CLINICAL PHARMACOLOGY REVIEW

BLA	761054
Submission Date:	03/21/2016
Proposed Brand Name:	Renflexis
Nonproprietary Name:	TBD
Clinical Pharmacology Reviewer:	Lei He, Ph.D.
Clinical Pharmacology Team Leader:	Anshu Marathe, Ph.D.
OCP Division:	Division of Clinical Pharmacology II
OND Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Sponsor:	Samsung
Submission Type; Code:	351(k); standard review
Formulation; Strength(s)	Lyophilized powder for intravenous infusion; 100 mg/vial
Proposed Indications:	Rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PA), plaque psoriasis (Ps), ulcerative colitis (UC), pediatric UC [1], Crohn's disease (CD), pediatric CD
Proposed Dosage Regimens:	RA: 3-10 mg/kg at 0, 2, 6 weeks, and then every 4-8 weeks. AS: 5 mg/kg at 0, 2, 6 weeks, and then every 6 weeks. Ps, PA, CD, UC, Pediatric UC, Pediatric CD: 5 mg/kg at 0, 2, 6 weeks, and then every 8 weeks.

[1] This reflects information for SB2 that Samsung submitted on March 21, 2016. 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. Executive Summary

Samsung submitted a Biologic License Application (BLA) for SB2, a chimeric human-murine immunoglobulin G1 (IgG1) monoclonal antibody (mAb) that binds to human tumor necrosis factor alpha (TNFα), under Section 351(k) of the Public Health Service Act (42 U.S.C. 262(k)). The applicant is seeking approval for SB2 as a biosimilar to US-licensed Remicade (BLA 103772) and licensure for all the indications currently approved for US-licensed Remicade. SB2 drug product is supplied as a sterile, white, lyophilized powder for intravenous infusion (100 mg/vial).

The clinical development for SB2 relevant to the submission in the United States (US) included two clinical studies. 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).

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%. 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-G31-RA). In Study SB2-G31-RA, serum trough concentrations were assessed 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.

The incidence of anti-drug antibody (ADA) formation in healthy subjects was comparable between treatments, which is 49.1%, 43.4%, and 43.4% for SB2, EU-approved Remicade, and US-licensed Remicade, respectively, and the formation of ADA did not appear to impact the PK similarity between these three treatment groups. After multiple doses of intravenous (IV) infusions, the ADA formation rate was also comparable between SB2 and EU-approved Remicade in patients with RA (Study SB2-G31-RA).

Overall, PK similarity has been demonstrated between SB2 and US-licensed Remicade, and the PK results add to the totality of evidence to support a demonstration of biosimilarity of SB2 and US-licensed Remicade.

1.1 Recommendations

The Office of Clinical Pharmacology has determined that PK similarity has been demonstrated between SB2 and US-licensed Remicade, and the PK results support a demonstration of no clinically meaningful differences between SB2 and US-licensed Remicade.

Labeling Recommendations

Please refer to Section 3 – Detailed Labeling Recommendations.

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Samsung submitted a Biologic License Application (BLA) for SB2, a chimeric human-murine IgG1 mAb that binds to human TNFα, under Section 351(k) of the Public Health Service Act (42 U.S.C. 262(k)). The applicant is seeking approval for SB2 as a biosimilar to US-licensed Remicade (BLA 103772) and licensure for all the indications currently approved for US-licensed Remicade. SB2 drug product is supplied as a sterile, white, lyophilized powder for intravenous infusion (100 mg/vial).

The clinical development for SB2 relevant to US submission included two clinical studies. 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 RA in Study SB2-G31-RA (n=325 for PK, n=584 for immunogenicity).

In the pivotal PK study, Study SB2-G11-NHV, the 90% CIs for the GMRs 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% (Table 1). 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-G31-RA). In Study SB2-G31-RA, serum trough concentrations were assessed 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.

Table 1. 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)

The analysis included data from 159 healthy subjects (53/treatment arm). The units of Cmax and AUC are µg/mL and µg*h/mL, respectively.

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

The incidence of ADA formation on Day 71 in healthy subjects was 49.1%, 43.4%, and 43.4% for SB2, EU-approved Remicade, and US-licensed Remicade, respectively. The formation of ADA did not appear to impact the PK similarity between these three treatment groups. After multiple doses of IV infusions, the ADA formation rate was similar between SB2 and EU-approved Remicade in patients with RA (Study SB2-G31-RA).

Overall, PK similarity has been demonstrated between SB2 and US-licensed Remicade, and the PK results add to the totality of evidence to support a demonstration of biosimilarity of SB2 and US-licensed Remicade.

2. Question Based Review

2.1 General Attributes

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

Samsung has developed SB2 as a proposed biosimilar product to Remicade® (infliximab). Remicade® was approved in the US in 1998. During the clinical development of SB2, five key regulatory interactions with Samsung occurred: the Type B pre-IND meeting on the chemical, pharmaceutical and biological, non-clinical, and the clinical development plan (February 12, 2012), the Type 2 BPD meeting on the proposed clinical development plan (December 07, 2012), the Type 3 BPD meeting on the acceptability of available CMC, nonclinical and PK

similarity study data (March 24, 2014), the Type 2 BPD meeting on the development program (July 20, 2015), the Type 4 BPD meeting on the format, content and database structure of the proposed BLA submission (December 14, 2015).

Samsung submitted the BLA submission for SB2 under Section 351(k) of the Public Health Service Act on March 21, 2016. The review of BLA761054 is standard.

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

SB2 drug substance is a chimeric human/mouse mAb, which is 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 of approximately 149 kDa. Each single HC contains a total of 450 residues, whereas each single LC contains 214 residues. These residues are linked by disulphide bonds. SB2 is a glycosylated protein containing one glycosylation site at each HC. SB2 drug substance is clear to opalescent and colorless to slightly yellowish solution and free of visible particles, with a pH of (b) (4) .

The SB2 drug product is a sterile, white, lyophilised concentrate for injection. It is intended for IV administration, after reconstitution with sterile water for injection to yield a single dose formulation of 10 mg/mL infliximab at pH 6.2, and is further diluted in 0.9% sodium chloride solution for infusion. One single-use vial contains 100 mg infliximab as the active substance, and the following excipients: 500 mg sucrose, 0.5 mg polysorbate 80, 5.55 mg monobasic sodium phosphate monohydrate, and 2.60 mg dibasic sodium phosphate heptahydrate.

