate therapeutic equivalence of SB2 to EU-Remicade at week 30, in terms of the proportion of patients achieving ACR20 response at Week 30, i.e., a 20% improvement by ACR criteria.

Study SB2-RA met its primary endpoint. Table 12 shows the primary analysis of ACR20 response rates between SB2 and EU-Remicade treatment groups. The proportion of patients who obtained an ACR20 response at Week 30 in the Per-protocol Set 1 was comparable between the SB2 and EU-treatment groups, 64% and 66%, respectively. The estimated absolute difference was -1.88% (90% CI: -8.91,+ 5.16; 95% CI: -10.26, +6.51). Both the 90% and 95% confidence intervals were contained within applicant pre-specified margin of [-15%, 15%] and within the FDA-recommended similarity margin of [-12%, 12%]. The FDA statistical review of efficacy was in agreement with the applicant's analyses.

Table 12. ACR20 Response Rate at Week 30 (Per-protocol Set 1)

Treatment	n/n'	%	Adjusted Difference Rate	95% CI	90% CI
SB2 (N=231)	148/231	64.1%	–1.88%	(-10.3, 6.5)	(-8.9, 5.2)
EU-Remicade (N=247)	163/247	66.0%			
Source: SB2-RA CSR Table 11-5, Clinical Overview, Table 2.5.4-2 . N-number of subjects in PPSI, n'-number of subjects with an assessment, n-number of responders					

Results from the Full Analysis Set (FAS) supported the results of the per-protocol set as shown in Table 13

Table 13. ACR20 Response Rate at Week 30 (Full Analysis Set)

Treatment	n/n'	%	Adjusted Difference Rate	95% CI	90% CI
SB2 (N=290)	161/290	55.5%	–2.95%	(-10.9, 5.0)	(-9.6, 3.7)
EU-Remicade (N=293)	173/293	59.0%			
Source: SB2-RA CSR Table 11-6, Clinical Overview, Section 2.5.4.2.4 . N-number of subjects in PPSI, n'-number of subjects with an assessment, n-number of responders					

The FAS was defined as all subjects who were randomized at the randomization visit. Following the intention-to-treat (ITT) principle, subjects were analyzed according to the treatment they were assigned to at randomization. Subjects who did not qualify for the randomization and were inadvertently randomized into the study were excluded from the FAS, provided these subjects did not receive IP. The PPS1 consisted of all FAS subjects who completed the Week 30 visit and had an adherence (from baseline to Week 30) within the range 80-120% of both the expected number of IP administrations and the expected sum of MTX doses without any major protocol deviations that could have impacted efficacy assessment.

Selection of Similarity Margin

Adapted from DPARP Statistical Review.

The determination of an equivalence margin is a critical aspect of the design of the comparative clinical study because it determines the null hypothesis being tested in the primary analysis, i.e., the differences in efficacy that the study will need to rule out at an acceptable significance level. The term equivalence margin is a misnomer because it is not possible to statistically demonstrate that two products are equivalent with respect to a particular endpoint. Instead, we describe the margin as a similarity margin to better reflect the goal of the efficacy evaluation: to determine whether the two products are similar, in that a certain magnitude of difference (the margin) in efficacy can be ruled out.

The applicant initially proposed to conduct the primary efficacy analysis by comparing the 95% confidence interval (CI) of the difference of 2 proportions with the pre-specified equivalence margin of [−15%, 15%]. However, FDA recommended a similarity margin of [-12%, 12%] at a type 4 meeting on Dec 14, 2015. FDA also recommended use of a 90% because it generally expects the type I error probability to be controlled at the overall 5% level in comparative clinical studies. The applicant agreed with this recommendation and performed additional analyses to calculate 90% CIs for the difference in ACR20 in the FAS and PPS. As the double blind period of the study was already completed, the results from the revised analysis were not included in the clinical study report. However, these results were reported in the Integrated Summary of Effectiveness and Summary of Clinical Efficacy report. The lack of a priori agreement between the applicant and FDA on a similarity margin is not of concern in this case because the primary analysis successfully ruled out the ±12% margin recommended by FDA.

For further details on the statistical considerations for the analysis of the efficacy endpoints, refer to Dr. Ginto's statistical review.

In summary, the primary analysis of study SB2-RA in patients with RA, met its objective of demonstrating similarity of efficacy between SB2 and EU-Remicade, and supports the demonstration of no clinically meaningful differences between SB2 and EU-approved Remicade in RA.

6.1.5 Analysis of Secondary Endpoints(s)

6.1.5.1 Study SB2-RA (weeks 0 – 54)

The comparative analyses of secondary endpoints also showed similar efficacy between the two treatment groups. Secondary endpoints in the study included ACR20 response at Week 54, ACR50 and ACR 70 at Weeks 30 and Week 54, ACR-N at Week 30 and Week 54, area under the curve of ACR-N up to Week 30, and disease activity score based on 28 joint counts (DAS 28 score) at Week 30 and Week 54, EULAR response at Week 30 and Week 54, and AUC of the change in DAS28 from baseline up to Week 30.

Overall, the results for the secondary endpoints support the primary efficacy analysis and support the demonstration of similarity between SB2 and US-Remicade.

Results from analysis of key secondary endpoints are presented below.

1. Individual Components of the ACR Criteria

In the all-randomized population, mean decreases from baseline week 30 were similar in the SB2 and EU-approved Remicade treatment groups for the individual ACR components. The degree of improvement for each RA disease activity component (swollen and tender joint counts, VAS/HAQ-DI scores and laboratory measures of inflammation) was also comparable between the treatment groups up to Week 54.

2. ACR20 response rate at week 54

The ACR20 response rate at Week 54 for the PPS2 was 65.3% (132/202) for the SB2 treatment group and 69.2% (144/208) for the EU-Remicade treatment groups as shown in Table 14

Table 14. Analysis of ACR20 Response Rate at Week 54

Dataset	*Treatment*	*n/N*	*%*	*Adjusted Difference Rate*	*90% CI*	*95% CI*
Per-protocol Set 2	SB2 (N=202)	132/202	(65.35%)	**-3.07%**	(-10.56, 4.43)	(-11.99, 5.86)
	EU-Remicade (N=208)	144/208	(69.23%)			
Full Analysis Set	SB2 (N=290)	147/290	(50.69%)	**- 1.15%**	(-7.88, 5.57)	(-9.16, 6.86)
	EU-Remicade (N=293)	154/293	(52.56%)			

Source: Adapted from BLA 761054 FDA Statistics Review

3. ACR50 and ACR 70 at week 30 and week 54

Similar to ACR20, the ACR50 and ACR70 are calculated as the respective percent improvement and were assessed as major secondary endpoints. Consistent with the

primary endpoint of the study, the proportion of patients achieving ACR50 and 70 at weeks 30 and 54 in study SB2-RA was similar between the two treatment groups, SB2 and EU-Remicade, as shown in Table 15.

Table 15. ACR50 and ACR70 Response Rate at Week 30 and Week 54

Timepoint	ACR response	Treatment	n/n'	(%)	Adjusted Difference Rate	95% CI
Week 30	ACR50	SB2 (N=290)	89/290	(30.7)	−2.53%	(−10.07%, 5.00%)
		Remicade® (N=293)	99/293	(33.8)		
	ACR70	SB2 (N=290)	45/290	(15.5)	−1.08%	(−7.06%, 4.91%)
		Remicade® (N=293)	50/293	(17.1)		
Week 54	ACR50	SB2 (N=290)	93/290	(32.1)	3.07	(−4.26%, 10.40%)
		Remicade® (N=293)	87/293	(29.7)		
	ACR70	SB2 (N=290)	53/290	(18.3)	1.10%	(−5.08, 7.28%)
		Remicade® (N=293)	52/293	(17.7)		

Source: SB2-RA CSR Table 11-11

4. ACR-N at week 30

Adapted from DPARP Statistical Review.

In addition to the similar results obtained from the analysis of binary ACR20 response, the analysis of different continuous endpoints also showed similarity between the two groups. As continuous endpoints may be more sensitive to detect differences in treatment effects, such results are reassuring. For example, the analysis of the continuous endpoint ACR-N at Week 30 indicates that the treatment effects were similar between the two groups. From, Table 16 the difference between the two treatment mean changes was -0.87 with a 90% confidence interval (- 5.16, 3.40).

