Cross-Discipline Team Leader Review/ Division Director Summary

Date	*Electronic Stamp Date*
From	Nikolay P. Nikolov, M.D. Badrul A. Chowdhury, M.D., Ph.D.
Subject	Cross-Discipline Team Leader Review Division Director Summary Review
BLA #	351(k) BLA 761054
Applicant	Samsung Bioepis Co., Ltd.
Date of Submission	March 21, 2016, Major Amendment December 9, 2016
Scientific BsUFA Goal Date	January 21, 2017, Extended to April 21, 2017
Proprietary Name (Proposed) / Nonproprietary names	Renflexis SB2[1], infliximab-abda
Dosage Forms / Strength	Sterile lyophilized powder in a 20 mL capacity vial/ 100 mg per vial
Route of Administration	Intravenous
Proposed Indication(s)	• Crohn's Disease (Adult and Pediatric) • Ulcerative colitis (Adult and Pediatric[2]) • Rheumatoid arthritis • Ankylosing spondylitis • Psoriatic arthritis • Plaque psoriasis
Recommended:	*Approval as a biosimilar to US-licensed Remicade for the same indications except for pediatric ulcerative colitis, as Remicade's indication for pediatric ulcerative colitis is protected by orphan drug exclusivity*

1) Introduction

Samsung Bioepis Co., Ltd. (referred to as Samsung or "the Applicant" in the rest of this document) has submitted a biologics license application (BLA) under section 351(k) of the Public Health Service Act (PHS Act) for SB2, a proposed biosimilar to Remicade (infliximab). BLA # 103772 for Remicade was initially licensed by FDA on August 24, 1998, and the BLA

[1] In this document, we generally refer to Samsung's proposed product by the Samsung descriptor "SB2" which was the name used to refer to this product during development. Subsequently, the nonproprietary name for this proposed product was determined to be "infliximab-abda."

[2] This reflects information for SB2 that Samsung submitted in the BLA. We note that Remicade's indication for pediatric ulcerative colitis is protected by orphan drug exclusivity expiring on September 23, 2018. See the Orphan Drug Designations and Approvals database at http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm. Accordingly, FDA will not license SB2 for this indication until the orphan drug exclusivity expires.

is currently held by Janssen Biotech, Inc. US-licensed Remicade is the reference product for Samsung's 351(k) BLA. Samsung is seeking licensure of SB2 for the same indications as US-licensed Remicade:[3]

1) Crohn's Disease (CD):
   - reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely 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.
2) Pediatric Crohn's Disease (pediatric CD):
   - 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.
3) 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.
4) Pediatric Ulcerative Colitis (pediatric UC):
   - 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.[4]
5) Rheumatoid Arthritis (RA) in combination with methotrexate:
   - reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis.
6) Ankylosing Spondylitis (AS):
   - reducing signs and symptoms in patients with active ankylosing spondylitis.
7) 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.
8) Plaque Psoriasis (PsO):
   - 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.

Although the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) is the lead division for this application and provided the written clinical review, clinical input pertaining to their respective indications was obtained from the Division of Gastroenterology

[3] Remicade USPI
[4] This indication 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.

and Inborn Errors Products (DGIEP), and the Division of Dermatology and Dental Products (DDDP) during the course of the review.

The application consists of:

- Extensive analytical data intended to support (i) a demonstration that SB2 and US-licensed Remicade are highly similar, (ii) a demonstration that SB2 can be manufactured in a well-controlled and consistent manner, leading to a product that is sufficient to meet appropriate quality standards and (iii) a justification of the relevance of comparative data generated using the European Union (EU)-approved Remicade to support a demonstration of biosimilarity of SB2 to US-licensed Remicade.

- A single-dose pharmacokinetic (PK) study (Study SB2-G11-NHV) providing a 3-way comparison of SB2, US-licensed Remicade, and EU-approved Remicade intended to (i) support PK similarity of SB2 and US-licensed Remicade and (ii) provide a PK bridge to support the relevance of the comparative data generated using EU-approved Remicade to support a demonstration of the biosimilarity of SB2 to US-licensed Remicade.

- A comparative clinical study (Study SB2-G31-RA) between SB2 and EU-approved Remicade in patients with RA to support a demonstration of no clinically meaningful differences in terms of safety, purity, and potency. This was a 54-week, randomized, double-blind, parallel group study conducted in 584 patients with moderate to severely active RA on background methotrexate (MTX). Subjects were randomized 1:1 to SB2 or EU-approved Remicade at a dose of 3 mg/kg through a 2-hr intravenous (IV) infusion at Weeks 0, 2, 6, and every 8 weeks thereafter, and remained on the background of methotrexate (MTX) throughout the study. At Week 54, patients treated with EU-approved Remicade were randomized to undergo a single transition to SB2 or continue on EU-approved Remicade up to Week 78.

- A scientific justification for extrapolation of data to support biosimilarity in each of the additional indications for which Samsung is seeking licensure, specifically Crohn's disease, pediatric Crohn's disease, ulcerative colitis, pediatric ulcerative colitis,[5] ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis.

Samsung submitted comparative analytical data on the SB2 lots used in clinical studies intended to support a demonstration of biosimilarity ("clinical product lots") and on the proposed commercial product. Based on our review of the data provided, Samsung's comparative analytical data for SB2 demonstrates that SB2 is highly similar to US-licensed Remicade notwithstanding minor differences in clinically inactive components.

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

Samsung used a non-US-licensed comparator (EU-approved Remicade) in some studies intended to support a demonstration of biosimilarity to US-licensed Remicade. Accordingly, Samsung provided scientific justification for the relevance of data from those studies to support a demonstration of biosimilarity of SB2 to US-licensed Remicade by establishing an adequate scientific bridge (analytical and PK) between EU-approved Remicade, US-licensed Remicade, and SB2.

The results of the comparative clinical efficacy, safety, immunogenicity, and PK studies indicate that Samsung's data support a demonstration of "no clinically meaningful differences" between SB2 and US-licensed Remicade in terms of safety, purity, and potency in the indications studied. Further, the single transition from EU-approved Remicade to SB2 during the second part of Study SB2-G31-RA in RA did not result in different safety or immunogenicity profiles. This would support the safety of a clinical scenario where non-treatment naïve patients may undergo a single transition to SB2.

In considering the totality of the evidence, the data submitted by Samsung support a demonstration that SB2 is highly similar to US-licensed Remicade, notwithstanding minor differences in clinically inactive components, and support a demonstration that there are no clinically meaningful differences between SB2 and US-licensed Remicade in terms of the safety, purity, and potency of the product, in the studied indication of RA.

The Applicant has also provided an extensive data package to address the scientific considerations for the extrapolation of data to support biosimilarity in other conditions of use and potential licensure of SB2 for each of the indications for which US-licensed Remicade is currently licensed and for which Samsung is seeking licensure.[6]

2) Background

The BPCI Act

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) was signed into law on March 23, 2010. The BPCI Act created an abbreviated licensure pathway for biological products shown to be "biosimilar" to or "interchangeable" with an FDA-licensed biological product (the "reference product"). This abbreviated licensure pathway under section 351(k) of the PHS Act permits reliance on certain existing scientific knowledge about the safety and effectiveness of the reference product, and enables a biosimilar biological product to be licensed based on less than a full complement of product-specific nonclinical and clinical data.

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

Section 351(i) of the PHS Act defines the terms "biosimilar" or "biosimilarity" to mean that "the 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 biological product and the reference product in terms of the safety, purity, and potency of the product." A 351(k) application must contain, among other things, information demonstrating that the proposed product is biosimilar to a reference product based upon data derived from analytical studies, animal studies, and a clinical study or studies, unless FDA determines, in its discretion, that certain studies are unnecessary in a 351(k) application (see section 351(k)(2) of the PHS Act).

Development of a biosimilar product differs from development of a biological product intended for submission under section 351(a) of the PHS Act (i.e., a "stand-alone" marketing application). The goal of a "stand-alone" development program is to demonstrate the safety, purity and potency of the proposed product based on data derived from a full complement of clinical and nonclinical studies. The goal of a biosimilar development program is to demonstrate that the proposed product is biosimilar to the reference product. While both stand-alone and biosimilar product development programs generate analytical, nonclinical, and clinical data, the number and types of studies conducted will differ based on differing goals and the different statutory standards for licensure.