Infliximab (US-licensed Remicade) is a chimeric IgG1κ monoclonal antibody specific for TNFα. It has a molecular weight of approximately 149.1 kilodaltons. Infliximab is produced by a recombinant cell line cultured by continuous perfusion and is purified by a series of steps that includes measures to inactivate and remove viruses.

US-licensed Remicade is supplied as a sterile, white, lyophilized powder for intravenous infusion. Following reconstitution with 10 mL of Sterile Water for Injection, USP, the resulting pH is approximately 7.2. Each single-use vial contains 100 mg infliximab, 500 mg sucrose, 0.5 mg polysorbate 80, 2.2 mg monobasic sodium phosphate, monohydrate, and 6.1 mg dibasic sodium phosphate, dihydrate. No preservatives are present.

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

SB2 is a chimeric human IgG1 mAb that binds with high affinity to the human TNF.

SB2 is proposed to be used for eight indications identical to US-licensed Remicade, which are Rheumatoid Arthritis (RA), Crohn's Disease (CD), pediatric CD, Ulcerative Colitis (UC), pediatric UC, Plaque Psoriasis (Ps), Psoriatic Arthritis (PA), and Ankylosing Spondylitis (AS). It was noted 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.

2.1.4 What are the proposed dosages and routes of administration?

The proposed dosages and routes of administration for SB2 are identical to those approved for US-licensed Remicade (Table 2).

Table 2. Dosage and routes of administration of US-licensed Remicade

Indication	Dosage and Administration
RA	In conjunction with methotrexate, 3 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. Some patients may benefit from increasing the dose up to 10 mg/kg or treating as often as every 4 weeks.
CD (Adult)	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.
CD (Pediatric)	5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.
UC (Pediatric)	
UC (Adult)	
Ps	
AS	5 mg/kg at 0, 2 and 6 weeks, then every 6 weeks.

2.2 General Clinical Pharmacology

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

Overall, the clinical development for SB2 included 2 completed clinical studies, Study SB2-G11-NHV and Study SB2-G31-RA (Table 3).

Table 3. Summary of SB2 clinical studies

Studies	Objective(s)	Study Design	Dosing Regimen	Study Population
SB2-G11-NHV	Primary: To evaluate and compare the PK profiles of SB2, EU-approved Remicade and US-licensed Remicade in healthy subjects Secondary: Safety, tolerability, immunogenicity	Randomized, double-blind, three-arm, parallel-group, single dose	SB2: 5 mg/kg IV US-licensed Remicade: 5 mg/kg IV EU-approved Remicade: 5 mg/kg IV	Healthy subjects (n=53/arm)
SB2-G31-RA	Primary: To demonstrate that SB2 is equivalent to EU-approved Remicade, in terms of efficacy as determined by clinical response according to ACR20 at Week 30 in patients with RA Secondary: To evaluate other efficacy endpoints (e.g. ACR50, ACR70, DAS28, hybrid ACR), long-term efficacy, PK, PD, and overall safety up to Week 54	Randomized, double-blind, two-arm, parallel-group, multiple dose	SB2 or EU-approved Remicade (3 mg/kg) administered as 2h IV infusion; at Weeks 0, 2 and 6, then every 8 weeks up to Week 54, co-administered with MTX (10-25 mg/week, oral or parenteral) and folic acid (5-10 mg/week, oral)	Male and female patients with moderate to severe RA who had an inadequate response to MTX (aged 18 to 75 years old) Randomized: 584 SB2: 291 EU-approved Remicade: 293

MTX: methotrexate

The pivotal 3-way PK-bridging study comparing SB2, EU-approved Remicade and US-licensed Remicade was conducted in healthy subjects (Study SB2-G11-NHV). In addition, PK comparison between SB2 and EU-approved Remicade was also assessed in adult patients with RA (Study SB2-G31-RA). This clinical pharmacology review primarily focused on the pivotal PK similarity Study SB2-G11-NHV. We also evaluated the PK and immunogenicity in Study SB2-G31-RA.

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

PK (AUC0-inf, AUC0-t, and Cmax) was assessed as primary endpoint in the Study SB2-G11-NHV to evaluate and compare the PK profiles of SB2, EU-approved Remicade and US-licensed Remicade in healthy subjects. Safety, tolerability and immunogenicity were the secondary endpoints.

Study SB2-G31-RA was the comparative efficacy trial in RA patients. Therefore, the primary efficacy endpoint was the proportion of patients achieving clinical response (according to the ACR20 criteria) at Week 30, whereas PK, safety, immunogenicity and other efficacy endpoints (ACR20, ACR50, and ACR70, ACR-N, mean decrease in Disease Activity Score 28 (DAS28), and EULAR response criteria, Change from Baseline in modified Total Sharp Score (mTSS) were the secondary endpoints. For the choice of efficacy and safety endpoints in Study SB2-G31-RA, see details in the medical review and statistical review.

2.2.3 What are the PK characteristics of the drug?

2.2.3.1 What are the single dose and multiple dose PK characteristics for SB2?

Single-Dose PK

The pivotal PK similarity Study SB2-G11-NHV was a randomized, double-blind, three-arm, parallel-group, single-dose study in healthy subjects. In each arm of the study, a total of 53 subjects received a single dose 5 mg/kg of either SB2, EU-approved Remicade, or US-licensed Remicade by IV infusion for 120 minutes. The PK, safety, tolerability, and immunogenicity of SB2, EU-approved Remicade and US-licensed Remicade were assessed. Mean serum concentration-time profiles were similar between the SB2, EU-approved Remicade and US-licensed Remicade treatment groups (Figure 1). For the 3-way PK similarity comparisons (SB2 vs. US-licensed Remicade, SB2 vs. EU-approved Remicade, and EU-approved Remicade vs. US-licensed Remicade), the 90% CIs for the geometric mean ratios of Cmax, AUC0-t and AUC0-inf were all within the PK similarity range of 80% –125% (Table 4).