Table 16. ACR-N at Week 30

TRT	MEAN	Difference Between Means	95% Confidence Limits	90% Confidence Limit
EU-Remicade	37.81	-0.87	(-5.98, 4.22)	(-5.16, 3.40)
SB2	36.63			

Source: BLA 761054 FDA Statistics Review

6.1.5.2 Transition-Extension Period of Study SB2-RA (weeks 54 – 78)

At Week 54, subjects receiving EU-Remicade from the randomized, double-blind period of the SB2-G31-RA study were randomized again in a 1:1 ratio to either continue on

EU-Remicade (EU-Remicade/EU-Remicade) or be transitioned to SB2 (EU-Remicade/SB2) up to Week 70. Patients receiving SB2 in the randomized, double-blind period continued on SB2 in the transition-extension period.

Table 17 shows the ACR20, 50 and 70 response rates across treatment groups at Weeks 54, 62, 70 and 78. Slight numerical differences are observed between the treatment arms but overall, there is consistent efficacy over time across treatment groups. Proportion of patients achieving ACR20, 50 and 70 responses at Weeks 54 and 78 are comparable between treatment groups.

Table 17. ACR Response Rates in the Transition-Extension Period of Study SB2-RA

ACR Response	Timepoint	SB2		Remicade®			
				SB2		Remicade®	
		n/n'	(%)	n/n'	(%)	n/n'	(%)
ACR20	Week 54	132/201	(65.7)	67/94	(71.3)	70/101	(69.3)
	Week 62	129/193	(66.8)	68/94	(72.3)	67/101	(66.3)
	Week 70	118/180	(65.6)	61/88	(69.3)	68/98	(69.4)
	Week 78	123/180	(68.3)	54/85	(63.5)	64/93	(68.8)
ACR50	Week 54	87/201	(43.3)	39/94	(41.5)	40/101	(39.6)
	Week 62	79/193	(40.9)	42/94	(44.7)	42/101	(41.6)
	Week 70	78/180	(43.3)	36/88	(40.9)	43/98	(43.9)
	Week 78	73/180	(40.6)	32/85	(37.6)	44/93	(47.3)
ACR70	Week 54	49/201	(24.4)	25/94	(26.6)	23/101	(22.8)
	Week 62	41/193	(21.2)	22/94	(23.4)	21/101	(20.8)
	Week 70	46/180	(25.6)	18/88	(20.5)	25/98	(25.5)
	Week 78	46/180	(25.6)	19/85	(22.4)	29/93	(31.2)

Source: SB2-RA 78-week CSR Table 11-14

The results from the transition-extension period, suggest that the overall efficacy is consistent with efficacy at earlier time points and is comparable between patients who underwent a single transition from EU-Remicade to SB2 and those who continue on SB2.

6.1.6 Other Endpoints

Refer to Dr. Ginto's detailed statistical review.

6.1.7 Subpopulations

Refer to Dr. Ginto's detailed statistical review.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable to this application.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Refer to Dr. Ginto's detailed statistical review.

6.1.10 Additional Efficacy Issues/Analyses

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

7 Review of Safety

Safety Summary

The submitted efficacy, safety, and immunogenicity data and analyses using one dosing regimen (3mg/kg IV on the background of MTX) in study SB2-RA, the comparative clinical study in RA, together with the PK, safety, and immunogenicity data from the single dose healthy subject study SB2-NHV (single 5mg/kg IV dose), are adequate to support the demonstration of no clinically meaningful differences between SB2 and US-Remicade in patients with RA. The safety database submitted for SB2 is adequate to provide a reasonable descriptive comparison between the products. The safety risks identified are consistent with the known adverse event profile of US-Remicade. The analysis of the data indicates a safety profile of SB2, similar to that of US-Remicade. There were no notable differences between SB2, US-Remicade, and EU-Remicade in treatment-emergent adverse events, serious adverse events, adverse events leading to discontinuations, or deaths between the treatment groups. No cases of drug-induced liver injury meeting Hy's law criteria were reported in the SB2 clinical program. The safety and immunogenicity data support the demonstration that there are no clinically meaningful differences between SB2 and US-Remicade in the populations studied. In addition, a single transition of non-treatment naïve patients, i.e., patients previously treated with Remicade, to SB2 does not appear to result in an increase of clinically significant adverse reactions or immunogenicity.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary safety data were derived from the comparative clinical study SB2-RA, a 54-week randomized, double-blind, parallel group, multicenter study followed by an additional 24 week randomized, double-blind, parallel group period, the transition-extension period. At week 54, a total of 94 patients underwent a single transition from EU-Remicade to SB2 to assess additional risks, if any, in safety and immunogenicity resulting from a single transition from EU-Remicade to SB2 to address the safety of the clinical scenario where non-treatment naïve patients transition to SB2. Supportive safety and immunogenicity information was also provided from the single dose PK study in healthy subjects (Study SB2-NHV).

The safety population, defined as patients exposed to at least one dose of study treatment, is comprised of 742 patients, summarized in Table 18 below. Of the 742 patients, 343 patients were exposed at least one dose of SB2, 346 patients to at least one dose of EU-Remicade and 53 patients to US-Remicade.

Table 18. Overall Extent of Exposure to Study Treatment

Study	Number of Subjects Administered ≥1 dose of Study Drug			
	SB2	EU-Remicade	US-Remicade	Total
SB2-RA	290	293	N/A	583
SB2-NHV	53	53	53	159
Total	343	346	53	742

Source: Summary of Clinical Safety, Table 2; FDA analysis of SB2 351(k)submission

In the 3-way PK bridging study, study SB2-NHV, a total of 159 healthy subjects were randomized to receive a single dose of infliximab (5 mg/kg via *i.v*. infusion), with 53 subjects in each of the three treatment groups (SB2, US-licensed Remicade and EU-approved Remicade). The safety set (SAF) comprised all subjects who received at least one dose of the study drug.

In the comparative clinical study SB2-RA, a total of 584 RA subjects were enrolled and randomized to receive infliximab (3 mg/kg by *i.v*. infusion at Weeks 0, 2, 6 and then every 8 weeks up to Week 46 or up to Week 70 for the transition-extension period; dose increments allowed from Week 30 at 1.5 mg/kg increments per visit up to a maximum of

7.5mg/kg). One subject in the SB2 treatment group who did not meet the inclusion/exclusion criteria was withdrawn prior to administration of the first dose; and therefore excluded from the Full Analysis Set (FAS). A total of 583 (99.8%) subjects were included in the FAS.

For the randomized, double-blind period, 583 subjects were included in the safety set with 290 subjects in the SB2 treatment group and 293 subjects in the EU-Remicade treatment group. For the transition-extension period (Week 54 to Week 78), 396 subjects were included in the extended safety set (ex-SAF) with 201 subjects in the SB2/SB2 treatment group, 94 subjects in the EU-Remicade/SB2 and 101 subjects in the EU-Remicade/EU-Remicade treatment group.

Majority of the safety data is derived from Study SB2-RA comparing SB2 and EU-approved Remicade. Samsung has provided robust and extensive comparative analytical data and clinical PK bridging data (Study SB2-NHV) that demonstrated similarity of analytical parameters (physio-chemical and biological quality attributes) and PK between SB2, US-Remicade, and EU-Remicade to support the relevance of the data generated using the EU-approved Remicade to support a demonstration of biosimilarity between SB2 and US-licensed Remicade.

US-Remicade was used only in the PK study (Study SB2-NHV). The objectives of the study were to establish a, 3-way PK bridge between SB2, EU-Remicade and the reference product, US-Remicade to further support the applicability of the data generated using EU-Remicade. Study SB2-NHV met its primary objective. And consequently study SB2-NHV in addition to the analytical bridging data justifies the use of safety and efficacy data from studies comparing SB2 to EU-Remicade in this biosimilar application.

Overall, the safety database is adequate to provide a reasonable comparative safety and immunogenicity assessment to support a demonstration of no clinically meaningful differences between SB2 and US-Remicade.

7.1.2 Categorization of Adverse Events

Safety was evaluated by monitoring of adverse events (AEs), serious adverse events (SAEs), treatment-emergent adverse events (TEAEs), death, hypersensitivity via vital signs, electrocardiogram (ECG), physical examination, clinical laboratory tests, concomitant medications and pregnancy. Adverse events of special interest (AESI) defined as serious infections, and signs and symptoms of tuberculosis (TB) were also closely monitored. Adverse events associated with infusion related reaction were also summarized separately. Safety parameters were selected based on the known safety profile of the reference product, US-Remicade.