To support a demonstration of biosimilarity, FDA recommends that applicants use a stepwise approach to developing the data and information needed. At each step, the applicant should evaluate the extent to which there is residual uncertainty about the biosimilarity of the proposed product to the reference product and identify next steps to try to address that uncertainty. The underlying presumption of an abbreviated development program is that a molecule that is shown to be structurally and functionally highly similar to a reference product is anticipated to behave like the reference product in the clinical setting(s). The stepwise approach should start with extensive structural and functional characterization of both the proposed biosimilar product and the reference product, as this analytical characterization serves as the foundation of a biosimilar development program. Based on these results, an assessment can be made regarding the analytical similarity of the proposed biosimilar product to the reference product and, once the applicant has established that the proposed biosimilar meets the analytical similarity prong of the biosimilarity standard, the amount of residual uncertainty remaining can be assessed with respect to both the structural/functional evaluation and the potential for clinically meaningful differences. Additional data, such as nonclinical and/or clinical data, can then be tailored to address these residual uncertainty(-ies).

The 'totality of the evidence' submitted by the applicant should be considered when evaluating whether an applicant has adequately demonstrated that a proposed product meets the statutory standard for biosimilarity to the reference product. Such evidence generally includes structural and functional characterization, animal study data, human PK and, if applicable, pharmacodynamics (PD) data, clinical immunogenicity data, and other clinical safety and effectiveness data.

Reference Product

In general, an applicant needs to provide information to demonstrate biosimilarity based on data directly comparing the proposed product with a reference product. When an applicant's proposed biosimilar development program includes data generated using a non-US-licensed comparator to support a demonstration of biosimilarity to the US-licensed reference product, the applicant should provide adequate data or information to scientifically justify the relevance of these comparative data to an assessment of biosimilarity and establish an acceptable bridge to the US-licensed reference product.

Relevant Regulatory History

The first interaction between Samsung and the FDA on the SB2 development program occurred at a Biosimilar Biological Product Development (BPD) meeting held on February 14, 2012 with follow up interactions to include a BPD Type 4 meeting held on December 14, 2015. Additional interactions occurred to discuss the initial Pediatric Study Plan (iPSP). During the pre-submission interactions, FDA provided product quality, nonclinical, and clinical comments, including recommendations to the Applicant regarding clinical development, such as:

- Design, endpoints, and selection of the similarity margin for the comparative clinical study in RA.
- Assessment of safety and immunogenicity in the setting of patients who undergo a single transition from EU-approved Remicade to SB2 to provide a descriptive comparison with patients who continue on EU-approved Remicade in the RA comparative clinical study.
- Demonstration of PK similarity between SB2, US-licensed Remicade, and EU-approved Remicade.
- Expectations for the scientific justification for extrapolation of biosimilarity.

At the BPD Type 4 meeting, general agreement was reached on the proposed format and content of the BLA, including the Agency's expectation for the information needed to support a demonstration of biosimilarity and extrapolation of clinical data to support the demonstration of biosimilarity for each indication for which licensure is sought.

3) CMC/Product Quality

CMC Reviewer: Xianghong Jing, Ph.D. (for drug substance) and Timothy Wadkins, PhD (for drug product);
CMC Statistical Reviewer: Yu-Ting Weng, Ph.D.; CMC Statistical Supervisor: Yi Tsong, Ph.D.;
Immunogenicity Reviewer: William Hallett, Ph.D.;
Microbiology Reviewers: Bo Chi, Ph.D. (for drug substance) and Jessica Hankins, Ph.D. (for drug product); Acting Branch Chief: Colleen Thomas, Ph.D.;
Facilities Reviewer: Wayne Seifert; Facilities supervisory Consumer Safety Officer: Zhihao (Peter) Qiu, Ph.D.

OBP Labeling: Jibril Abdus-Samad, Pharm.D.
OBP Director: Steven Kozlowski, M.D.
Application Technical Lead: Christopher Downey, Ph.D.

- **General product quality considerations**

SB2 (infliximab-abda) is a chimeric human/mouse IgG1 monoclonal antibody. It consists of 1328 amino acids and has a molecular weight of approximately 149.1 kDa. The SB2 drug substance (DS) manufacturing process involves (b) (4) resulting in highly purified SB2 DS. All drug substance lots were manufactured at (b) (4). The stability data support an SB2 DS expiration dating period of (b) (4) months when stored at (b) (4) C.

SB2 drug product (DP) is a sterile, white, lyophilized concentrate for intravenous injection in a single-use, 20 mL vial. Lyophilized SB2 DP is reconstituted with 10 mL of sterile water for injection (WFI) to yield a single dose formulation of 10 mg/mL infliximab-abda at pH 6.2, and is further diluted in 0.9% sodium chloride solution for infusion. SB2 DP does not contain preservatives. The SB2 DP is manufactured in (b) (4). The stability data support SB2 DP expiration dating period of 30 months when stored between 2ºC and 8ºC.

The SB2 final DS and DP processes are fully validated, and the manufactured product is of a consistent quality. The controls that have been established for the routine manufacture of SB2 DS and SB2 DP meet regulatory requirements. However, the product quality review team recommends, and we agree with, the following post-marketing commitments (PMCs):

1. Implement the reducing CE-SDS purity test into the Drug Substance and Drug Product release and stability specifications.
2. Implement a test for FcγRIIIa binding affinity into the Drug Substance Release specification.

During the review cycle, additional microbiology information was submitted. This constituted a major amendment resulting in 3-month extension of the review and BsUFA goal dates. The Division of Microbiology Assessment review teams concluded, and we concur, that the DS and the DP are recommended for approval from a quality microbiology perspective with several post-marketing commitments (PMCs), as detailed in the section on Recommendation for other Postmarketing Requirements and Commitments at the end of this document.

- **Analytical Similarity Assessment**

To determine whether SB2 is highly similar to US-licensed Remicade, and to establish the adequacy of the analytical portion of the scientific bridge between SB2, US-licensed Remicade, and EU-approved Remicade, Samsung evaluated and compared analytical data from multiple lots of each of the three products. The FDA performed confirmatory statistical

analysis of the submitted data. All methods were validated or qualified prior to the time of testing and demonstrated to be suitable for intended use.

Samsung's analytical comparison of multiple lots of SB2, US-licensed Remicade, and EU-approved Remicade included comparison of the following attributes:

- Amino acid sequence/primary structure
- TNF-α binding and neutralization
- Fc-mediated *in vitro* biological activities (bioactivities)
- Fc receptor binding affinity
- Additional *in vitro* bioactivities (membrane TNF-α binding, reverse signaling, regulatory macrophage induction)
- Purity
- Protein content
- Physicochemical attributes
- High Molecular Weight Variants/Aggregates
- Higher order structure
- Sub-visible particles

Samsung's analytical comparisons of the above attributes support a demonstration that SB2 is highly similar to US-licensed Remicade and support the scientific bridge between SB2, US-licensed Remicade, and EU-approved Remicade

TNF-α binding and neutralization, the main mechanism of action of infliximab products, were assessed by a TNF-α binding assay using FRET and the TNF-α neutralization assay using an NF-κB reporter gene.

The product quality team concluded, and we agree, that the data from the TNF-α binding FRET assay, and the TNF-α neutralization report gene assay met the criteria for statistical equivalence between SB2, US-licensed Remicade, and EU-approved Remicade supporting a demonstration that SB2 is highly similar to US-licensed Remicade. These data also support, in part, the scientific bridge to justify the relevance of the data obtained using EU-approved Remicade in the clinical study, SB2-G31-RA.

Additional potential mechanisms of action have been proposed for infliximab in the scientific literature. These include antibody dependent cell-mediated cytotoxicity (ADCC) against cells expressing membrane-bound TNF-α (mTNF-α), complement dependent cytotoxicity (CDC) against mTNF-α positive cells, "reverse signaling" (signal transduction into cells by activation mTNF-α), and induction of regulatory macrophages in mucosal healing. To the extent these potential mechanisms of action are relevant for infliximab, it is likely that the relative role for each of these mechanisms differs between indications. The Applicant conducted functional assays to assess similarity between SB2, US-licensed Remicade, and EU-approved Remicade with regard to each of these potential mechanisms. In each case, the results were similar and met pre-determined similarity criteria between SB2, US-licensed Remicade, and EU-approved Remicade.