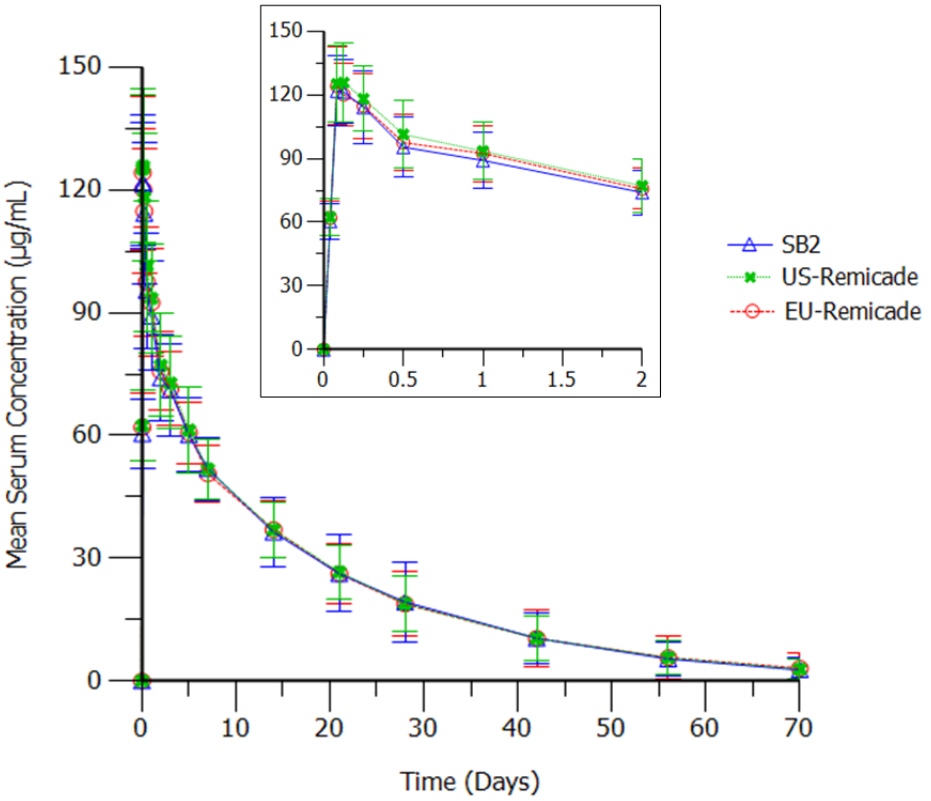

Figure 1. Infliximab PK profiles following a single IV dose 5 mg/kg of SB2, EU-approved Remicade, or US-licensed Remicade in healthy subjects (n=53/treatment group, Study SB2-G11-NHV)

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

Table 4. Statistical analysis for PK parameters (SB2-G11-NHV)

Average Bioequivalence Approach						
Parameter	**LSM (T)**	**N**	**LSM (R)**	**N**	**GMR (%)**	**90% CI (%)**
SB2 (T) vs US-licensed Remicade (R)						
Cmax	125.3	53	127.8	53	98.01	(93.77, 102.52)
AUC0-t	36023	53	36965	53	97.45	(89.58, 106.02)
AUC∞	37463	53	38552	53	97.18	(88.52, 106.67)
SB2 (T) vs EU-approved Remicade (R)						
Cmax	125.3	53	125.05	53	100.23	(95.96, 104.69)
AUC0-t	36023	53	36501	53	98.69	(90.61, 107.48)

AUC∞	37463	53	38288	53	97.85	(88.82, 107.79)
EU-approved Remicade (T) vs US-licensed Remicade (R)						
Cmax	125.05	53	127.8	53	97.82	(93.48, 102.36)
AUC0-t	36501	53	36965	53	98.74	(91.52, 106.53)
AUC∞	38288	53	38552	53	99.31	(90.97, 108.42)

The units of Cmax and AUC are µg/mL and µg*h/mL, respectively.

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

Multiple-Dose PK

The PK of SB2 and EU-approved Remicade was compared in the comparative efficacy Study SB2-G31-RA. This prospective Phase III study was designed to assess the overall efficacy and safety of multiple doses of either SB2 or EU-approved Remicade in patients with moderate and sever RA who had an inadequate response to MTX and were on a stable dose of MTX 10–25 mg/week given orally or parenterally for at least 4 weeks prior to Screening. Five hundred and eighty-four male or female RA patients were enrolled and were randomly assigned in a 1:1 ratio to receive either SB2 3 mg/kg or EU-approved Remicade 3 mg/kg via a 2-hour IV infusion at Weeks 0, 2 and 6 and then every 8 weeks until Week 46. At Week 54, subjects receiving EU-approved Remicade during double-blind period were randomized again in a 1:1 ratio to either continue on EU-approved Remicade or be transitioned to SB2 up to Week 70. Subjects receiving SB2 during double-blind period continued to receive extended treatment of SB2 up to Week 70 but they also followed the randomization procedure to maintain blinding.

The primary endpoint of the study is efficacy and PK is one of the secondary endpoints. PK samples 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. Overall, the serum trough concentrations (Ctrough) of SB2 and EU-approved Remicade were highly variable and the range of Ctrough appeared to be comparable between SB2 and EU-approved Remicade in RA patients (Figure 2, Table 5). It was noted that since the median elimination half-life of infliximab has been reported to be 7.7-9.5 days in RA patients and only pre-dose trough PK samples were collected in this study, serum concentrations were undetectable in ~36% patients at Week 30 (59 out of 139 and 42 out of 143 in SB2 and EU-approved Remicade treatment, respectively). Therefore, the PK data from this study was considered limited.

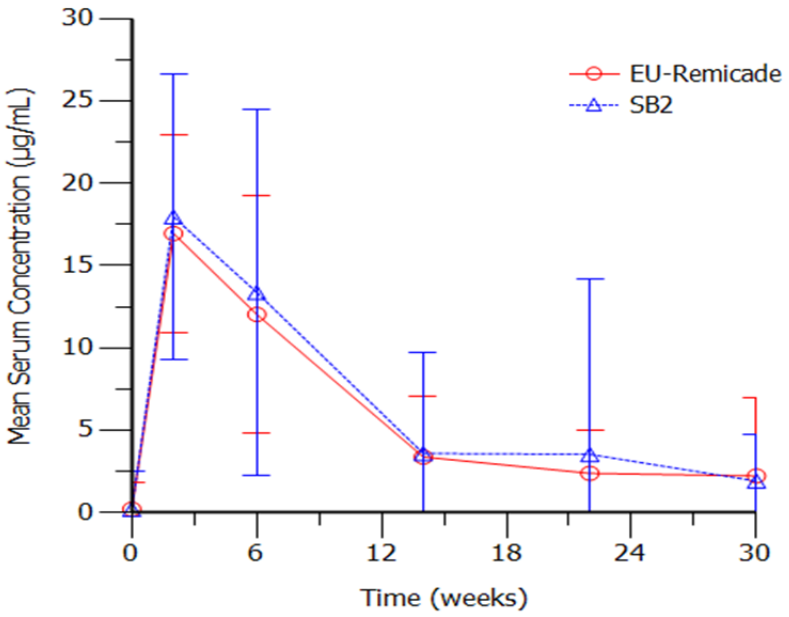

Figure 2. Infliximab serum trough concentrations following multiple IV dose (3 mg/kg) of SB2 or EU-approved Remicade in RA patients (Study SB2-G31-RA)