AE was defined as any untoward medical occurrence, including a clinically significant laboratory finding, symptom, or disease in a patient enrolled in the study regardless of its causal relationship to study drug. TEAE was defined as any event not present before exposure to study drug or any event already present that worsened in either severity or frequency after exposure to study drug. SAE was defined as an event that resulted in death, was immediately life-threatening (including events which put patients at risk of death at the time of the event but not events which may have caused patient death if more severe), required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, was considered medically important by the investigator or was a congenital anomaly/birth defect.

Laboratory evaluations included reporting for biochemistry, hematology, inflammatory makers, serology and urinalysis parameters. Drug-induced liver injury will be assessed through the number of possible Hy's law cases as follows:

- ALT or AST > 3 × ULN, and
- ALP < 2 × ULN, and
- Total bilirubin ≥ 2 × ULN

All parameters above were measured at the same visit.

AEs were coded using MedDRA 16.0. A treatment-emergent AE (TEAE) will be defined as any AE with an onset date on or after the date of the first administration of study treatment. For all TEAE and serious adverse event (SAE) tables, subjects were counted once at the most for each SOC and PT. And AEs were listed.

AESI for study SB2-RA were defined in the protocol as serious infections (i.e., an infection that was an SAE) and tuberculosis. If a serious infection or TB was diagnosed, the IP (investigational product, either SB2 or EU-Remicade) was discontinued and appropriate treatment and observation was undertaken.

Infusion-related reactions to the investigational product (IP), anaphylaxis, or delayed hypersensitivity including serum sickness-like reactions, were also assessed. During the infusion, mild to moderate infusion reactions could improve after slowing or suspension of the infusion, and upon resolution of the reactions, with re-initiation at a lower infusion rate and/or therapeutic administration of antihistamines, paracetamol and/or corticosteroids. For subjects that did not tolerate the infusion following these interventions, the IP was discontinued.

The applicant adequately captured and classified adverse events related to infusion-related reactions as what is generally expected in practice and described in the USPI for US-Remicade (such like flu-like symptoms, headache, dyspnea, hypotension, transient fever, chills, gastrointestinal symptoms, and skin rashes, etc.). Specifically for the SB2 clinical program, AEs associated with IRR included the following System organ class (SOC) and Preferred term (PT) using MedDRA version 16.0 coding dictionary: Eye

disorders (pruritus, eyelid edema), General disorders and administration site conditions (asthenia, chest discomfort, chills, feeling cold, peripheral edema, pyrexia), immune system disorders (hypersensitivity, anaphylactic reaction, anaphylactic shock), injury, poisoning and procedural complications (infusion related reaction), investigations (increased blood pressure), nervous system disorders (headache), respiratory, thoracic and mediastinal disorders (bronchospasm), skin and subcutaneous tissue disorders (rash, dermatitis allergic, erythema nodosum, pruritus, pruritus allergic, pruritus generalized, rash generalized, urticaria), vascular disorders (flushing, hypotension).

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

All reported AEs are presented per individual study without integrating data across studies and indications. A pooled safety analysis of the two clinical studies was not justified due to the differences in study design and population. . The Applicant provided sufficient analyses to allow review by individual studies and across both studies.

7.2 Adequacy of Safety Assessments

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

Study SB2-NHV

All subjects enrolled in the 3-way PK study received a single dose of treatment with SB2, EU-Remicade or US-Remicade.

Study SB2-RA
The number of patients randomized to each dose is comparable between the SB2 and EU-Remicade treatment groups at week 30. In the randomized, double-blind 54-week period, the mean duration of exposure was 282.2 days in the SB2 and 287.8 days in the EU-Remicade treatment groups. In the transition-extension period, the mean duration of exposure (from week 54) was comparable between the 3 treatment groups at 107.1 days in the SB2/SB2 treatment group, 110.9 days in the EU-Remicade/SB2 treatment group and 110.1 days in the EU-Remicade/EU-Remicade treatment group.

The protocol allowed for dose increments by 1.5mg/kg every after week 30. Patients who required an increase in dose also remains comparable between the two treatment groups at different doses (3 mg/kg, 4.5 mg/kg, and 6 mg/kg through week 46. 5 patients in the EU-Remicade (~2%) of the study population required a dose of 7.5 mg/kg at week

46 and none in the SB2 group. See Section 7.2.1.1 Dosing Increments of SB2 and EU-Remicade for details.

The overall exposure of patients was balanced for the two treatment groups (SB2 and EU-Remicade) throughout the controlled studies.

7.2.1.1 Dosing Increments of SB2 and EU-Remicade

Study SB2-NHV

In study SB2-NHV, a single dose of 5mg/kg was administered across all treatment groups, SB2, EU- and US-Remicade, respectively. Dose increment was not applicable and did not occur.

Study SB2-RA

Infliximab is approved in the US for the treatment of RA at a dose of 3 mg/kg given as an *i.v.* infusion followed by additional 3 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter increasing up to 10mg/kg or treating every 4 weeks. In study SB2-RA, dosing followed the approved dosing of infliximab; dosing at 3mg/kg occurred via 2 hours (h) intravenous (IV) infusion, at Week 0, 2, 6 and then every 8 weeks. From Week 30 the dose level could be increased step-wise by 1.5 mg/kg, up to a maximum of 7.5 mg/kg, every 8 weeks if the subject's RA symptoms were not well controlled by the existing dose until week 46 or week 70 for the transition-extension period. Table 10 lists the distribution of doses given to patients at Weeks 30, 38 and 46. Five patients in the EU-Remicade required the highest allowed dose of 7.5mg/kg and none in SB2 treatment group. Overall, the increment pattern in treatment dosing in the SB2 and EU-Remicade treatment groups was similar throughout the 54-week randomized period of the study.

The doses of treatment drug (3.0 to 7.5 mg/kg) given to subjects in the transition-extension period are presented by treatment group in Table 11. The increment pattern in treatment dosing in the 3 treatment groups (SB2/SB2, EU-Remicade/SB2 and EU-Remicade/EU-Remicade) was comparable at various time points from Week 54 to Week 70.

7.2.2 Explorations for Dose Response

In this BLA, the dose and dosing regimen of SB2 is identical to the reference product, US-Remicade. As such, dose-exploration studies were not conducted and were not required.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable to this BLA.

7.2.4 Routine Clinical Testing

Not applicable to this BLA.

7.2.5 Metabolic, Clearance, and Interaction Workup

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

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

SB2 is a proposed biosimilar to the reference product, US-Remicade, a TNF inhibitor. The safety profile of SB2 was assessed in the context of known adverse event profile of US-Remicade, other DMARDs and biologics.

7.3 Major Safety Results

A summary of treatment-emergent adverse events across the controlled studies is found in Table 19 below. Controlled studies include the comparative clinical study SB2-RA in RA patients (54-week, randomized, double-blind period) and PK-bridging study SB2-NHV in healthy subjects. Similar trends in safety were noted for the transition-extension period of study SB2-RA (data not shown).

Table 19. Summary of TEAEs (Controlled Studies)

	Rheumatoid Arthritis Study SB2-RA		Healthy Subjects Study SB2-NHV		
	SB2 3mg/kg (n=290)	EU-Remi 3mg/kg (n=293)	SB2 3mg/kg (n=53)	EU-Remi 3mg/kg (n=53)	US-Remi 3mg/kg (n=53)
TEAEs, n (%)	179(62)	191(65)	27(51)	21(40)	23(43)
SAEs, n (%)	29(10)	31(11)	2(4)	0	0
TEAEs leading to discontinuation, n (%)	30(10)	24(8)	0	0	0
Infections, n (%)	85(29)	110(38)	13(25)	7(13)	6(11)
Malignancies n (%)	2(0.7))	0	0	0	0
AESI	9(3)	7(2)	-	-	-
Infusion-related reactions, n (%)	18(6)	17(6)	0	0	0
Anaphylaxis, n	1(0.3)	1(0.3)	0	0	0
Death, n	0	1(0.3)	0	0	0

Source: FDA analysis of data from SB2 351(k) BLA submission, SB2-NHV CSR Table 14.3.1.2.1, Summary of Clinical Safety Table 2.7.4.2-3, SB2-RA CSR Table 14.3.1-1.2, SB2-RA 78wk CSR Section 12.3.3
AESI-adverse events of special interest (defined as serious infections and tuberculosis). No specific adverse events were classified as AESI for study SB2-NHV
US-Remi: US-licensed Remicade; EU-Remi: EU-approved Remicade; AE: adverse event; SAE: serious adverse event

No new safety signals were identified in the SB2 group compared to the known adverse event profile of the reference product, US-Remicade[1]. Overall, there were no major differences in treatment-emergent adverse events, serious adverse events, and adverse events leading to discontinuations, and deaths between the treatment groups. Infections were the most common adverse event in all treatment groups, SB2, US-Remicade, and EU-Remicade.