Each protein biochemistry and biological activity attribute met the pre-determined criteria for the pairwise comparisons between SB2, US-licensed Remicade, and EU-approved Remicade, with the following exceptions:

- FcγRIIIa binding affinity did not meet pre-determined similarity criteria for one of the orthogonal assays utilized (Alphascreen assay for binding to FcγRIIIa-expressing NK cells)
- High-molecular weight (HMW) species
- Percent basic product-related variants
- Percent non-glycosylated heavy chain
- Percent charged glycans

Additionally,

- FcRn binding affinity met pre-defined acceptance criteria for the SB2 to US-licensed Remicade comparison but not for the SB2 to EU-approved Remicade comparison,
- C1q binding affinity met pre-defined acceptance criteria for the SB2 to EU-approved Remicade comparison but not for the SB2 to US-licensed Remicade comparison.

In each of these cases, the differences were modest and the impact of the slight differences in the attributes and resulting residual uncertainty was adequately mitigated by additional information and analysis provided by the Applicant:

- In the cases of FcγRIIIa binding affinity, percent basic variants, percent non-glycosylated heavy chain, percent charged glycans, and C1q binding affinity, functional assays that assess biological activity known to be influenced by the listed physicochemical attributes were evaluated in each case. The data from the functional assays all demonstrated that the modest potential differences suggested by physicochemical testing do not correspond to a change in product bioactivity or function. Basic variants were isolated, identified, characterized, and found to have no impact on function. FcγRIIIa binding affinity, percent basic variants, and percent non-glycosylated heavy chain are each controlled by in-process or lot release tests with acceptance criteria sufficiently stringent to assure that these attributes will remain in the range that yielded similar functional assay results in the analytical similarity assessment.
- In the case of high-molecular weight (HMW) species, additional characterization data support that the HMW species observed by size exclusion chromatography are non-covalent and reversible. Stability data demonstrate that the slightly higher levels for SB2 (0.6 – 0.9% versus ≤ 0.5 % for US-licensed and EU-licensed Remicade) do not impact product stability or lead to excessive sub-visible particle formation. All protein therapeutics contain HMW species at varying levels, and SB2 is a highly (>99%) pure product with respect to HWM variants.
- In the case of FcRn binding affinity, the magnitude of difference between SB2 and EU-approved Remicade was negligible. FcRn binding is linked to circulating half life *in vivo*, and there was no significant difference between the SB2 and EU-approved Remicade in pharmacokinetics studies.

Based on the above considerations, the product quality team concluded, and we agree, that the totality of analytical similarity data supports a demonstration that SB2 is highly similar to US-

licensed Remicade, notwithstanding minor differences in clinically inactive components, and supports the scientific bridge between the three products to justify the relevance of comparative data generated from the clinical study that used EU-approved Remicade, to support a demonstration of biosimilarity of SB2 to US-licensed Remicade.

- **Facilities review/inspection**

FDA's Office of Process and Facilities (OPF) conducted an assessment of the manufacturing facilities for this BLA. A pre-approval inspection (PAI) of the DS manufacturing facility at (b) (4) was conducted on (b) (4). The outcome of the inspection was No Action Indicated (NAI). The PAI of DP site at (b) (4)) was conducted on (b) (4) with a Voluntary Action Indicated (VAI) recommendation. The PAI of the site where the analytical similarity studies were performed and that will perform several in-process tests for commercial manufacture was conducted at Samsung Incheon on Aug 16-19, 2016 with a VAI recommendation. The OPF team recommended that BLA 761054 be approved from the standpoint of facilities assessment. We concur with this recommendation.

4) Nonclinical Pharmacology/Toxicology

Pharmacology/Toxicology Reviewer: Andrew Goodwin, Ph.D.
Pharmacology/Toxicology Team Leader: Timothy W. Robison, Ph.D.

The SB2 nonclinical development program was considered adequate to support clinical development. The pharmacology-toxicology review 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. In the study with Tg197 mice, SB2, US-licensed Remicade, and EU-approved Remicade each demonstrated comparable, dose-dependent increases in body weight gain as well as efficacy measured by Arthritis Score or Histopathological Score. At 10 mg/kg, SB2 exposure was comparable to that of the EU-approved Remicade and US-licensed Remicade groups. The significance of the single-dose pharmacokinetic study in Sprague-Dawley rats was uncertain due to the fact that the rat is not a pharmacologically relevant species for SB2, US-licensed Remicade, or EU-approved Remicade (e.g., no binding to rat TNFα). Respectively, repeat dose toxicology studies were not conducted as there are no pharmacologically relevant species in which to conduct a general toxicology assessment of SB2, EU- approved Remicade, and US-licensed Remicade. This was agreed upon in pre-submission communications with the Agency.

In summary, the animal studies submitted, demonstrate the similarity of SB2 to US-licensed Remicade in terms of the nonclinical pharmacology and pharmacokinetics data. The Pharmacology and Toxicology team concluded, and we agree, that the results of these animal

studies can be taken together with the data from the analytical bridging studies (refer to the CMC section of this document for details) to support a demonstration that SB2 is biosimilar to US-licensed Remicade. No residual uncertainties have been identified by this discipline.

5) Clinical Pharmacology/Biopharmaceutics

Clinical Pharmacology Reviewer: Lei He, Ph.D.
Clinical Pharmacology Team Leader: Anshu Marathe, Ph.D.

- **General clinical pharmacology/biopharmaceutics considerations**

The objectives of the SB2 clinical pharmacology program were to evaluate the pharmacokinetic similarity between SB2 and US-licensed Remicade, and to support 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 to support a demonstration of the biosimilarity of SB2 to US-licensed Remicade.

The clinical development for SB2 relevant to the submission in the United States (US) included two clinical studies, and the key design features of the studies are summarized in Table 1. Pharmacokinetic (PK) similarity of SB2 to US-licensed 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-G11-NHV). PK and immunogenicity were also assessed for SB2 and EU-approved Remicade in patients with active rheumatoid arthritis (RA) in Study SB2-G31-RA (n=325 for PK, n=584 for immunogenicity).

Table 1. Key Design Features of SB2 Clinical Studies

Study	Objective	Design	Subjects	Treatments
PK Similarity Study				
SB2-G11-NHV	3-way PK similarity, safety, immunogenicity	R, PG, SD, 3-way PK bridging	159 Healthy Subjects	5 mg/kg IV: • SB2 • US-Remicade • EU-Remicade
Comparative Clinical Study				
SB2-G31-RA	Efficacy, safety, immunogenicity in RA	R, DB, PG Re-randomized at Week 30 to either continue EU-Remicade or transition to SB2	584 Patients with RA who had an inadequate response to MTX	3 mg/kg IV+MTX at Weeks 0, 2 and 6, then every 8 weeks: • SB2 • EU-Remicade

R: randomized; PG: parallel group; SD: single dose; DB: double-blind; RA: rheumatoid arthritis; SC: subcutaneous; MTX: methotrexate

In the pivotal PK study, Study SB2-G11-NHV, 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% as shown in Table 2. These pairwise comparisons met the pre-specified criteria for PK similarity between SB2, US-licensed Remicade, and EU-approved Remicade. Thus, PK similarity was established between SB2 and the US-licensed Remicade and a PK bridge was established to support the relevance of the data generated using EU-approved Remicade in the comparative clinical efficacy study (Study SB2-G31-RA). In Study SB2-G31-RA, serum trough concentrations were assessed at Weeks 2, 6, 14, 22 and 30. Due to the relatively short half-life of the products and limited pre-dose Ctrough sampling, the PK data from this study is limited.

Table 2. Statistical Analysis for PK Parameters (SB2-G11-NHV)

Comparison	Parameter	GMR%	90% CI (%)
SB2 vs US-licensed Remicade	Cmax	98.01	(93.77, 102.52)
	AUC0-t	97.45	(89.58, 106.02)
	AUC0-inf	97.18	(88.52, 106.67)
SB2 vs EU-approved Remicade	Cmax	100.23	(95.96, 104.69)
	AUC0-t	98.69	(90.61, 107.48)
	AUC0-inf	97.85	(88.82, 107.79)
EU-approved Remicade vs US-licensed Remicade	Cmax	97.82	(93.48, 102.36)
	AUC0-t	98.74	(91.52, 106.53)
	AUC0-inf	99.31	(90.97, 108.42)
Source: FDA analysis of data from Samsung 351(k) BLA submission			

The Office of Clinical Pharmacology (OCP) has determined that PK similarity has been demonstrated between SB2 and US-licensed Remicade and that the PK data supported the scientific bridge justifying the relevance of the comparative data generated using EU-approved Remicade to support a demonstration of the biosimilarity of SB2 and US-licensed Remicade. The OCP has concluded that the clinical pharmacology results from the SB2 program add to the totality of evidence to support a demonstration of no clinically meaningful differences between SB2 and US-licensed Remicade. We concur with this assessment. The PK studies have not raised any new uncertainties and the clinical pharmacology data support a demonstration of biosimilarity between SB2 and US-licensed Remicade.