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

Table 5. Summary of infliximab serum trough concentrations of SB2 and EU-approved Remicade in Study SB2-G31-RA

Timepoint	Statistics	SB2 n=165	EU Remicade® n=160
Week 0	n	160	149
	Mean (SD)	0.000 (0.0000)	0.000 (0.0000)
	CV%	NC	NC
	Min, Max	0.00, 0.00	0.00, 0.00
Week 2	n	161	156
	Mean (SD)	17.965 (8.6612)	16.954 (6.0218)
	CV%	48.2125	35.5191
	Min, Max	0.00, 90.08	0.00, 34.79
Week 6	n	155	153
	Mean (SD)	13.374 (11.1216)	12.039 (7.1710)
	CV%	83.1586	59.5654
	Min, Max	0.00, 73.32	0.00, 35.87
Week 14	n	153	143
	Mean (SD)	3.593 (6.0938)	3.380 (3.6535)
	CV%	169.6090	108.0864
	Min, Max	0.00, 54.66	0.00, 23.24
Week 22	n	146	147
	Mean (SD)	3.538 (10.6475)	2.390 (2.6090)
	CV%	300.9453	109.1630
	Min, Max	0.00, 110.54	0.00, 12.90
Week 30	n	139	143
	Mean (SD)	1.915 (2.8055)	2.224 (4.7326)
	CV%	146.5085	212.7572
	Min, Max	0.00, 19.33	0.00, 50.71

5 subjects from the SB2 group and 9 subjects from the Remicade® group were excluded from summary statistics due to quantifiable pre-dose concentration at Baseline.
CV%: coefficient of variation; Max: maximum; Min: minimum; SD: standard deviation
Source: Section 5.3.5.1 CSR SB2-G31-RA (78-week CSR), Table 11-18

(Source: CSR SB2-G31-RA Table 2.7.2.2-8)

2.2.3.2 How does the PK of SB2 in healthy adults compare to that in patients with the target disease?

In this submission, the PK profile of SB2 was assessed in healthy subjects up to 71 days following a single IV dose of 5 mg/kg, but only trough serum concentration of SB2 were assessed in patients with RA following multiple IV doses of 3 mg/kg at Weeks 0, 2 and 6, then every 8 weeks. Therefore, the PK of SB2 was not compared between healthy subjects and RA patients in this submission.

2.2.3.3 What is the variability of the PK parameters in volunteers and patients with the target disease?

The variability of Cmax and AUC evaluated as coefficient of variation (%CV) was about or less than 30% after single dose administration of 5 mg/kg for all the three products. After multiple dose administration, the variability of Cmin at week 30 is 212% for EU-approved Remicade and 146% for SB2 in patients with RA (Table 6).

Table 6. Variability of infliximab exposure

Product	**%CV**			**Dose**
SB2-G11-NHV				
	Cmax N=53	AUC0-t N=53	AUC0-inf N=53	
US-licensed Remicade	14.5	21.8	25.1	5 mg/kg single IV dose
EU-approved Remicade	14.2	24.8	30.7	
SB2	13.4	26.3	29.8	
SB2-G31-RA				
	Cmin (at Week 30)			
EU-approved Remicade	212 (n=143)			3 mg/kg IV doses at Weeks 0, 2, 6 and then every 8 weeks
SB2	146 (n=139)			

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

2.3 Intrinsic Factors

2.3.1 Immunogenicity

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

A validated electrochemiluminescent (ECL) bridging immunogenicity assay using SB2-labelled intermediates was used for detection of ADAs in Studies SB2-G11-NHV and SB2-G31-RA. For detection of neutralizing ADA (nAb), a cell-based assay was used in Study SB2-G11-NHV and a ligand-binding assay was used Study SB2-G31-RA. Please refer to OBP review for more detailed information regarding assay validation.

In Study SB2-G11-NHV, serum samples were collected at baseline, Day 29, and the end-of-study visit (Day 71) for assessment of the ADA and nAb of SB2, EU-approved Remicade and US-licensed Remicade. Overall, following a single 5 mg/kg IV dose of study drug, the incidence of ADAs was similar between all three treatment arms in healthy subjects (Table 7).

Note that the ADA incidence has been originally reported to be 25/53 (47.2%), 20/53 (37.3%) and 20/53 (37.7%) for SB2, EU-approved Remicade and US-licensed Remicade, respectively, in the study report. After the bioanalytical site inspection, the ADA incidence was updated as shown below but there was no update regarding the nAb incidence (Table 7). It should be noted that the reported incidence of neutralizing antibody (nAb/ADA) for Study SB2-G11-NHV was considered inaccurate due to the assay limitation and bioanalytical inspection issue (See section 2.3.1.3 for further detail). Please refer to bioanalytical inspection report (reviews by Drs. Kara Scheibner, Michael Skelly, and Himanshu Gupta dated September 1, 2016) and the OBP review for more detailed information regarding the immunogenicity assays and immunogenicity update.

Table 7. Immunogenicity results of Study SB-G11-NHV in healthy subjects

Immunogenicity	The number (%) of subjects at different visit	SB2 (N=53)	EU-approved Remicade (N=53)	US-licensed Remicade (N=53)
ADA+	Day 1 (Baseline)	0/53 (0)	0/53 (0)	0/53 (0)
	Day 29	2/53 (3.8%)	0/53 (0)	1/53 (1.9%)
	Day 71	26/53 (49.1%)	23/53 (43.4%)	23/53 (43.4%)
nAb+/ADA+*	Day 1 (Baseline)	0/0 (0)	0/0 (0)	0/0 (0)
	Day 29	1/2 (50%)	0/0 (0)	0/1 (0)
	Day 71	14/26 (53.8%)	14/23 (60.9%)	7/23 (30.4%)

*The reported incidence of nAB/ADA for Study SB2-G11-NHV was considered inaccurate due to the assay limitation and bioanalytical inspection issue.