One death occurred in the SB2 development program which occurred in the EU-Remicade treatment groups. Cause of death was noted as heart failure. Cases of infusion related reactions including anaphylaxis were balanced between the two groups, with 1 case of anaphylaxis in each group (SB2 and EU-Remicade). Rates of infusion-related reactions and anaphylaxis did not increase following transition from EU-Remicade to SB2.

7.3.1 Deaths

Study SB2-RA
One death was reported in the SB2 clinical program. This was a 71 year old white female in the EU-Remicade treatment group during the randomized, double-blind

[1] FDA-approved Remicade labeling

period. The death was due to severe worsening of the left ventricular heart failure on Day 68. The last administration of study drug prior to death was on Day 43. The left ventricular heart failure was preceded by another SAE of pneumonia.

There were no deaths reported during the transition-extension period.

No deaths occurred in Study SB2-NHV.

7.3.2 Nonfatal Serious Adverse Events

The incidence of serious adverse events (SAEs) was comparable between the SB2 and EU-Remicade treatment groups. Infections were the most common SAE in both groups. The incidence and types of SAEs reported are comparable to what is known for infliximab products.

Study SB2-RA

Randomized, double-blind period

The proportions of subjects who experienced SAEs were comparable between the two treatment groups. A total of 68 serious AEs were reported in 60 (10.3%) subjects for the study; 33 serious TEAEs were reported for 29 (10.0%) subjects in the SB2 treatment group and 35 serious AEs were reported for 31 (10.6%) subjects in the EU Remicade treatment group.

The most frequent SAE's by SOC (system organ class) were infections in both treatment groups, 12 subjects (4%) in the SB2 group and 7 subjects (2%) in the EU-Remicade group, followed by musculoskeletal and connective tissue disorders (3 subjects (1%) in the SB2 group, and 6 subjects (2%) in the EU-Remicade group), and gastrointestinal disorders, 2 subjects (0.7%) in the SB2 and 4 subjects (1%) in the EU-Remicade treatment group.

Transition-Extension Period

The proportion of subjects who experienced SAEs during the transition-extension period was also comparable between the transition treatment groups. A total of 18 SAEs were reported in 16 (4.0%) of the subjects: 8 SAEs in 7 (3.5%) subjects SB2/SB2 treatment group, 7 SAEs in 6 (6.4%) subjects in the EU-Remicade/SB2 treatment group and 3 SAEs in 3 (3.0%) subjects in the EU-Remicade/EU-Remicade treatment group.

Study SB2-NHV

Three SAEs in two subjects in the SB2 treatment group were reported in the single-dose PK study in healthy subjects. One subject had a *Borrelia* infection which was

assessed to be related to study treatment. The other subject had a concussion and a ruptured renal cyst (due to a car accident) which were assessed not to be related to SB2.

7.3.3 Dropouts and/or Discontinuations

Adverse events leading to treatment discontinuation were overall balanced between the two treatment groups, SB2 and EU-Remicade, in both the 54-week, randomized, double-blind period and in the transition extension period (weeks 54-78) of Study SB2-RA.

Study SB2-RA

Randomized, Double-blind Period
A total of 30 (10%) subjects in the SB2 treatment group, and 24 (8%) subjects in the EU-Remicade treatment group experienced AEs that led to treatment discontinuation. The types of AEs were varied. At the PT(preferred term, MedDRA 16.0) level, the TEAEs leading to treatment discontinuation reported in more than 3 subjects in any treatment were latent tuberculosis (2 [0.7%] subjects in the SB2 treatment group and 4 [1.4%] subjects in the EU-Remicade treatment group), RA (4 [1.4%] subjects in the SB2 treatment group only), pneumonia (3 [1.0%] subjects in the SB2 treatment group and 1 event in 1 [0.3%] subject in the EU-Remicade treatment group, respectively) and hypersensitivity (3 events in 3 [1.0%] subjects in the SB2 treatment group only).

Transition-Extension Period
AE's resulting in treatment discontinuation were reported in 3 (1.5%) subjects in the SB2/SB2 treatment group, in 3 (3%) subjects in the EU-Remicade/SB2 treatment group, and in 3 (3%) subjects in the EU-Remicade/EU-Remicade treatment group. Types of AE's were varied and none were reported in more than three subjects.

Study SB2-NHV
No subject was discontinued from the study due to an AE(s) in study SB2-NHV

7.3.4 Significant Adverse Events

The incidence of adverse events of special interest (serious infections and Tb), malignancy, and infusion-related reactions were comparable between the SB2 and EU-Remicade treatment groups.

Study SB2-RA

Adverse events of special interest (AESI)

AESI were comparable between the SB2 and EU-Remicade.

AESI for study SB2-RA were defined in the protocol as serious infections (i.e., an infection that was an SAE) and tuberculosis. If a serious infection or TB was diagnosed, the IP (investigational product, either SB2 or EU-Remicade) was discontinued and appropriate treatment and observation was undertaken. AESI are summarized in Table 20. Serious infections make up most of the AESI. There are two cases of TB, one each in SB2 and EU-Remicade treatment groups, respectively.

Table 20. Adverse Events of Special Interest (Study SB2-RA)

	SB2 (N=290) n(%)	**EU-Remicade (N=293) n(%)**
Any AESI (Serious Infection or TB)	9(3)	7(2)
Pneumonia	3(1)	2(0.7)
Clostridium Difficile Colitis	1(0.3)	0
Pneumonia Bacterial	1(0.3)	0
Pyelonephritis	1(0.3)	0
Soft Tissue Infection	1(0.3)	0
Tuberculosis Pleurisy	1(0.3)	0
Urinary Tract Infection	1(0.3)	0
Cellulitis	0	1(0.3)
Diabetic Foot Infection	0	1(0.3)
Erysipelas		1(0.3)
Pulmonary Tuberculosis		1(0.3)
Wound Infection		1(0.3)

Source:SB2-RA CSR Table 14.3.1-1.6

Tuberculosis

The incidence of active TB was comparable between the two treatment groups: 1 (0.3%) case of tuberculous pleurisy in the SB2 treatment group and 1 (0.3%) case of pulmonary TB in the EU-Remicade treatment group were reported. At Screening, neither of these two subjects with TB had a positive Quantiferon® Gold test or were reported to have latent TB.

All of the subjects with latent TB before Randomization underwent TB prophylaxis according to country-specific TB guidelines; none of them developed active TB later during the study. The proportion of subjects who were reported to have latent TB after randomization were comparable between the 2 treatment groups; 19 (6.6%) subjects in

the SB2 treatment group and 21 (7.2%) subjects in the EU-Remicade treatment group reported a TEAE of latent TB.

Infusion Related Reactions

The incidences of total infusion-related reactions and anaphylaxis, were comparable between the 2 treatment groups.

SB2-RA (Randomized, double-blind period)
Infusion related reactions were reported in a total of 18 (6%) subjects in the SB2 treatment group and 17 (6%) subjects in the EU-Remicade group. There were 5 serious infusion related reactions (i.e., an infusion-related reaction that was an SAE): 2 events of hypersensitivity and 1 event of anaphylactic reaction in 3 (1.0%) subjects in the SB2 treatment group, and 1 event of urticaria and 1 event of anaphylactic shock in 2 (0.7%) subjects in the EU-Remicade treatment. There was 1 serious infusion-related reaction that occurred after a dose increment. This was the anaphylactic reaction in a subject from the SB2 treatment group following 2 steps of dose increment to a dose of 6.0 mg/kg. All of the serious infusion-related reactions were ADA-positive. There were no reported events of serum sickness or delayed hypersensitivity.