6) Clinical Microbiology

Not applicable.

7) Clinical/Statistical-Efficacy

Primary Statistical Reviewer: Ginto Pottackal, Ph.D.
Statistical Team Leader: Gregory Levin, Ph.D.
Primary Clinical Reviewer: Juwaria Waheed, M.D.
Clinical Team Leader: Nikolay Nikolov, M.D.

Overview of the Clinical Program

To support the demonstration of no clinically meaningful differences between SB2 and US-licensed Remicade, in addition to the PK similarity study in healthy volunteers (Study SB2-G11-NHV) discussed in the section on Clinical Pharmacology above, Samsung submitted clinical safety, immunogenicity, and efficacy data from one comparative clinical study (SB2-G31-RA) in patients with RA, described in detail in this section below. The key design features of these studies are summarized in Table 1 above. Of note, the comparative clinical efficacy data in SB2-G31-RA were derived using EU-approved Remicade as the comparator. However, Samsung provided sufficient analytical and clinical PK bridging data (Study SB2-G11-NHV) between SB2, US-licensed Remicade, and EU-approved Remicade to justify the relevance of the comparative data generated using EU-approved Remicade in Study SB2-G31-RA to support a demonstration of no clinically meaningful differences between SB2 to US-licensed Remicade.

Study SB2-G31-RA was a randomized, double blind, parallel group, multicenter comparative clinical study to evaluate the efficacy, safety, pharmacokinetics, and immunogenicity of SB2 compared to EU-approved Remicade in subjects with moderate to severe RA despite MTX therapy. The study was conducted in approximately 80 investigator sites in Europe, Philippines, and South Korea. The study consisted of two distinct periods:

1) Randomized double blind period up to Week 54 to either SB2 or EU-approved Remicade. A total of 584 subjects with moderate to severe RA were randomized in a 1:1 ratio to receive SB2 3 mg/kg or EU-approved Remicade 3 mg/kg via a 2 hour (h) intravenous (IV) infusion, at Weeks 0, 2, and 6, and then every 8 weeks until 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.
2) Transition extension period between Weeks 54 and 78 where patients originally randomized to the EU-approved Remicade group remained in the study and were re-randomized in a 1:1 ratio to transition to SB2 or continue on EU-approved Remicade. Subjects originally randomized to the SB2 arm continued the same treatment in this stage. There were 201 subjects in the SB2 arm and 195 subjects in the EU-Remicade arm at the start of the transition period. The 195 subjects in the EU-approved Remicade arm were re-randomized to SB2 (94 subjects) or EU-approved Remicade (101 subjects). Study objectives in this period were to compare the long-term safety, tolerability, immunogenicity and efficacy of SB2 in subjects with RA who transitioned from EU-approved Remicade treatment to SB2 to subjects who maintained the EU-approved Remicade treatment.

Treatment groups were balanced with respect to demographics and disease characteristics.

The primary endpoint of the study was the proportion of patients who remained in the study and achieved an American College of Rheumatology 20% (ACR20) response at Week 30. This endpoint is considered sufficiently sensitive for the assessment of similarity in clinical efficacy. Further, the similarity margin has been informed by information from the published literature. As shown in Table 3, the proportion of patients who achieved an ACR20 response at Week 30 was similar between SB2 and EU-approved Remicade, and contained within the similarity margin of [−12%, +12%] recommended by FDA. The ACR20 response probabilities over time comparing the two treatments up to Week 30 also supported similarity (data not shown).

Table 3. Analysis of ACR20 Response Rate at Week 30, Study SB2-G31-RA

	n/N	**%**	**Adjusted Difference Rate**	**90% CI**	**95% CI**
Primary analysis of ACR20 response rate at Week 30 (Per-protocol Set)					
SB2 (N=231) **EU-Remicade (N=247)**	148/231 163/247	(64.1%) (66.0%)	−1.88%	(-8.91, 5.16)	(-10.26, 6.51)
Analysis of ACR20 response rate at Week 30 (Full Analysis Set)					
SB2 (N=290) **EU-Remicade (N=293)**	161/290 173/293	(55.52%) (59.04%)	-2.95%	(-9.60, 3.70)	(-10.87, 4.97)

Source: FDA analysis of data from SB2 351(k) BLA submission

ACR20 response rate at Week 54 was also similar between the two treatment groups (data not shown). The comparative analyses of secondary endpoints, such as ACR components, HAQ-DI scores, DAS28, and ACR-N also showed similar efficacy between the two treatment groups (data not shown).

Up to Week 30, 78 (13.4%) patients had withdrawn from the study: 44 patients (15.4%) from the SB2 treatment group and 34 patients (11.6%) from the EU-approved Remicade treatment group with similar distributions of reasons for early withdrawal. To assess the impact of the high rates of treatment discontinuation and missing data in Study SB2-G31-RA, the FDA statistical team conducted tipping point sensitivity analyses. The results from these analyses largely support the findings of the key efficacy analyses in Study SB2-G31-RA.

The design, conduct, and within-group response rates of Study SB2-G31-RA were largely similar to those characteristics in historical clinical trials that demonstrated relatively large and consistent treatment effects of infliximab over placebo. Therefore, the totality of available information supports the sufficiency of the assay sensitivity of Study SB2-G31-RA, in addition to the constancy assumption. The FDA's analyses were consistent with those conducted by the Applicant.

The FDA statistical review team concluded, and we concur, that the totality of the evidence from the comparative clinical study SB2-G31-RA supports a demonstration of no clinically meaningful differences between SB2 and US-licensed Remicade.

- **Discussion of statistical and clinical efficacy reviews with explanation for CDTL's conclusions**

In summary, the Applicant has provided statistically robust comparative clinical data demonstrating similar efficacy between SB2 and US-licensed Remicade in patients with moderate-to-severe RA despite methotrexate in Study SB2-G31-RA. The primary analyses were supported by the analyses of key secondary endpoints and sensitivity analyses accounting for missing data. The FDA statistical and clinical teams concluded, and we agree, that the results from Study SB2-G31-RA support a demonstration of no clinically meaningful differences between SB2 and US-licensed Remicade.

- **Includes discussion of notable efficacy issues both resolved and outstanding**

None.

8) Safety

Primary Clinical Reviewer: Juwaria Waheed, M.D.
Clinical Team Leader: Nikolay Nikolov, M.D.
OBP Immunogenicity Reviewer: William Hallett, Ph.D.

- **Studies contributing to safety analyses**

The primary safety data were derived from one comparative clinical study in 584 patients with moderate-to-severe RA (Study SB2-G31-RA). In Period 2 of the study at Week 54, a total of 94 subjects underwent a single transition from EU-approved Remicade to SB2 to assess additional risks, if any, in safety and immunogenicity resulting from a single transition from EU-approved Remicade to SB2 to address the safety of the clinical scenario where non-treatment naïve patients transition to SB2. Of note, Study SB2-G31-RA used EU-approved Remicade. To justify the relevance of comparative data, including safety data, generated using EU-approved Remicade to support a demonstration of the biosimilarity of SB2 to US-licensed Remicade, Samsung provided robust comparative analytical data and clinical PK bridging data (Study SB2-G11-NHV). Supportive safety and immunogenicity information was also provided from one single dose PK study in healthy subjects (Study SB2-G11-NHV). The safety and immunogenicity data were reviewed for each individual study. Overall, the safety database is adequate to provide a reasonable comparative safety assessment to support a demonstration of no clinically meaningful differences between SB2 and US-licensed Remicade.