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

In Study SB2-G31-RA, immunogenicity samples were collected at Weeks 0 (baseline), 2, 6, 14, 22, 30, 38, 46, 54, 62, 70, and 78 for assessment of the ADA and nAb of SB2 and EU-approved

Remicade. Overall, following multiple 3 mg/kg IV dose of study drug, the incidence of ADAs was comparable between SB2 and EU-approved Remicade throughout the study, including the transition-extension period (Table 8).

Table 8. Immunogenicity results of Study SB-G31-RA in RA patients

	Double blind period at Week 30		**Transition-extension period at Week 78**		
n/total (%)	SB2	EU-Remicade	SB2	EU-Remicade →SB2	EU-Remicade → EU-Remicade
ADA+	133/251 (53.0%)	116/264 (43.9%)	133/201 (61.5%)	59/94 (62.8%)	61/101 (60.4%)
nAb+/ADA+	129/133 (92.4%)	109/116 (94.0%)	126/133 (94.7%)	49/59 (83.1%)	55/61 (90.2%)

Note that the percentages for nAb result are based on the number of positive ADA results at that visit.

(Source: Adapted from Tables 12-20 and 12-21 of Study SB2-G31-RA 78-week Clinical Study report)

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

Per the product labeling for Remicade, patients who were antibody-positive were more likely to have higher rates of clearance of infliximab. In this submission, the systemic exposures of SB2 or Remicade in subjects who were antibody-positive were about 20-30% lower as compared to those in patients who were antibody-negative (Table 9). However, additional analyses according to subject antibody (ADA) status indicated that the ADA formation did not affect the PK similarity (Tables 10 and 11).

Table 9. Mean (%CV) serum PK parameters of infliximab (Study SB2-G11-NHV)

Parameter	**SB2**	**N**	**US-licensed Remicade**	**N**	**EU-approved Remicade**	**N**
ADA- Population						
Cmax	128.78 (14.6)	27	127.56 (14.1)	30	127.22 (16.3)	30
AUC0-t	42242 (18.8)	27	41382 (18.4)	30	42506 (20.7)	30
AUC0-inf	45299 (22.8)	27	44198 (21.3)	30	46378 (26.2)	30
ADA+ Population						
Cmax	123.98 (12.0)	26	131.22 (15.2)	23	124.96 (10.9)	23
AUC0-t	32383 (28.2)	26	33373 (20.8)	23	31109 (16.4)	23
AUC0-inf	32935 (29.4)	26	34084 (22.5)	23	31445 (16.8)	23

The units of Cmax and AUC are µg/mL and µg*hr/mL, respectively.

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

Table 10. Analysis of PK parameters of infliximab in Study SB2-G11-NHV (ADA negative population)

SB2 (T) vs US-licensed Remicade (R)						
Parameter	**LSM (T)**	**N**	**LSM (R)**	**N**	**GMR**	**90% CI**
Cmax	127.50	27	126.31	30	100.95	(94.69, 107.62)
AUC0-t	41523	27	40632	30	102.19	(93.68, 111.48)
AUC∞	44232	27	43168	30	102.46	(92.76, 113.19)
SB2 (T) vs EU-approved Remicade (R)						
Parameter	**T**	**N**	**R**	**N**	**GMR**	**90% CI**
Cmax	127.50	27	125.67	30	101.46	(94.86, 108.53)
AUC0-t	41523	27	41655	30	99.68	(91.32, 108.81)
AUC∞	44231	27	44973	30	98.35	(88.56, 109.23)
EU-approved Remicade (T) vs US-licensed Remicade (R)						
Parameter	**T**	**N**	**R**	**N**	**GMR**	**90% CI**
Cmax	125.66	30	126.31	30	99.49	(93.20, 106.21)
AUC0-t	41655	30	40632	30	102.52	(93.92, 111.90)
AUC∞	44973	30	43168	30	104.18	(93.99, 115.48)

The units of Cmax and AUC are µg/mL and µg*h/mL, respectively.

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

Table 11. Analysis of PK parameters of infliximab in Study SB2-G11-NHV (ADA positive population)

SB2 (T) vs US-licensed Remicade (R)						
Parameter	**LSM (T)**	**N**	**LSM (R)**	**N**	**GMR**	**90% CI**
Cmax	123.13	26	129.87	23	94.81	(88.98, 101.03)
AUC0-t	31081	26	32674	23	95.12	(83.82, 107.96)

AUC∞	31529	26	33265	23	94.78	(83.08, 108.12)
SB2 (T) vs EU-approved Remicade (R)						
Parameter	**T**	**N**	**R**	**N**	**GMR**	**90% CI**
Cmax	123.13	26	124.26	23	99.09	(93.80, 104.68)
AUC0-t	31081	26	30725	23	101.16	(89.91, 113.82)
AUC∞	31529	26	31038	23	101.58	(89.99, 114.66)
EU-approved Remicade (T) vs US-licensed Remicade (R)						
Parameter	**T**	**N**	**R**	**N**	**GMR**	**90% CI**
Cmax	124.26	23	129.87	23	95.68	(89.80, 101.95)
AUC0-t	30725	23	32674	23	94.03	(85.66, 103.22)
AUC∞	31038	23	33265	23	93.30	(84.60, 102.91)

The units of Cmax and AUC are µg/mL and µg*h/mL, respectively.

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

In patients with RA, additional analyses according to subject antibody (ADA) status showed that Ctrough of SB2 or EU-approved Remicade in RA patients who were antibody-positive were highly variable and also lower as compared to those in patients who were antibody-negative (Study SB2-G31-RA). The numerical difference observed in the comparison of concentrations between the SB2 and EU-approved Remicade treatment in each ADA subgroup analysis was likely due to the high inter-subject variability of trough serum concentrations, especially in ADA positive subgroups (CV is 252% and 352% for SB2 and EU-approved Remicade treatment, respectively) (Table 12).

It was also noted that since only trough PK sample were collected, serum concentrations were undetectable in ~36% RA patients at Week 30 (59 out of 139 (42%) and 42 out of 143 (29%) in SB2 and EU-approved Remicade treatment, respectively), especially in ADA-positive subgroups (56 out of 75 (75%) and 34 out of 69 (49%) in SB2 and EU-approved Remicade treatment, respectively). Therefore, the PK data from Study SB2-G31-RA is limited to draw any meaningful conclusion on the impact of immunogenicity on PK.