Transition Extension Period of SB2-RA (Week 54-78)
A total of 7 (4%) subjects in the SB2/SB2 treatment group, 3 (3%) subjects in the EU-Remicade/SB2 treatment group and 2 (2%) subjects in the EU-Remicade/EU-Remicade treatment group reported infusion-related reactions. There were 2 serious infusion-related reactions (i.e., an infusion-related reaction that was an SAE): 1 event of anaphylactic reaction in 1 (0.5%) subject in the SB2/SB2 treatment group and 1 event of drug hypersensitivity in 1 (1%) subject in the EU-Remicade/SB2 treatment group. No serious infusion-related reaction occurred after a dose increment during the transition-extension period (the anaphylactic reaction occurred at a 6.0 mg/kg dose continued from the double-blind, randomized period). There were no reported events of serum sickness or delayed hypersensitivity. Importantly, there was no increase in the incidence of infusion-related reactions in the patients who underwent a transition from EU-Remicade to SB2.

Discussion of Infusion-Related Reactions

The applicant captured and classified adverse events related to infusion-related reactions (IRRs) as what is generally expected in practice and described in the USPI for US-Remicade. See Section 7.1.2 Categorization of Adverse Events for details. Overall, the applicant's methodology was appropriate. However, since there were no particular set criteria prospectively applied across the program for capturing anaphylaxis, the Agency requested the applicant to provide an assessment of any potential cases of anaphylaxis using the criteria discussed in the statement paper from the Second Symposium on the Definition and Management of Anaphylaxis (Sampson HA et al., J

Allergy Clin Immunol. 2006 Feb;117(2):391-7). Noting that these criteria are designed to prospectively capture potential cases of anaphylaxis, the applicant was asked to provide details on the methodology used to retrospectively query the SB2 safety database.

Results from applicant's retrospective analysis after applying the Sampson's criteria of anaphylaxis identified 3 additional cases of infusion-related reactions: 1 case of mild abdominal pain in the SB2 group, 1 case of mild skin erythema in the EU-Remicade group, and 1 case of mild facial erythema in the EU-Remicade group. All three AEs resolved without any sequelae and the treatment continued without a change in dose. The rest of the cases identified in the retrospective anaphylaxis overlapped with what the applicant presented in the study report as AE's associated with infusion related reactions, captured in Table 19 above. The three additional cases were added to the broad category of infusion-related reactions in this review. The incidence of infusion related reactions reflected in Table 21 includes these 3 additional mild cases. Additional analysis did not impact the conclusions about infusion-related reactions.

Overall, the applicant adequately captured and classified infusion-related reactions, including anaphylaxis. The incidence of infusion-related reactions and anaphylaxis is comparable between SB2 and EU-Remicade treatment groups. Importantly, the incidence of such reactions did not increase after patients transitioned from EU-Remicade to SB2.

Malignancy

SB2-RA

Neoplasms (benign or malignant) were reported in 5 (2%) subjects in the SB2 treatment group and 2 (0.7%) subjects in the EU-Remicade treatment group. The malignancies reported were breast cancer and prostate cancer (each reported for 1 subject in the SB2 treatment group). Benign neoplasms included a benign lung neoplasm, gastrointestinal submuscosal tumor, and hemangioma of the liver reported by 1 subject each in the SB2 treatment group, and a benign salivary gland neoplasm and colon adenoma in 1 subject from the EU-Remicade treatment group. There was one case of "brain neoplasm" reported in the SB2 group, on further investigation, this was a suspected diagnosis as a result of CT/MR brain imaging for epilepsy. As there was no pathological confirmation, it was not considered a neoplasm.

In the transition-extension period, malignancies were reported for 2 subjects in the EU-Remicade/SB2 treatment group treatment group (lip and/or oral cavity cancer and basal cell carcinoma) and 1 subject in EU-Remicade/EU-Remicade treatment group (papillary thyroid cancer). No malignant neoplasms were reported in the SB2/SB2 treatment group.

The incidence and types of malignancies reported are generally expected for the study population and the class of drug.

SB2-NHV

In the single-dose PK study in healthy subjects (study SB2-NHV), there were no reported case of malignancies, tuberculosis infection and infusion-related reaction. There was one case of serious infection (Borrelia infection) in the SB2 treatment group.

LFT Elevation
Elevations in ALT (alanine aminotransferase) and AST (aspartate aminotransferase) were observed in both treatment groups, SB2 and EU-Remicade in study SB2-RA among the common adverse events (AEs) occurring in ≥2% of subjects. See Table 22.

AST increase was comparable in the two treatment groups, reported in 12(4%) of patients in the SB2 group, and 10 (3%) of patients in the EU-Remicade group. ALT increase was reported in more patients in the SB2 group compared to the EU-Remicade group, reported in 23 (8%) and 9 (3%) of patients in the SB2 and EU-Remicade groups, respectively. There was one case drug induced liver injury reported which occurred in the EU-Remicade group prior to week 54. The event was considered a non-serious AE and treatment was discontinued. No cases of Hy's law associated liver injury were reported. Comparable LFT results were seen between the treatment groups in transition-extension period. No cases of Hy's law were reported. AST and ALT results for study SB2-RA are summarized in Table 21.

Table 21. AST and ALT in Study SB2-RA

TEAE Preferred Term	**Study SB2-RA Rheumatoid Arthritis**				
	Randomized, double-blind Period		**Transition-Extension Period**		
	Treatment		**Treatment**		
				EU-Remicade	
	SB2 (n=290) n(%)	EU-Remi (n=293) n(%)	SB2 contd. n=201 n(%)	EURemi→SB2 n=94 n(%)	EURemi→EURemi n=101 n(%)
ALT increase	23 (8)	9(3)	5(3)	4(4)	1(1)
AST increase	12(4)	10(3)	4(2)	4(4)	2(2)

Source: FDA analysis of data from SB2 351(k) BLA submission, Summary of Clinical Safety, Table 2.7.4.2-4, Table 2.7.4.2-8
US-Remi: US-licensed Remicade; EU-Remi: EU-approved Remicade; AE: adverse event

Overall, the types and frequency of liver enzyme elevation AEs were consistent with those reported infliximab products and there was no notable difference in the incidence of elevated liver enzyme-related AEs following transition from EU-Remicade to SB2 in RA subjects compared to the other treatment arms.

7.3.5 Submission Specific Primary Safety Concerns

None. The safety profile of SB2 in this biosimilar clinical development program was evaluated in the context of the known safety profile of the reference product, US-Remicade. Refer to Section 7.3.4 Significant Adverse Events.

7.4 Supportive Safety Results

Common adverse events, reported by >2% of subjects in the controlled studies and the transition-extension period of study SB2-RA are summarized in Table 22 and Table 23 below. In the comparative clinical study SB2-RA in RA, the incidence of treatment-emergent adverse events (TEAS) was similar across both treatment groups, SB2 and EU-Remicade. The proportion of patients reporting TEAEs was similar in both treatment groups across both studies. In study SB2-NHV, single-dose, PK bridging study in healthy volunteers, the number of TEAEs was similar between SB2, US-Remicade and EU-Remicade. The majority of TEAEs were mild to moderate in severity. For further discussion of serious adverse events, see Section 7.3.2 Nonfatal Serious Adverse Events.

In patients with RA, the most frequently reported adverse events in both SB2 and EU-Remicade groups include latent TB, nasopharyngitis, ALT elevation, RA, headache, upper respiratory tract infection. The AEs observed were in line with the expected incidence of AEs for this patient population and this class of medication.

In summary, the incidence and types of common adverse events were similar between treatment arms and were consistent with the known safety profile of US-Remicade. There were no new safety concerns or signals that were identified. Single transition to SB2 from EU-approved Remicade also did not identify any new safety concerns.

7.4.1 Common Adverse Events

SB2-RA

Randomized, double-blind Period
Common adverse events occurring at the Preferred Term (PT) level in ≥2% of patients in the randomized double-blind period of Study SB2-RA are comparable between SB2 and EU-Remicade treatment groups and summarized in Table 22.