- **General discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests.**

Overall, there were no major differences in adverse events (AEs), serious adverse events (SAEs), or AEs leading to discontinuations between the treatment groups. Infections were the most common AE in all treatment groups (SB2, US-licensed Remicade, and EU-approved Remicade). Adverse events leading to discontinuation were infrequent and balanced between treatment arms. Reports of hypersensitivity and injection site reactions were balanced between treatment arms with a single case of anaphylaxis in each treatment arm in Study SB2-G31-RA. An overview of AEs across the controlled studies is summarized in Table 4. No new safety signals were identified in the SB2 group compared to the known adverse event profile of US-licensed Remicade, as described in the FDA-approved labeling for Remicade.[7]

Table 4. Overview of Deaths, SAEs, and Events of Interest in SB2 Clinical Program

	Rheumatoid Arthritis Study SB2-RA		**Healthy Subjects Study SB2-NHV**		
	SB2 3mg/kg (n=290)	EU-Remicade 3mg/kg (n=293)	SB2 3mg/kg (n=53)	EU-Remicade 3mg/kg (n=53)	US-Remicade 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
AESI-adverse events of special interest (defined as serious infections and tuberculosis). No specific adverse events were classified as AESI for study SB2-NHV
AE: adverse event; SAE: serious adverse event

Death

One death was reported in the SB2 clinical program. This was a 71 year old white female in the EU-approved Remicade treatment group. The death was due to severe worsening of 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-G11-NHV.

[7] FDA-approved Remicade labeling

Nonfatal Serious Adverse Events (SAE)

The proportion of patients who experienced at least one SAE was similar between the treatment groups during the controlled period of clinical studies as detailed in Table 4 above. The most frequently reported SAEs were infections which were overall similar between the treatment groups. SAEs across the system organ classes (SOCs) showed a similar distribution with minor numerical differences between each group. There was no notable difference in the incidence of SAEs following a single transition in Period 2 from EU-approved Remicade to SB2 in Study SB2-G31-RA. The different SOCs of SAEs or the pattern of SAEs in the SB2 clinical program were consistent with the known safety profile of US-licensed Remicade as presented in the FDA-approved Remicade labeling. Three SAEs in two subjects in the SB2 treatment group were reported in the single-dose PK study in healthy subjects (Study SB2-G11-NHV). 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.

Discontinuations due to Adverse Events

The proportion of patients discontinuing due to an adverse event was similar between SB2 and EU-approved Remicade as detailed in Table 4 above. Infections, disease activity, and hypersensitivity were the most common reason for discontinuation in Study SB2-G31-RA. There was no notable difference in the incidence of treatment discontinuation due to adverse events following the single transition from EU-approved Remicade to SB2 in Period 2 of Study SB2-G31-RA.

Adverse Events of Special Interest (AESI)

The selection of AESI was informed by the known safety profile of US-licensed Remicade as presented in the FDA-approved Remicade labeling and other published data. Overall, the incidence of AESI, including serious infections, tuberculosis, infusion-related reaction, anaphylaxis,[8] malignancy, and liver abnormalities, between the SB2, US-licensed Remicade, and EU-approved Remicade treatment arms was similar across the controlled portions of the clinical studies. No increase in AESI was observed following a single transition from EU-approved Remicade to SB2 in Period 2 of Study SB2-G31-RA.

Common AE

Nasopharyngitis, latent tuberculosis, ALT elevations, and disease activity, were the most common adverse events in the Study SB2-G31-RA with event rates similar between SB2 and EU-approved Remicade. Following the single transition in Period 2 of Study SB2-G31-RA, the common adverse event profile remained consistent and similar between subjects who underwent the single transition from EU-approved Remicade to SB2 and those who continued

[8] Sampson HA et al., J Allergy Clin Immunol. 2006 Feb;117(2):391-7

on EU-approved Remicade. The incidence and types of common adverse events were similar between the treatment arms and were consistent with the known safety profile of US-licensed Remicade as presented in the FDA-approved Remicade labeling, further supporting a demonstration that there are no clinically meaningful differences between SB2 and US-licensed Remicade in the indication studied.

Laboratory Abnormalities, Vital Signs and Electrocardiograms (ECGs)

No unexpected laboratory findings were reported in the SB2 clinical program.

- **Immunogenicity**

In the SB2 clinical studies, determination of anti-drug antibodies (ADA) consisted of a multi-tiered approach with sequential screening, confirmation, and characterization using validated assays.

Immunogenicity in Study SB2-G31-RA

In Study SB2-G31-RA, ADAs 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. As shown in Table 5, at Week 30, 158 (55%) subjects in the SB2 treatment group and 145 (50%) subjects in the EU-approved Remicade treatment group reported an overall ADA-positive result. Of these, 146 (92%) subjects in the SB2 treatment group and 130 (90%) subjects in the EU-approved Remicade treatment group reported positive NAb 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. 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-approved Remicade group at various time points). Of note, these differences did not increase over time to indicate different immunogenicity profiles between the products.

Table 5. Proportion of ADA Positive Patients Following Repeat Dosing in Study SB2-G31-RA (Weeks 0-54)

		SB2 N=290		**EU-approved Remicade** N=293	
		n'	n(%)	n'	n(%)
Screening		290	5 (2)	293	7 (2)
Week 30 Overall[a]	ADA	287	158 (55)	292	145 (50)
	NAb	*158*	*146 (92)*	*145*	*130 (90)*
Week 54 Overall[a]	ADA	287	179 (62)	292	168 (58)
	NAb	*179*	*166 (93)*	*168*	*147 (88)*

Source: FDA analysis of data from SB2 351(k) BLA submission
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
[a]Overall ADA: defined as "positive" for patients with at least one ADA (or NAb) positive up to Week 54 after Week 0

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-approved Remicade to SB2 compared to that of patients who continued EU-approved Remicade or SB2. Of 195 subjects who received EU-approved Remicade through Week 54, 94 subjects underwent a single transition to SB2 (EU-Remicade→SB2 treatment group**)** and 101 subjects continued on EU-approved 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). As summarized in Table 6, 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-approved Remicade to SB2 as compared with those who continued EU-approved Remicade or SB2. Consistent with the observations through Week 54, a majority of ADA-positive samples were confirmed to be NAbs.

Table 6. Proportion of ADA Positive Patients Following Repeat Dosing in Transition-Extension Period of Study SB2-RA (Weeks 54 through 78)

		SB2 contd. N=201		EU-Remicade			
				EU-Remicade→SB2 N=94		EU-Remicade→EU-Remicade N=101	
		n'	n(%)	n'	n(%)	n'	n(%)
Extension-period Baseline		198	101(51)	92	31(34)	101	44(44)
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)*

Source: FDA analysis of data from SB2 351(k) BLA submission
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

Impact of immunogenicity on clinical endpoints

To investigate the potential impact of the ADA on clinical outcomes in study SB2-G31-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 in efficacy or safety outcomes (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-approved Remicade in infusion-related reactions. As summarized in Table 7, in a 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-approved Remicade had similar impact on clinically relevant safety.

Table 7. Incidence of Infusion-related Reactions by ADA Status in Study SB2-G31-RA

	ADA Subgroup	SB2 (n=290)	EU-approved Remicade (n=293)
Infusion-related Reaction	ADA positive	15(5%)	12(4%)
	ADA negative	3(1%)	5(2%)

Source: FDA analysis of data from SB2 351(k) BLA submission

Immunogenicity was assessed at the same time as the 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 8 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 8. ACR20 Response by ADA Status (Study SB2-G31-RA, Per-Protocol Set 1)

	Treatment	Week 30 n/N (%)	Week 54 n/N (%)
ADA positive	SB2 EU-approved Remicade	72/127 (57) 74/126 (59)	66/117(56) 69/106(65)
ADA negative	SB2 EU-approved Remicade	76/104 (73) 89/121 (74)	73/98 (75) 81/111 (73)
Source: FDA analysis of data from SB2 351(k) BLA submission			

Since only trough PK samples were collected in the study, serum concentrations of SB2 or EU-approved Remicade 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 SB2 and US-licensed Remicade.

Immunogenicity in Study SB2-G11-NHV

In this single-dose PK study, the only study to directly compare SB2 and US-licensed Remicade, a total of 159 healthy subjects were enrolled and randomized, with 53 subjects in each of the SB2, US-licensed Remicade, and EU-approved Remicade treatment groups. Blood samples for immunogenicity were collected at Days 0 (pre-dose), 29 and 71 (Weeks 0, 4 and 10, respectively). The products were administered as a single dose 5 mg/kg intravenous infusion. In this study, ADAs were measured using the ECL method similar to the assay used in Study SB2-G31-RA. Of note, 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 SB2-G31-RA.