Table 12. Mean (%CV) serum trough concentrations of infliximab at Week 30 (Study SB2-G31-RA)

Parameter	SB2	N	EU-approved Remicade	N
ADA- Population				
Cmin,ss	3.682 (86.51)	64	2.604 (85.89)	74
ADA+ Population				
Cmin,ss	0.407 (252.22)	75	1.818 (352.63)	69

The unit of serum concentration is µg/mL.

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

2.3.1.3 Do the anti-drug antibodies have neutralizing activities?

A cell based assay and a ligand based assay was used for neutralizing antibody assessment in Study SB2-G11-NHV and Studies SB2-G31-RA, respectively. In Study SB2-G11-NHV, 53.8% (14/26), 60.9% (14/23), and 30.4% (7/23) subjects who devloped ADAs developed neutralizing antibodies in SB2, EU-approved Remicade and US-licensed Remicade treatment group, respectively (Table 7). In Studies SB2-G31-RA, nearly all subjects who devloped ADAs developed neutralizing antibodies (Tables 8).

It should be noted that the cell based assay which was used in Study SB2-G11-NHV was considered less sensitive as compared to the ligand based assay. In addition, according to the bioanalytical inspection review for Study SB2-G11-NHV, the ADA status was updated for 7 subjects, however there was no update regarding the nAb status (the nAb status was unknown for 5 subjects, of which 1 subject was with SB2, 2 subjects were with EU-approved Remicade, and 2 subjects were with US-licensed Remicade). Therefore, the reported percentage of nAb/ADA for Study SB2-G11-NHV was considered inaccurate. Please refer to bioanalytical inspection report (reviews by Drs. Kara Scheibner, Michael Skelly, and Himanshu Gupta dated September 1, 2016) and the OBP review for more detailed information regarding the immunogenicity assays and immunogenicity update.

Additional exploratory analyses according to subject nAb status showed that AUC of SB2, EU-approved Remicade, and US-licensed Remicade in helathy subjects who were positive for nAb and ADA were lower as compared to subjects who were negative for nAb but positive for ADA (Table 13). However, due to the limited sample size and innacurate nAb incidence, the impact of neutralizing antibodies on the demonstration of PK similarity was inconclusive.

Table 13. Mean (%CV) serum PK parameters of infliximab by nAb status (Study SB2-G11-NHV)

Product	Cmax		AUC0-t		AUC0-inf	
	ADA+/nAb+	ADA+/nAb-	ADA+/nAb+	ADA+/nAb-	ADA+/nAb+	ADA+/nAb-
SB2	121.4 (12.2) (n=14)	127.0 (11.7) (n=12)	27621 (24.8) (n=14)	37938 (22.3) (n=12)	27709 (24.7) (n=14)	39032 (23.1) (n=12)
US-licensed Remicade	138.8 (15.1) (n=7)	127.9 (15.0) (n=16)	27535 (17.5) (n=7)	35927 (17.2) (n=16)	27721 (17.7) (n=7)	36868 (19.1) (n=16)
EU-approved Remicade	125.53 (13.0) (n=14)	124.05 (6.9) (n=9)	29611 (14.0) (n=14)	33438 (17.3) (n=9)	29816 (13.9) (n=14)	33978 (17.9) (n=9)

The units of Cmax and AUC are µg/mL and µg*h/mL, respectively.

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

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

The immunogenicity does not appear to affect the efficacy comparison between SB2, US-licensed Remicade, and EU-approved Remicade.

Per the product labeling for Remicade, patients who were antibody-positive were more likely to have reduced efficacy. In this submission, the ACR20 response rate of SB2 or EU-approved Remicade in subjects who were antibody-positive were about 20% lower as compared to those in patients who were antibody-negative. However, the establishment of efficacy similarity between SB2 and EU-approved Remicade Study SB2-G31-RA indicated that the ADA formation did not significantly affect the efficacy similarity (Table 14). Please refer to the medical review and statistical review for further details.

Table 14. ANCOVA for ACR20 response at week 30 by ADA result and treatment

30-week ADA Result	Treatment	Responder n'	n	(%)	Adjusted Difference Rate (SE)	95% CI	P value
Positive	SB2 (N=127)	127	72	(56.7)	−0.88% (5.966%)	(−12.63%, 10.87%)	
	Remicade® (N=126)	126	74	(58.7)			
							0.989
Negative	SB2 (N=104)	104	76	(73.1)	−1.57% (5.914%)	(−13.23%, 10.08%)	
	Remicade® (N=121)	121	89	(73.6)			

ACR = American College of Rheumatology; ADA = anti-drug antibodies; ANCOVA = analysis of covariance; CI = confidence interval; N = number of subjects in the per-protocol set 1; n' = number of subjects with available assessment results; n = number of responders; SE = standard error
The p- value is for the interaction term.
Source: 54-week CSR Table 14.2-2.6

(Source: Study SB2-G31-RA 78-week Clinical Study report, Table 11-17)

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

No, the immunogenicity does not appear to affect the safety comparison between SB2 and EU-approved Remicade. Overall, the incidence of infusion-related reactions was higher in the ADA-

positive subgroup than the ADA-negative subgroup, but was comparable between 2 treatment groups within each ADA subgroup. Please refer to medical review for further details.

2.4 General Biopharmaceutics

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

The clinical formulation was the same as the proposed to-be-marketed formulation. Therefore, no bridging study is needed.

2.5 Analytical Section

2.5.1 What are the analytical methods used to measure SB2 or Remicade in serum?

The serum concentrations of SB2, EU-approved Remicade and US-licensed Remicade were quantified by a validated enzyme-linked immunosorbent assay. Based on the bioanalytical inspection report, the bioanalytical portions of Study SB2-G11-NHV (Validation Report (b) (4)) are acceptable (reviews by Drs. Kara Scheibner, Michael Skelly, and Himanshu Gupta dated September 1, 2016).

The bioanalytical assay used in Study SB2-G31-RA (Validation Report (b) (4) is the same as Study SB2-G11-NHV, except that methotrexate interference was further evaluated before analyzing PK samples from Study SB2-G31-RA. Results indicated that there is no effect from up to 5000 ng/mL methotrexate on the quantitation of infliximab in human serum.

The assay validation (Validation Report (b) (4)) was described as below and summarized in Table 15.