Table 22. Common Adverse Events in (≥2%) of Subjects - Study SB2-RA

Rheumatoid Arthritis SB2-RA Randomized, Double-blind Period		
TEAEs By Preferred Term (PT)	**SB2 n=290 n(%)**	**EU-Remicade n=293 n(%)**
Any TEAEs	179(62)	191(65)
Latent Tuberculosis (TB)	19(7)	21(7)
Nasopharyngitis	18(6)	20(7)
ALT increased	23(8)	9(3)
Rheumatoid arthritis	20(7)	11(4)
Headache	16(6)	13(4)
Upper respiratory tract infection	12(4)	11(4)
AST increased	12(4)	10(3)
Bronchitis	9(3)	13(4)
Back pain	7(2)	11(4)
Arthralgia	8(3)	8(3)
Pneumonia	7(2)	8(3)
Urinary tract infection	8(3)	6(2)
Hypertension	5(2)	9(3)
Cough	6(2)	7(2)
Rash	6(2)	6(2)
Pharyngitis	5(2)	7(2)
Pyrexia	3(1)	8(3)
Abdominal pain upper	4(1)	6(2)
Dizziness	2(0.7)	6(2)
Dyspepsia	1(0.3)	7(2)

Source: SB2-RA CSR Table 12-4, Table 14.3.1-1.2

The most frequently occurring AEs by PT (preferred term) levels, occurring in ≥2% of subjects in any treatment group were latent TB, nasopharyngitis and ALT elevations.

In both treatment groups, the most frequently affected AE's by SOC (system organ class) occurring in ≥10% of patients in any treatment group were infections and infestations with 29% of patients in the SB2 and 38% of patients in the EU-Remicade groups, Table 19. The difference in infection rate between the two treatment groups was driven by a small numerical imbalance. There was no product-specific trend for infections in one group compared to the other. Most common infections among both groups were latent TB (7% in SB2, 7% in EU-Remicade), nasopharyngitis (6% in SB2, and 7% in EU-Remicade), upper respiratory infection (4% in SB2 and 4% in EU-Remicade), bronchitis (3% in SB2, and 4% in EU-Remicade), urinary tract infection (3%

in SB2, and 2% in EU-Remicade), pneumonia (2% in SB2, and 3% in EU-Remicade), and pharyngitis (2% in SB2 and 3% in EU-Remicade). Additionally, there were varying types of infections in 1-2 patients occurring in either treatment group, which include 2 cases of herpes zoster in each treatment group, 1 case of TB in each group, 1 case of clostridium difficile colitis in SB2, 1 case of atypical mycobacterial pneumonia in EU-Remicade, 1 case of bacterial pneumonia in SB2, and 1 case of osteomyelitis in EU-Remicade.

Infections, including serious infections, are a well-recognized safety risk with TNF inhibition, including infliximab. The slight numerical imbalance in the incidence of all infections between SB2 and EU-Remicade is not unexpected for the study of this size and design. Further, there was no imbalance in the incidence and types of serious infections, as discussed in subsection Significant Adverse Events above. Overall, the types and rates of infection seen in each treatment group are within the expected range of infections for infliximab products. In that context, the infection rates are comparable between SB2 and EU-Remicade treatment groups.

Transition-extension Period

Common adverse events occurring in ≥2% of patients in the transition-extension period of Study SB2-RA are comparable between all treatment groups and summarized in Table 23. There was no increased incidence of AE's in patients who transitioned from EU-Remicade to SB2 compared to those remained on either SB2 or EU-Remicade alone.

Table 23. Common Adverse Events in (≥2%) of Subjects - Transition-extension Period of Study SB2-RA

Rheumatoid Arthritis SB2-RA Transition Extension Period (Weeks 54-78)			
TEAEs **By Preferred Term (PT)**	**SB2 contd. n=201 n(%)**	**EU-Remicade**	
		EU-Remicade→SB2 n=94 n(%)	**EU-Remicade→ EU-Remicade n=101 n(%)**
Any TEAEs	81(40)	34(36)	36(36)
Latent Tb	11(6)	7(7)	4(4)
Nasopharyngitis	11(6)	2(2)	4(4)
Rheumatoid arthritis	7(4)	2(2)	4(4)
ALT increased	5(3)	4(4)	1(1)
AST increased	4(2)	4(4)	2(2)
Upper respiratory tract infection	1(0.5)	3(3)	5(5)
Bronchitis	5(3)	1(1)	2(2)
Pharyngitis	1(0.5)	2(2)	0
Tonsillitis	0	2(2)	1(1)
Headache	1(0.5)	2(2)	0
Antinuclear antibody positive	0	0	2(2)

Source: Summary of Clinical Safety Table 2.7.4.2-8

Study SB2-NHV

The proportions of subjects who experienced TEAEs were comparable between all three treatment groups, SB2, EU-Remicade and US-Remicade, respectively. Common adverse events occurring in ≥5% of subjects are listed in Table 24. All reported TEAEs were mild or moderate in severity. The most frequent TEAEs by PT were nasopharyngitis and headache.

Table 24. Common Adverse Events (≥5%) of Subjects - Study SB2-NHV

Healthy Subjects SB2-NHV			
TEAEs By Preferred Term (PT)	**SB2 (N=53) n(%)**	**EU-Remicade (N=53) n(%)**	**US-Remicade (N=53) n(%)**
Any TEAEs	27(51)	21(40)	23(43)
Nasopharyngitis	6(11)	4(8)	3(6)
Headache	5(10)	6(11)	7(13)
Diarrhea	3(6)	2(4)	1(2)
Rhinitis	3(6)	2(4)	1(2)
Dry Skin	3(6)	0	1(2)
Source: Study SB2-NHV CSR Table 12-1			

By system organ class (SOC), infections were among the most common AE in Study-NHV. Nasopharyngitis was the most common infection in all treatment groups.

In the SB2-NHV study, a slightly higher trend of infections was noted in the SB2 group compared to EU- and US-Remicade treatment groups, see Table 25. All reported infections were of mild to moderate severity. Although slight numerical differences were observed between the treatment groups, the incidence is within the expected range for infliximab products. Further, limited conclusions can be drawn from this small (n=53 subjects per treatment arm), single-dose study in healthy subjects.

Table 25. SB2-NHV TEAEs - Infections and Infestations

Healthy Subjects SB2-NHV			
TEAEs By SOC Infections and Infestations Preferred Term	**SB2 (N=53) n(%)**	**EU-Remicade (N=53) n(%)**	**US-Remicade (N=53) n(%)**
Infections and Infestations	13(25)	7(13)	6(11)
Nasopharyngitis	6(11)	4(8)	3(6)
Rhinitis	3(6)	2(4)	1(2)
Borrelia infection	1(2)	0	0
Oral herpes	1(2)	1(2)	0
Pharyngitis	1(2)	0	0
Rash pustular	1(2)	0	0
Gastroenteritis	0	0	1(2)
Genital herpes	0	0	1(2)
Source: SB2-NHV 14.3.1.2, Table 14.3.1.2.1			

7.4.2-4 Laboratory Findings, Vital Signs and Electrocardiograms (ECGs)

The distribution of laboratory findings, vital signs and electrocardiogram (ECGs) findings was balanced between the SB2 and EU-approved Remicade groups. No new or unexpected laboratory findings were reported in SB2 clinical program.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies with SB2 have been submitted in the BLA.

7.4.6 Immunogenicity

Assessment of immunogenicity is generally expected as part of the biosimilar development program. See FDA guidance, "Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product".

Therefore, an application submitted under section 351(k) of the PHS Act contains, among other things, information demonstrating that the biological product is biosimilar to a reference product based upon data derived from "a clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product."[1] Immune responses against therapeutic biological products are a concern because they can negatively impact the drug's pharmacokinetics, safety, and efficacy. Unwanted immune reactions to therapeutic biological products are mostly caused by antibodies against the drug (anti-drug antibodies; ADA). Therefore, immunogenicity assessment for therapeutic biological products focuses on measuring ADA. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of ADA (including neutralizing antibodies, NAb) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Infliximab is known to be immunogenic and anti-infliximab antibodies have implications on both safety and efficacy.[2] Immunogenicity was prospectively evaluated in the SB2 development program; the comparative assessment of immunogenicity was one of the secondary objectives of both the clinical phase 1 PK study (SB2-NHV) in healthy subjects and the phase 3 comparative clinical study (SB2-RA) in RA patients. The

[1] Section 351(k)(2)(A)(i)(I) of the PHS Act.
[2] FDA-approved Remicade labeling

incidence of ADAs (anti-drug antibodies) and Nabs (neutralizing antibodies) were the respective immunogenicity endpoints in these studies. Immunogenicity data will be reviewed in this section. For a discussion of the assays used to evaluate immunogenicity, please refer to OBP Review.