Immunogenicity results from Study SB2-NHV are summarized in Table 9 below. Based on the original analyses by the Applicant, the ADA incidence appeared numerically higher in SB2 treated subjects as compared with both US-licensed Remicade, and EU-approved Remicade treated subjects. 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 apparent differences seen in the original analyses decreased 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-approved Remicade and US-licensed 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 (data not shown). The overall rates of NAbs were lower than the ones observed in the repeat dose comparative clinical study SB2-G31-RA, suggesting that the NAb assay in study SB2-G11-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 9. 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 and EU-approved Remicade in Study SB2-G31-RA, and between SB2 and US-licensed Remicade or EU-approved Remicade in Study SB2-G11-NHV. In evaluating the significance of the imbalance seen, Dr. Waheed, the product quality immunogenicity team, the clinical pharmacology team, and we considered the following:

- 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

- Immunogenicity impacted PK similarly between the three products in Study SB2-G11-NHV (the PK data from Study SB2-G31-RA were limited for this assessment as discussed above)
- Differences in the incidence of ADA and NAb between the SB2 and EU-approved Remicade in Study SB2-G31-RA were small and did not increase over time through Week 78
- ADA formation impacted safety and efficacy outcomes similarly between SB2 and EU-approved Remicade treated patients in the Study SB2-G31-RA
- Importantly, the ADA rates did not increase differentially between patients who underwent a single transition at Week 54 from EU-approved Remicade to SB2 as compared with those who continued EU-approved Remicade or SB2.

In light of these additional contextual pieces, we do not believe that the apparent numerical imbalance in the incidence of ADA formation precludes a finding of no clinically meaningful differences between SB2, US-licensed Remicade, and EU-approved Remicade. Collectively, these data do not indicate that the ADA formation differentially impacts safety or efficacy between patients treated with SB2 and EU-approved Remicade (Study SB2-G31-RA). Therefore, there are sufficient data supporting similar immunogenicity between SB2, US-licensed Remicade, and EU-approved Remicade and that immunogenicity data adds to the totality of the evidence to support a demonstration of no clinically meaningful differences between SB2 and US-licensed Remicade. Further, the product quality immunogenicity review team recommends approval of the BLA from an immunogenicity perspective and we agree with this recommendation.

- **Discussion of primary reviewer's comments and conclusions**

The safety database submitted for SB2 is adequate to provide a reasonable descriptive comparison between the SB2 and US-licensed Remicade. The safety and immunogenicity analysis of the SB2 clinical program in the studied condition of use, RA, and in healthy subjects in the PK single dose Study SB2-G11-NHV, has not identified notable differences in the safety profile between SB2, US-licensed Remicade, and EU-approved Remicade. No new safety signals have been identified compared to the known adverse event profile of US-licensed Remicade. Further, the single transition from EU-approved Remicade to SB2 after Week 54 in Study SB2-G31-RA did not result in an increase in adverse events, supporting the safety of the clinical scenario where non-treatment naïve patients transition to SB2. The FDA safety analysis is consistent with the Applicant's analysis.

The clinical safety and immunogenicity data using the lowest labeled dose for US-licensed Remicade in combination with methotrexate in patients with RA, showed a similar safety profile between SB2 and EU-approved Remicade. Dr. Waheed and we are in agreement that the submitted safety and immunogenicity data and analyses are adequate to support the conclusion of no clinically meaningful differences between SB2 and US-approved Remicade in the indication studied.

- **Highlight differences between CDTL and review team with explanation for CDTL's conclusion**

None.

- **Discussion of notable safety issues (resolved or outstanding)**

None.

9) Extrapolation of Data to Support Biosimilarity in Other Conditions of Use

Samsung is seeking licensure for the following indications for which US-licensed Remicade is licensed (i.e., RA, PsA, AS, CD, pediatric CD, UC, pediatric UC, and PsO). The SB2 clinical program however, provides direct comparative clinical data from one clinical study in patients with RA and safety and immunogenicity data in healthy subjects.

The Agency has determined that it may be appropriate for a biosimilar product to be licensed for one or more conditions of use (e.g., indications) for which the reference product is licensed, based on data from a clinical study(ies) performed in another condition of use. This concept is known as extrapolation. As described in the Guidance for Industry: *"Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009,"* if a biological product meets the statutory requirements for licensure as a biosimilar product under section 351(k) of the PHS Act based on, among other things, data derived from a clinical study or studies sufficient to demonstrate safety, purity, and potency in an appropriate condition of use, the potential exists for that product to be licensed for one or more additional conditions of use for which the reference product is licensed.[9] The Applicant needs to provide sufficient scientific justification for extrapolation, which should address, for example, the following issues for the tested and extrapolated conditions of use:

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

[9] Guidance for Industry on Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 (April 2015)
http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444661.pdf

As a scientific matter, the FDA has determined that differences between conditions of use with respect to the factors addressed in a scientific justification for extrapolation do not necessarily preclude extrapolation. Consistent with the principles outlined in the above FDA guidance, Samsung has provided a justification for the proposed extrapolation of data, including direct comparative clinical data in RA, to each of the other indications approved for US-licensed Remicade for which Samsung is seeking licensure of SB2, as summarized in this section.

First, Samsung's extensive analytical characterization data support a demonstration that SB2 is highly similar to US-licensed Remicade notwithstanding minor differences in clinically inactive components, and that the data support a demonstration there are no clinically meaningful differences between SB2 and US-licensed Remicade in terms of safety, purity and potency based on similar clinical pharmacokinetics, and similar efficacy, safety, and immunogenicity in RA.

Further, the additional points considered in the scientific justification for extrapolation of data to support biosimilarity in the indications for which Samsung is seeking licensure of SB2 (adult and pediatric CD, adult and pediatric UC, PsA, AS, and PsO) include:

- Similar PK was demonstrated between SB2 and US-licensed Remicade, as discussed in the section on Clinical Pharmacology above. Importantly, SB2 was demonstrated to be highly similar to US-licensed Remicade, as discussed in the section on CMC/Product Quality, and there are no product-related attributes that would increase the uncertainty that the PK/biodistribution may differ between SB2 and US-licensed Remicade in the indications sought for licensure. Thus, a similar PK profile would be expected between SB2 and US-licensed Remicade in patients across all the indications being sought for licensure.

- In general, immunogenicity of the US-licensed Remicade was affected primarily by the dosing regimen and the use of concomitant immunosuppressive therapy across different indications rather than by patient population, and the results were influenced by the type of immunoassay used.[10] As stated previously in this document, the Agency has concluded that there is sufficient data to support similar immunogenicity between SB2 and EU-approved Remicade with repeat dosing in patients with RA, and between SB2, EU-approved Remicade, and US-licensed Remicade after a single dose in healthy subjects. Accordingly, similar immunogenicity would be expected between SB2 and US-licensed Remicade for adult and pediatric CD, adult and pediatric UC, PsA, AS, PsO.

- A similar clinical safety profile with chronic dosing was demonstrated between SB2 and EU-approved Remicade in patients with RA, and between SB2, EU-approved Remicade, and US-licensed Remicade following single doses in healthy subjects. As analytical and PK similarity was demonstrated between SB2 and US-licensed

[10] FDA-approved Remicade labeling

Remicade, a similar safety profile would be expected between SB2 and US-licensed Remicade for adult and pediatric CD, adult and pediatric UC, PsA, AS, PsO.

- The mechanism(s) of action (MOA) relevant to the extrapolation of data to support biosimilarity in specific indications are summarized in Table 10 and discussed below.

Table 10. Known and Potential (Likely or Plausible) Mechanisms of Action of US-licensed Remicade in the Conditions of Use Sought for Licensure of SB2

MOA of Remicade	RA	AS	PsA	PsO	CD, Pediatric CD	UC, Pediatric UC
Mechanisms involving the Fab (antigen binding) region:						
Blocking TNFR1 and TNFR2 activity via binding and neutralization of s/tmTNF	Known	Known	Known	Known	Likely	Likely
Reverse (outside-to-inside) signaling via binding to tmTNF	-	-	-	-	Likely	Likely
Mechanisms involving the Fc (constant) region:						
Induction of CDC on tmTNF-expressing target cells (via C1q binding)	-	-	-	-	Plausible	Plausible
6yInduction of ADCC on tmTNF-expressing target cells (via FcγRIIIa binding expressed on effector cells)	-	-	-	-	Plausible	Plausible
Induction of regulatory macrophages in mucosal healing	-	-	-	-	Plausible	Plausible
ADCC: antibody-dependent cellular cytotoxicity; AS: ankylosing spondylitis; CD: Crohn's disease; CDC: complement-dependent cytotoxicity; MOA: mechanism of action; PsA: psoriatic arthritis; PsO: plaque psoriasis; RA: rheumatoid arthritis; UC: ulcerative colitis; sTNF: soluble TNF; tmTNF: transmembrane TNF						