Human serum concentrations of SB2, US-licensed Remicade and EU-approved Remicade were measured with an enzyme-linked immunosorbent assay. Standard (STD) and quality control (QC) samples were prepared by spiking infliximab into human serum. In this assay, infliximab is captured by TNFα (Product No. 210-TA-001MG/CF lot AA2712051, R&D Systems) coated in wells of an ELISA plate. A horseradish peroxidase (HRP) conjugated anti-human IgG antibody (Product No. A0170, lot 062M4819, Sigma,) is used to detect the bound analyte. Tetramethylbenzidine is used as a substrate for colorimetric readout following addition of the stop solution. Colorimetric intensity is determined using a Spectramax plate reader at 450 nm.

<u>Intra-run and inter-run precision and accuracy</u>

Intra-assay precision and accuracy are evaluated by analyzing each QC level (100, 300, 900, 2400, and 3200 ng/mL) containing SB2, US-licensed Remicade, and EU-approved Remicade (n = 6) during three validation runs. Inter-assay precision and accuracy were calculated from the QC in each validation run for SB2, from at least six inter-assay precision and accuracy runs for

US-licensed Remicade, and EU-approved Remicade. Precision of the method, defined by the percent coefficient of variation (%CV = [(standard deviation / mean) x 100]), was determined from the interpolated (observed) results. Accuracy of the method was defined by the percent relative error (%Accuracy = [100 x (mean observed concentration / nominal concentration]). The QC samples met the acceptance criteria: the intra-run or inter-run accuracy should not deviate by more than ± 20.0% of the nominal value (± 25.0% at the lower limit of quantitation (LLOQ)) and the intra-run or inter-run precision should not deviate by more than 20.0% (25.0% at LLOQ).

Limits of quantification

The lower limit of quantitation (LLOQ) is defined as the lowest analyte concentration that can be quantitated with acceptable accuracy and precision (± 25.0%). The concentration that met this criterion was determined to be 100 ng/mL.

An upper limit of quantitation (ULOQ) is defined as the highest analyte concentration that can be quantitated with acceptable accuracy and precision (± 25.0%). The concentration that met this criterion was determined to be 3200 ng/mL.

Matrix effect/selectivity

Normal human serum and RA human serum samples from ten individuals were analyzed for matrix interference. Normal human serum and RA human serum specificity samples, fortified with either SB2, US-licensed Remicade, or EU-approved Remicade at 300 ng/mL, were prepared from ten individuals and analyzed. Selectivity met the acceptance criteria for both normal and RA serum: the observed concentrations of at least 80% of the QC samples must be within ± 20.0% of their nominal values and precision ≤ 20.0%; the observed concentrations of the blank matrix must be < LLOQ in at least 80% of the lots tested.

The possible effects of hemolysis and lipemia were also assessed. There were no observed effects of hemolysis and lipemia since all QC samples were within ± 20.0% of their nominal values and precision ≤ 20.0%.

The possible effect of TNFα was also assessed. Results indicated that there was no effect from TNFα on the quantitation of SB2 and EU-approved Remicade. There was no effect from TNFα on the quantitation of US-licensed Remicade, except at 5.00 ng/mL TNFα at low QC level (300 ng/mL).

Dilution Integrity

QC sample was prepared containing SB2, EU-approved Remicade or US-licensed Remicade at a concentration of 150000 ng/mL in 100% human serum and followed by 500-fold dilution with the final concentrations of 300 ng/mL for SB2, EU-approved Remicade or US-licensed Remicade, respectively. The reported dilution integrity is 1:500 since the QC samples met the acceptance criteria: the %CV for the dilution QC pools' replicate determinations must be ≤ 20.0 % and the mean accuracy must be within ± 20.0 %.

The prozone or "hook effect" was evaluated for SB2, EU-approved Remicade or US-licensed Remicade by analyzing a 150000 ng/mL QC sample undiluted and at 5-, 10-, 25-, 150-, and 500-fold dilutions. The absence of a hook effect will be demonstrated if the dilution where the expected concentration (after dilution) is above the highest calibration curve point, the result reads above the highest calibration standard or greater than the ULOQ, and if no systematic negative slope is observed with increasing drug concentration. Results indicated that no apparent "hook effect" was observed at concentrations up to 150000 ng/mL.

Specificity

Selectivity and matrix effect experiments provide appropriate evaluation of specificity of the method.

Stability

Solution stability: Stock B solutions were made by diluting subsequently reconstituted lyophilized standard (SB2, EU-approved Remicade, and US-licensed Remicade), and were then used for preparation of all calibration standards, QCs, and validation test samples. Stock B solution stability was evaluated by (b) (4) (b) (4) by analyzing solutions that had been stored for 73 days at -70 °C or colder and comparing the absorbance to the original absorbance measured on the day of reconstitution (prepared for use in original validation preparations). The percent difference of the same Stock B preparations were within 5 % of the original absorbance.

Benchtop stability: Analyte stability in thawed matrix for SB2, EU-approved Remicade, and US-licensed Remicade was evaluated by allowing a set (n=6) of low- and high-level QCs samples (300 ng/mL and 2400 ng/mL in 100% human serum) to thaw and remain at room temperature for at least 24 hours prior to analysis. Results indicate that SB2, EU-approved Remicade, and US-licensed Remicade are stable in human serum for at least 24 hours at ambient temperature since at least two-thirds of the QC samples did not deviate by more than ± 20.0% from their nominal concentration and the precision was ≤ 20.0%.

Freeze-thaw stability: Freeze/thaw stability for SB2, EU-approved Remicade, and US-licensed Remicade was evaluated by analyzing a set (n=6) of low- and high-level QC samples (300 ng/mL and 2400 ng/mL in 100% human serum) that were subjected to five freeze/thaw cycles. Samples were frozen at -70 °C or colder and thawed at room temperature. The results indicate that SB2, EU-approved Remicade, and US-licensed Remicade are stable in human serum for at least five freeze/thaw cycles before analysis since at least two-thirds of the QC samples did not deviate by more than ± 20.0% from their nominal concentration and the precision was ≤ 20.0%.

Long term storage stability: Analyte stability in frozen matrix for SB2, EU-approved Remicade, and US-licensed Remicade was evaluated by analyzing samples which had been stored for 30 days at -20 °C and for 21days at -70 °C or colder versus freshly prepared calibration standards. Results indicated SB2, EU-approved Remicade, and US-licensed Remicade are stable in human serum for 30 days at -20°C and for 21 days at -70°C since the QC samples did not deviate by more than ± 20.0% from their nominal concentration and the precision was ≤ 20.0%. On December 09, 2016, sponsor submitted "Method Validation Report Addendum 4, (b) (4)

Project (b) (4) " per the Agency's information request dated November 30, 2016, in which the long term storage stability in frozen matrix was updated to be 118 days at -25 °C ± 5 °C and 875 days at -80 °C ± 10 °C in normal human serum and 494 days -25 °C ± 5 °C and 462 days at -80 °C ± 10 °C in RA human serum. Further long term freezer storage stability evaluations will be conducted at appropriate time points and updated when they are available.