Immunogenicity Results

The determination of anti-drug antibodies (ADA) consisted of multi-tiered approach with sequential screening, confirmation, and characterization using validated assays.

Study SB2-RA

In the comparative clinical study SB2-RA, immunogenicity in terms of the incidence of ADA and NAbs was evaluated as a secondary endpoint. Anti-drug antibodies were assessed at sequential time points starting at baseline (screening), and weeks 2, 6, and every 8 weeks until week 54 for the randomized, double-blind period or until week 78 for the transition-extension period. The determination of ADAs in human serum samples was conducted by using a validated Meso Scale Discovery (MSD) platform bridging ligand-binding electrochemiluminescent (ECL) assay. The overall ADA result was defined as positive if the subject had at least one positive ADA result during the study. Serum samples with an ADA-positive result underwent a NAb (neutralizing antibody) assay using a competitive ligand binding (CLB) assay to evaluate the effect of the ADA on the biological activity of infliximab.

Study SB2-RA Weeks 0 to 54

In the randomized, double-blind 54-week period of Study SB2-RA, 291 and 293 RA patients were randomized to the SB2 and EU-approved Remicade treatment groups, respectively. Both treatments were administered as a 3mg/kg intravenous infusion over two hours at weeks 0, 2, 6 and every 8 weeks up to week 46 for the randomized, double-blind period, and up to week 70 for the transition-extension period. Dose increments were allowed from Week 30 by 1.5mg/kg per visit, to a maximum of 7.5 mg/kg.

As shown in Table 26, at Week 30, 158 (55%) subjects in the SB2 treatment group and 145 (50%) subjects in the EU-Remicade treatment group reported an overall ADA-positive result. In terms of NAbs, 146 (92%) subjects in the SB2 treatment group and 130 (90%) subjects in the EU-Remicade treatment group reported positive NAb results among the subjects with overall post-dose ADA-positive results.

At Week 54, 179 (62%) subjects in the SB2 treatment group and 168 (58%) subjects in the EU-Remicade treatment group tested positive for screening ADA at some point. Most of these ADAs were confirmed to be NAbs, 166 (93%) subjects in the SB2 treatment group and 147 (88%) subjects in the EU-Remicade treatment group.

Table 26. Proportion of ADA Positive Patients Following Repeat Dosing in Study SB2-RA (Weeks 0-54)

Rheumatoid Arthritis Study SB2-RA (Weeks 0 through 54)					
		SB2 N=290		EU-Remicade N=293	
		n'	n(%)	n'	n(%)
Screening		290	5(2)	293	7(2)
Week 2		286	10(4)	291	14(5)
Week 6		282	21(7)	286	16(6)
Week 14		274	73(27)	280	63(23)
Week 22		268	121(45)	273	108(40)
Week 30		251	133(53)	264	116(44)
Week 30 Overall[a]	ADA	287	158(55)	292	145(50)
	NAb	158	146(92)	145	130(90)
Week 38		243	123(51)	255	115(45)
Week 46		237	121(51)	231	99(43)
Week 54		223	118(53)	222	89(40)
Week 54 Overall[a]	ADA	287	179(62)	292	168(58)
	NAb	179	166(93)	168	147(88)

ADA: anti-drug Antibody, NAb:Neutralizing Antibody (Proportion of ADA positive patients with a positive Nab)
n'-number of patients with available ADA/NAb results
Source: CSR SB2-G31-RA Table 12-10; Summary of Clinical Pharmacology Table 2.7.24-4
[a]Overall ADA: defined as "positive" for patients with at least one ADA (or NAb) positive up to Week 54 after Week 0

The proportion of patients testing positive for ADA was comparable between SB2 and EU-approved Remicade treatment groups with a slightly higher incidence of ADA in the SB2 group (~5% higher than the EU-Remicade group at various time points). Of note, these differences did not increase over time to indicate different immunogenicity profiles between the products. To further assess any potential impact of these differences on clinically relevant outcomes, the Applicant conducted the additional analyses described below.

Assessment of Impact of Immunogenicity on PK, Safety, and Efficacy Outcomes

To investigate the potential impact of the ADA on comparative clinical outcomes in study SB2-RA, the relationship between ADA, primary efficacy endpoints (ACR20), and select relevant safety outcomes associated with ADA (such as infusion-related reactions) was examined. We acknowledge that such analyses are exploratory in nature and limited by the small sample sizes within subgroups and the non-randomized nature of comparisons, as ADA status is a post-randomization variable and observed differences (or lack thereof) could be attributable to ADA formation or to other confounding variables.

Within each ADA subpopulation there were no notable differences between SB2 and EU-Remicade in infusion-related reactions. As summarized in Table 28, in sub-group analysis evaluating these adverse events up to week 54, the incidence of infusion related reactions was higher in ADA positive patients compared to ADA negative patients with similar rates in both treatment groups. A similar trend was noted in the transition-extension period. These results suggest that ADA formation against SB2 or EU-Remicade had similar impact on clinically-relevant safety.

Table 27. Incidence of Infusion-related Reactions by ADA Status (Study SB2-RA)

TEAE	ADA Subgroup	SB2 (n=290)	EU-Remicade (n=293)
Infusion-related Reaction	ADA positive	15(5%)	12(4%)
	ADA negative	3(1%)	5(2%)
Source: SB2-CSR Section , Listing 14.3.2-1.5, Listing 16.2.9-1.7			

Immunogenicity was assessed at the same time as efficacy endpoint (ACR20) assessment, i.e. at Weeks 30 and 54 in the randomized, double-blind period, and at weeks 78 in the transition-extension period.

ACR20 response was observed in a majority of the patients despite ADA status. ACR20 response was lower in ADA positive patients compared to ADA negative patients; however, it was consistent between the SB2 and EU-approved Remicade groups. Table 29 provides a summary of results from the randomized, double-blind period up to week 54. Similar trends were noted in the transition-extension period. These results suggest that ADA formation against SB2 or EU-approved Remicade had similar impact on clinical efficacy.

Table 28. ACR20 Response by ADA Status (Study SB2-RA, per-protocol set 1)

ADA Subgroup	Treatment	Week 30 n/N (%)	Week 54 n/N (%)
ADA positive	SB2	72/127 (57)	66/117(56)
	EU-Remicade	74/126 (59)	69/106(65)
ADA negative	SB2	76/104 (73)	73/98 (75)
	EU-Remicade	89/121 (74)	81/111 (73)

Source: SB2-RA Table 11-14, Table 14.2-1.5

Since only trough PK samples were collected in the study, serum concentrations were undetectable in significant proportions of patients in both groups, especially in ADA-positive subgroups. Therefore, the PK data from Study SB2-RA are limited to draw meaningful conclusion on the impact of immunogenicity on PK.

Based on the above considerations, the small numerical differences in ADA incidence, did not have a differential impact on clinically relevant endpoints and do not preclude a demonstration of no clinically meaningful differences between the SB2 and EU-Remicade.

Study SB2-RA Transition-Extension Period

To further supplement the immunogenicity assessment of SB2, the Applicant provided immunogenicity data out to Week 78, including immunogenicity in patients undergoing a single transition from EU-Remicade to SB2 compared to that of patients who continued EU-Remicade. At Week 54, a total of 201 subjects from the SB2 treatment group and 195 subjects from the EU-Remicade treatment group were enrolled in the transition-extension period. Patients that were initially randomized to receive EU-Remicade were re-randomized in a 1:1 manner to continue EU-Remicade treatment or transition to SB2. Of 195 subjects who received EU-Remicade during the randomized, double-blind period, 94 subjects were transitioned to SB2 (EU-Remicade→SB2 treatment group**)** and 101 subjects continued on EU-Remicade (EU-Remicade→EU-Remicade treatment group). The 201 subjects who received SB2 during the randomized, double-blind period continued to receive SB2 (SB2 contd. treatment group). Blood samples for determination of immunogenicity were collected at Weeks 54, 62, 70 and 78 (Week 54 is from the randomized, double-blind period). ADA positivity results are summarized in Table 27.