Source: FDA summary of current literature on the topic of mechanisms of action of TNF inhibitors[11,12,13]

Extrapolation of Data to Support Biosimilarity in PsA, AS, and PsO

The primary MOA of infliximab products is to block TNF receptor-mediated biological activities (see Table 10 above). Infliximab binds to both soluble (s) and transmembrane (tm) TNF, thus blocking TNF binding to its receptors TNFR1 and TNFR2 and the resulting downstream pro-inflammatory cascade of events. The published scientific literature indicates that this MOA is the primary MOA in RA, PsA, AS, and PsO. The *in vitro* data provided by Samsung showed similar TNF binding and potency to neutralize TNF-α, supporting the demonstration of analytical similarity pertinent to this MOA. Therefore, based on the above considerations, it is reasonable to extrapolate conclusions regarding similar efficacy and safety of SB2 and US-licensed Remicade in RA to PsA and AS. Further, the DDDP review team concluded, and we agree, that

[11] Oikonomopoulos A et al., Current Drug Targets, 2013, 14, 1421-1432.
[12] Tracey D et al., Pharmacology & Therapeutics 117 (2008) 244–279.
[13] Olesen, C.M, et.al., Pharmacology & Therapeutics 159 (2016), 110-119.

based on the totality of the data establishing analytical similarity, PK similarity, and no clinically meaningful differences in RA between SB2 and EU-approved Remicade, the extrapolation of data to support a finding of biosimilarity for SB2 and US-licensed Remicade to PsO is scientifically justified.

Extrapolation of Data to Support Biosimilarity in Inflammatory Bowel Disease (IBD) Indications

TNF plays a central role in the pathogenesis of the IBD indications (Crohn's disease, pediatric Crohn's disease, ulcerative colitis and pediatric ulcerative colitis[14]), and TNF inhibition is important in treating the diseases, as evidenced by the efficacy of the approved TNF monoclonal antibodies, but the detailed cellular and molecular mechanisms involved have not been fully elucidated.[15] However, the available scientific evidence suggests that for TNF inhibitors in IBD, in addition to binding and neutralization of sTNF, other MOA, listed in Table 10 may play a role.[16] Binding to sTNF and tmTNF involves the Fab region of the antibody, while the other plausible mechanisms of action involve the Fc region of the molecule.

As outlined in the section on CMC/Product Quality above, Samsung provided experimental data supporting a demonstration that SB2 and US-licensed Remicade are highly similar based on extensive structural and functional analytical characterization. Further, Samsung addressed each of the known and potential mechanisms of action of US-licensed Remicade listed in Table 10 and submitted data to support the conclusion that SB2 and US-licensed Remicade have the same mechanisms of action for each of the requested indications, to the extent that the mechanisms of action are known or can reasonably be determined.

Thus, the DGIEP review team concluded, and we agree, that based on the totality of the data establishing analytical similarity, PK similarity, and no clinically meaningful differences in RA between SB2 and EU-approved Remicade, the extrapolation of data to support a finding of biosimilarity for SB2 and US-licensed Remicade to the IBD conditions of use is scientifically justified.

In aggregate, based on the above considerations, extrapolation of data to the additional indications for which Samsung is seeking licensure (CD, pediatric CD, UC, pediatric UC,[17]

[14] Remicade's indication for pediatric ulcerative colitis is protected by orphan drug exclusivity expiring on September 23, 2018. See the Orphan Drug Designations and Approvals database at http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm. Accordingly, FDA will not license SB2 for this indication until the orphan drug exclusivity expires.
[15] Oikonomopoulos A et al., "Anti-TNF Antibodies in Inflammatory Bowel Disease: Do We Finally Know How it Works?", Current Drug Targets, 2013, 14, 1421-1432
[16] Tracey D et al., "Tumor necrosis factor antagonist mechanisms of action: A comprehensive review", Pharmacology & Therapeutics 117 (2008) 244–279
[17] Remicade's 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

AS, PsA, and PsO) is scientifically justified and supports licensure of SB2 for the indications being sought; however, SB2 currently is eligible for licensure for only certain indications (CD, pediatric CD, UC, AS, PsA and PsO).

10) Advisory Committee Meeting

An Advisory Committee (AC) meeting was determined not to be necessary as there were no issues where the Agency needed input from the committee.

11) Pediatrics

- **PeRC Review Outcome-PMCs, deferrals, waivers, pediatric plan, pediatric assessment**

The Applicant submitted an agreed initial pediatric study plan (iPSP) to address the PREA requirements for the indications sought for licensure as detailed below:

- Rheumatoid Arthritis (RA): Samsung proposed that the pediatric assessment is fulfilled for polyarticular juvenile idiopathic arthritis (PJIA) patients between 4 and 17 years old by satisfying the statutory requirements for showing biosimilarity and providing an adequate scientific justification for extrapolating the pediatric information from the reference product to SB2. The applicant requested a waiver of the requirement to submit a pediatric assessment for (1) patients ages 2 to < 4 years old because SB2 does not represent a meaningful therapeutic benefit over existing therapies and is not likely to be used in a substantial number of pediatric patients with the condition and (2) patients < 2 years old because the condition is rare in this age group and such studies would be impossible or highly impracticable.

- Ankylosing Spondylitis (AS), Psoriatic Arthritis (PsA): The applicant requested a waiver of the requirement to submit a pediatric assessment for juvenile AS and juvenile PsA because the studies would be impossible or highly impracticable due to the difficulty of making specific diagnoses of juvenile PsA or juvenile AS in the pediatric age range.

- Crohn's Disease (CD), Pediatric CD, Ulcerative Colitis (UC), Pediatric UC: The applicant proposed that the pediatric assessment is fulfilled for pediatric CD and pediatric UC patients 6 years of age and older, by satisfying the statutory requirements for showing biosimilarity and providing an adequate scientific justification for extrapolating the pediatric information from the reference product to SB2. It should be noted that the reference product has orphan drug exclusivity for pediatric UC, which precludes approval

http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm. Accordingly, FDA will not license SB2 for this indication until the orphan drug exclusivity expires.

of SB2 for the protected indication until the expiration of orphan exclusivity on September 23, 2018. Accordingly, the following statement will be included in the labeling for SB2: "A pediatric assessment for Renflexis demonstrates that Renflexis is safe and effective in another pediatric indication. However, Renflexis is not approved for such indication due to marketing exclusivity for Remicade (infliximab)." The applicant requested a waiver of the requirement to submit a pediatric assessment for pediatric CD and pediatric UC patients younger than 6 years of age because such studies are impossible or highly impracticable. As a scientific matter, the Agency has determined that, based on recent epidemiologic data, a pediatric assessment for pediatric CD and pediatric UC patients should be conducted in patients 2 years and older, as opposed to previously recommended cut-off of 6 years of age and older. However, FDA acknowledges that, in this case, designing dedicated pediatric studies in pediatric CD and pediatric UC patients limited to ages 2 to 5 years old would be impossible or highly impracticable due to the low incidence of the disease in this specific pediatric age group.

- Plaque Psoriasis (PsO): The applicant requested a waiver of the requirements for a pediatric assessment in patients with pediatric chronic severe plaque psoriasis ages 0 to less than 17 years old due to safety concerns with increased risk of lymphoma and other cancers associated with the use of TNF blockers in children and adolescents. The Agency's current view is that this safety information does not necessarily apply across the class of TNF-alpha inhibitors, and thus would not necessarily support a waiver of the pediatric assessment for SB2 in PsO patients on safety grounds However, unlike certain other TNF-alpha inhibitors with a broader PsO indication, Remicade is approved only for treatment of adult patients with chronic severe (i.e., extensive and/or disabling) PsO who are candidates for systemic therapy and when other systemic therapies are medically less appropriate. Accordingly, a waiver of the requirement for a pediatric assessment in PsO is justified because such studies would be impossible or highly impracticable for this narrow indication of chronic severe PsO.

The Division of Pediatric and Maternal Health (DPMH) agreed with the proposed pediatric study plans as outlined above. The SB2 pediatric study plan was also reviewed by the Pediatric Review Committee (PeRC) on November 16, 2016 and PeRC agreed with the proposed plan, including granting all the requested waivers. We agree with DPMH and PeRC's conclusions.

12) Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP)—**Not warranted, no issues.
- **Exclusivity**—There is no unexpired exclusivity under section 351(k)(7) of the Public Health Service (PHS) Act for Remicade (infliximab) (BLA # 103772, Janssen Biotech, Inc) that would prohibit the approval of SB2.
- **Financial disclosures**—No issues.
- **Other GCP issues—**No issues.

- **OSI audits—**Two clinical sites that enrolled patients in the comparative clinical study were selected for inspection. The Applicant, Samsung Bioepis Co., Ltd., was also inspected. One of the two clinical investigator sites (Site SB21403) was issued a Form FDA 483 and received a classification of VAI. The other clinical investigator site (Site SB21012) and the Applicant inspection conducted at the U.S. Agent's location received a final classification of No Action Indicated (NAI). The OSI investigators concluded that the data submitted were acceptable to support the current BLA. In addition to information related to FDA inspections, the CIS contained European Medicines Agency (EMA) inspection reports provided by EMA and shared with FDA under the confidentiality agreements between the two regulatory authorities. Detailed EMA inspection findings are not made publically available at this time. However, the EMA inspection summary indicated (b) (4)
- **Other discipline consults**—Not applicable.
- **Any other outstanding regulatory issues**—Not applicable.

13) Labeling

- **Proprietary name**

The Applicant submitted the proposed proprietary name Renflexis for review on March 21, 2016. The name has been reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) and by the Office of Prescription Drug Promotion (OPDP, formerly the Division of Drug Marketing and Advertising) and was found to be conditionally acceptable. We agree with this assessment.

- **Non-proprietary/Proper name**

FDA has determined that the use of a distinguishing suffix in the nonproprietary name for Samsung's Renflexis product is necessary to distinguish this proposed product from Remicade (infliximab). As explained in FDA's Guidance for Industry, Nonproprietary Naming of Biological Products, FDA expects that a nonproprietary name that includes a distinguishing suffix will facilitate safe use and optimal pharmacovigilance of biological products.[18]

On October 18, 2016, the Applicant submitted a list of suffixes to be used in the nonproprietary name of SB2 along with supporting analyses intended to demonstrate that the proposed suffixes satisfied the factors described in section V of the Draft Guidance for Industry, Nonproprietary Naming of Biological Products. The DMEPA review concluded, and we agree, that Samsung's proposed distinguishing suffix "abda" is acceptable and the

[18] See the FDA Guidance for Industry on Nonproprietary Naming of Biological Products (January 2017). The guidances referenced in this document are available on the FDA Drugs guidance Web page at http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf

nonproprietary name "infliximab-abda" should be reflected in the product label and labeling accordingly.

- **Important issues raised by brief discussion of OPDP and OSE Division comments**

None

- **Physician labeling**

The Applicant-proposed labeling is closely tracking the labeling of US-licensed Remicade. In addition, the Applicant proposed revisions to Section 8, to conform to PLLR formatting requirements.

During the BLA labeling review, revisions were made for consistency with the Draft Guidance for Industry, *Labeling for Biosimilar Products* (March 2016).

The proprietary name "Renflexis," and the non-proprietary name "infliximab-abda," should be reflected in the product labeling as appropriate.

- **Highlight major issues that were discussed, resolved, or not resolved at the time of completion of the CDTL review**

As discussed above.

- **Carton and immediate container labels**

As discussed above in the DMEPA review and recommendations, the proprietary name "Renflexis" and the non-proprietary name "infliximab-abda," should be reflected in the product Patient labeling/Medication guide as appropriate.

- **Patient labeling/Medication guide**

The Applicant proposed a Patient labeling/Medication guide closely tracking that of US-licensed Remicade. The proprietary name "Renflexis" and the non-proprietary name "infliximab-abda," should be reflected in the product Patient labeling/Medication guide as appropriate.

14) Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

We recommend approval of the 351(k) BLA 761,054 for SB2 to receive licensure as a biosimilar product to US-licensed Remicade for each of the following indications US-licensed

Remicade is currently licensed for which Samsung is seeking licensure of SB2; however, SB2 currently is eligible for licensure for only certain indications (CD, pediatric CD, UC, AS, PsA and PsO).[19]

- **Totality of the Evidence**

The conclusion of the comparison of the structural and functional properties of the clinical and commercial product lots of SB2 and US-licensed Remicade was that they were highly similar, notwithstanding minor differences in clinically inactive components.

Samsung provided extensive analytical and clinical pharmacology bridging data to scientifically justify the relevance of data obtained using EU-approved Remicade to support a demonstration of biosimilarity of SB2 to US-licensed Remicade.

The submitted clinical pharmacology studies are adequate to (1) support the demonstration of PK similarity between SB2 and US-licensed Remicade, and (2) establish the PK component of the scientific bridge to justify the relevance of the data generated using EU-approved Remicade.

The results of the clinical development program indicate that Applicant's data meet the requirement for a demonstration of no clinically meaningful differences between SB2 and US-licensed Remicade in terms of safety, purity, and potency in the indication studied. Specifically, the results from the comparative clinical efficacy, safety, and PK studies, which included the use of a chronic dosing regimen of SB2 and EU-approved Remicade in patients with RA, adequately support a demonstration that there are no clinically meaningful differences between SB2 and US-licensed Remicade in RA. The single transition from EU-approved Remicade to SB2 during the second part of Study SB2-G31-RA did not result in different safety or immunogenicity profile. This would support the safety of a clinical scenario where non-treatment naïve patients may undergo a single transition to SB2.

The Applicant has also provided an extensive data package to address the scientific considerations for extrapolation of data to support biosimilarity to conditions of use not directly studied to support licensure of SB2 for each of the indications for which US-licensed Remicade is currently licensed and for which Samsung is seeking licensure of SB2; however, SB2 currently is eligible for licensure for only certain indications (CD, pediatric CD, UC, AS, PsA and PsO).

In considering the totality of the evidence submitted, the data submitted by the Applicant show that SB2 is highly similar to US-licensed Remicade, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between SB2 and US-licensed Remicade in terms of the safety, purity, and potency of the product. The

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

information submitted by the Applicant demonstrates that SB2 is biosimilar to US-licensed Remicade and should be licensed.[20]

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies**

None.

- **Recommendation for other Postmarketing Requirements and Commitments**

We do not recommend any postmarketing required studies for this application.

Postmarketing Commitments (PMC):

We concur with the post-marketing commitments recommended by the product quality review team, as listed below:

1. Implement a test for FcγRIIIa binding affinity into the Drug Substance release specification. Submit the proposed release specification as a CBE-30 supplement described under 21 CFR 601.12 (c).

   Final Report Submission: January 21, 2018

2. Implement the reducing CE-SDS purity test into the Drug Substance and Drug Product release specifications. Submit the proposed release specification as a CBE-30 supplement described under 21 CFR 601.12 (c).

   Final Report Submission: January 21, 2018

We concur with the post-marketing commitments recommended by the microbiology review team, as listed below:

3. Re-evaluate and establish final in-process (b) (4) limits (b) (4) In addition, provide the qualification test data for the (b) (4) samples. Submit the proposed limits as a CBE-30 supplement described under 21 CFR 601.12 (c).

   Final Report Submission: March 31, 2018

[20] The proposed SB2 labeling states: "Biosimilarity of RENFLEXIS has been demonstrated for the condition(s) of use (e.g. indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information."

4. Re-evaluate and establish final endotoxin limits for the (b) (4) sucrose, pH 6.2 solution and (b) (4) polysorbate 80 solution. Submit the proposed limits as a CBE-30 supplement described under 21 CFR 601.12 (c).

   Final Report Submission: October 31, 2019

5. Repeat the container closure integrity test (CCIT) validation for the SB2 drug product using a positive control with a defect size of no more than (b) (4) microns. Submit the CCIT validation study report as a CBE-30 supplement described under 21 CFR 601.12 (c).

   Final Report Submission: November 30, 2017

6. Qualify an in-process (b) (4) method and establish an in-process (b) (4) limit for the (b) (4) of the SB2 drug product manufacturing process. Submit the proposed limit as a CBE-30 supplement described under 21 CFR 601.12 (c).

   Final Report Submission: December 15, 2017

7. Conduct endotoxin, bioburden, and sterility test method qualification study using one additional batch of SB2 Drug Product manufactured according to the commercial drug product manufacturing processes.

   Final Report Submission: December 15, 2017

8. Conduct the (b) (4) determination study of the (b) (4) with two additional lots of SB2 drug product.

   Final Report Submission: November 30, 2017

- **Recommended Comments to Applicant**

None.

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/s/

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04/21/2017

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