Table 29. Proportion of ADA Positive Patients Following Repeat Dosing in Transition-Extension Period of Study SB2-RA (Weeks 54 through 78)

Rheumatoid Arthritis SB2-RA Transition Extension Period (Weeks 54-78)							
		SB2 contd. N=201		EU-Remicade			
				EU-Remicade→SB2 N=94		EU-Remicade→EU-Remicade N=101	
		n'	n(%)	n'	n(%)	n'	n(%)
Screening Baseline		201	4(2)	94	3(3)	101	0
Extension-period Baseline		198	101(51)	92	31(34)	101	44(44)
Week 62		193	92(48)	94	35 (37)	101	44(44)
Week 70		188	89(47)	91	34(37)	100	42(42)
Week 78		187	88(47)	88	32(36)	94	38(40)
Week 78 Overall[a]	ADA	201	133(66)	94	59(63)	101	61(60)
	NAb	*133*	*126(95)*	*59*	*49(83)*	*61*	*55(90)*
Week 78 Overall[b]	ADA	194	104(54)	94	43(46)	101	51(51)
	NAb	*104*	*95(91)*	*43*	*38(88)*	*51*	*45(88)*

Extension Period Baseline: Extended Study Baseline; Nab: Neutralizing Antibody (Proportion of ADA positive patients with a positive Nab) n'-number of patients with avaiable ADA/NAb results
[a] Overall ADA: defined as "positive" for patients with at least one ADA (or NAb) positive up to Week 78 after Week 0
[b] Overall ADA: defined as "positive" for patients with at least one ADA (or NAb) positive up to Week 78 after Week 54
Source: CSR 78wk SB2-G31-RA Table 12-21; Summary of Clinical Pharmacology Table 2.7.2.4-5

In the transition-extension period, at Week 78, similar proportions of patients tested positive for ADA in all three treatment groups. The proportion of ADA-positive patients who developed NAbs was also comparable between the three groups. Importantly, the ADA rates did not increase differentially between patients who underwent a single transition from EU-Remicade to SB2 as compared with those who continued EU-Remicade or SB2. Consistent with the observations through Week 54, a majority of ADA-positive samples were confirmed to be NAbs.

Study SB2-NHV

In the single-dose PK study SB2-NHV, the only study to directly compare SB2 and US-Remicade, a total of 159 healthy subjects were enrolled and randomized, with 53

subjects in each of the SB2, US-Remicade, and EU-Remicade treatment groups. Blood samples for determination of immunogenicity, in terms of the incidence of ADA and NAbs were collected at Days 0 (pre-dose), 29 and 71 (Weeks 0, 4 and 10, respectively). The products were administered as a single dose 5mg/kg intravenous infusion.

In this study, ADAs were measured using the ECL method similar to the assay used in Study SB2-RA. NAbs were measured using a cell-based method which is different and assessed as less sensitive than the NAb assay (CLB assay) used in the comparative clinical study.

Immunogenicity results from Study SB2-NHV are summarized in Table 30 below. Based on the original analyses by the Applicant, the ADA incidence appeared numerically higher in SB2 treated subjects as compared with both US-Remicade, and EU-Remicade treated subjects. As noted however, these analyses differ slightly from the FDA's additional analyses because the Applicant used a confirmatory cut point with a 99.9% confidence interval for the ADA confirmatory assays as compared with the rate of 99.0%, recommended by the FDA product quality review team. Using the FDA-recommended 99.0% confidence interval cut-point for the confirmatory assay, additional 7 samples were identified to be ADA-positive. FDA analysis includes the additional 7 samples: 1 in the SB2 group, 3 each in EU-Remicade and US-Remicade treatment groups. Based on the additional data, the differences seen in the original analyses appeared to decrease and the proportions of ADA positive healthy subjects at Day 71, was comparable between the three treatment groups; 49% in SB2, 43% each in EU-Remicade and US-Remicade, respectively. To further assess the potential impact of ADA formation on clinically relevant outcomes, the FDA clinical pharmacology team conducted analyses on PK parameters by ADA status and concluded that the formation of ADA did not appear to impact the PK similarity between these three treatment groups.

In terms of NAbs, the overall rates were lower than the ones observed in the repeat dose comparative clinical study SB2-RA, suggesting that the NAb assay in study SB2-NHV may have underestimated the true NAb incidence. Of note, in the FDA analyses, the additional ADA positive samples were not tested for NAbs and were not available for testing.

Table 30. Immunogenicity in Single-dose Study SB2-NHV

Assay	The number (%) of ADA positive subjects at different visits	**PK Study SB2-NHV Healthy Subjects** (5 mg/kg single dose)		
		SB2 (N=53)	EU-Remicade (N=53)	US-Remicade (N=53)
ADA-Applicant analysis	Screening	0	0	0
	Day 29	2 (4%)	0	1 (2%)
	Day 71	25 (47%)	20 (38%)	20 (38%)
ADA – FDA Analysis	Day 71	26 (49%)	23 (43%)	23 (43%)
NAb (NAb+/ADA+)-Applicant analysis	Day 29	1 (50%)	0	0
	Day 71	14 (56%)	14 (70%)	7 (35%)
NAb – FDA Analysis	Day 71	-*		

ADA: anti-drug antibody; NAb: Neutralizing Antibody (Proportion of ADA positive patients with a positive Nab)
-*: NAb were not tested on the additional ADA-positive samples
Source: Summary of Clinical Pharmacology, Table 2.7.2.4-2; FDA analysis of SB2 351(k) submission

Conclusions about Immunogenicity

As noted above, small numerical differences in ADA formation were seen between SB2, EU-Remicade in Study SB2-RA and between SB2, and US-Remicade, and EU-Remicade. In evaluating the significance of the imbalance seen I considered the following:

- The analyses of product quality attributes that could potentially result in higher immunogenicity, such as subvisible particles, support the conclusion that SB2 is highly similar to US-licensed Remicade and confirm the relevance of clinical immunogenicity data from comparative studies using EU-approved Remicade
- The immunogenicity impacted PK similarly between the three products in Study SB2-NHV (the PK data from Study SB2-RA were limited for this assessment as discussed above)
- The differences between the SB2 and EU-Remicade in Study SB2-RA is small and did not increase over time through Week 78
- ADA formation impacted safety and efficacy outcomes similarly between SB2 and EU-Remicade treated patients in the Study SB2-RA
- Importantly, the ADA rates did not increase differentially between patients who underwent a single transition at Week 54 from EU-Remicade to SB2 as compared with those who continued EU-Remicade or SB2.

Based on these considerations, the immunogenicity differences observed in SB2 clinical program, do not represent clinically meaningful differences and do not preclude a demonstration of biosimilarity between SB2 and US-licensed Remicade.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Not applicable.

7.5.2 Time Dependency for Adverse Events

Not applicable.

7.5.3 Drug-Demographic Interactions

No significant safety signals were identified based on drug-demographic interactions.

7.5.4 Drug-Disease Interactions

Not applicable.

7.5.5 Drug-Drug Interactions

Not applicable.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Malignancies, including lymphoma, have been identified as potential risk with US-licensed Remicade and other TNF-inhibitors as described in the Warnings and Precautions section of US-Remicade's USPI. The incidence and types of these malignancies is expected for the study population and treatment.

7.6.2 Human Reproduction and Pregnancy Data

Not applicable.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable.

7.7 Additional Submissions / Safety Issues

The Applicant submitted complete study reports for both studies SB2-RA and SB2-NHV at the time of BLA submission. There were no additional ongoing clinical or post marketing studies. Therefore, there were no additional 120-day safety updates.

8 Postmarket Experience

The Applicant has not submitted any postmarketing data for SB2. At the time of the 120-day safety update (March 2016), there were no ongoing post marketing studies.

9 Appendices

9.1 Literature Review/References

FDA Guidance: Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product

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

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

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

USPI Remicade (infliximab), October 2015

9.2 Labeling Recommendations

Labeling review is ongoing at the time of this review. Key considerations include updating the label to comply with PLLR requirements.

9.3 Advisory Committee Meeting

An advisory committee meeting was not held for this application.

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

/s/

JUWARIA F WAHEED
01/19/2017

NIKOLAY P NIKOLOV
01/19/2017