Whole blood stability: not assessed.

Processed sample stability: not assessed.

Table 15. Summary of infliximab PK assay validation

(b) (4) **Project Code**	(b) (4)			
Method ID				
Analyte	SB2, US Remicade®, and EU Remicade®			
Minimum Required Dilution	1:100			
Matrix	Human Serum			
Anticoagulant	None			
Method Description	ELISA			
Sample Volume (µL)	20.0-µL aliquot			
Sample Storage Temperature	-70 °C or colder			
Lower Limit of Quantitation (LLOQ)	100 ng/mL			
Upper Limit of Quantitation (ULOQ)	3200 ng/mL			
Regression, Weighting	four-parameter logistic, 1/response^2			
Standard Curve Concentrations	50.0 to 4000 ng/mL			
QC Concentrations	100, 300, 900, 2400, and 3200 ng/mL			
QC Intra-assay Statistics (%) SB2	Level	Conc. (ng/mL)	Precision	Accuracy
	LLOQ	100	6.64 %	9.94 %
	Low	300	6.17 %	10.6 %
	Mid	900	6.56 %	10.5 %
	High	2400	5.03 %	4.30 %
	ULOQ	3200	8.98 %	2.86 %
QC Intra-assay Statistics (%) US Remicade®	Level	Conc. (ng/mL)	Precision	Accuracy
	LLOQ	100	13.3 %	1.57 %
	Low	300	8.86 %	-0.882 %
	Mid	900	6.48 %	4.23 %
	High	2400	11.7 %	-0.202 %
	ULOQ	3200	7.06 %	3.44 %
QC Intra-assay Statistics (%) EU Remicade®	Level	Conc. (ng/mL)	Precision	Accuracy
	LLOQ	100	12.2 %	-16.1 %
	Low	300	12.6 %	-10.6 %
	Mid	900	5.79 %	9.35 %
	High	2400	6.72 %	13.6 %
	ULOQ	3200	2.78 %	4.94 %
QC Inter-assay Statistics (%) SB2	Level	Conc. (ng/mL)	Precision	Accuracy
	LLOQ	100	9.41 %	-0.555 %
	Low	300	7.47 %	4.16 %
	Mid	900	10.5 %	7.93 %
	High	2400	12.3 %	6.04 %
	ULOQ	3200	9.88 %	6.49 %
QC Inter-assay Statistics (%) US Remicade®	Level	Conc. (ng/mL)	Precision	Accuracy
	LLOQ	100	10.2 %	-1.59 %
	Low	300	10.3 %	2.42 %
	Mid	900	11.7 %	5.07 %
	High	2400	12.1 %	3.49 %
	ULOQ	3200	13.5 %	7.16 %

QC Inter-assay Statistics (%) **EU Remicade®**	Level	Conc. (ng/mL)	Precision	Accuracy
	LLOQ	100	11.2 %	7.26 %
	Low	300	7.30 %	6.19 %
	Mid	900	10.7 %	8.37 %
	High	2400	14.8 %	9.09 %
	ULOQ	3200	11.8 %	6.88 %
Thawed Matrix Stability (hrs)	24 hours at room temperature			
Freeze-thaw Stability (cycles)	Five cycles thawed at room temperature			
Frozen Matrix Storage Stability (days)	30 days at -20 °C and 21 days at -70 °C or colder			
Dilutional Linearity	150000 ng/mL diluted 500-fold			
Selectivity	Acceptable with ten out of ten specificity sample lots meeting the acceptance criteria for normal and RA serum. Acceptable fortified specificity for SB2 with ten out of ten normal serum lots and nine out of ten RA serum lots meeting acceptance criteria. Acceptable fortified specificity US Remicade® with nine out of ten specificity sample lots meeting the acceptance criteria for normal and RA serum. Acceptable fortified specificity for EU Remicade® with ten out of ten normal serum lots and nine out of ten RA serum lots meeting acceptance criteria.			
Hook Effect	No apparent hook effect observed at concentrations up to 150000 ng/mL for SB2, US Remicade®, and EU Remicade®			
Hemolysis	No effect from hemolysis on the quantitation of SB2, US Remicade®, and EU Remicade®			
Lipemia	No effect from lipemia on the quantitation of SB2, US Remicade®, and EU Remicade®			
Analyte Interference	No effect from TNFα on the quantitation of SB2. No effect from TNFα on the quantitation of US Remicade® except at 5.00 ng/mL TNFα at low QC level. No effect from TNFα on the quantitation of EU Remicade® at any TNFα concentration evaluated.			

(Source: Method validation report of Project (b) (4) Page 9 of 146)

Note that on December 09, 2016, sponsor submitted "Method Validation Report Addendum 4, (b) (4) Project (b) (4) " per the Agency's information request dated November 30, 2016, in which the long term storage stability in frozen matrix was updated to be 118 days at -25 °C ± 5 °C and 875 days at -80 °C ± 10 °C in normal human serum and 494 days -25 °C ± 5 °C and 462 days at -80 °C ± 10 °C in RA human serum..

2.5.2 What bioanalytical methods are used to assess concentrations of the measured moieties?

Details of the bioanalytical method for determination of serum concentrations of SB2, EU-approved Remicade and US- Remicade are discussed in section 2.5.1.

2.5.3 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?

The standard curve for SB2, EU-approved Remicade and US-licensed Remicade serum concentration analysis ranged from 50 to 4000 ng/mL. A four-parameter logistic, 1/response² weighted, least-squares regression algorithm was used.

2.5.4 What is the sample stability under conditions used in the study?

Details of stability conditions are described in section 2.5.1.

2.5.5 What bioanalytical methods are used to assess the immunogenicity?

A single bridging ligand-binding assay (SB2) was used for the determination of ADAs in the clinical Phase I and Phase III studies (see Figure 3). In this assay, the qualitative and quasi-quantitative determination of ADAs in human serum samples was conducted by using a validated Meso Scale Discovery (MSD) platform, in which, the ADAs were pulled out using streptavidin-coated magnetic beads from acidified clinical samples and biotinylated (BT)-SB2 and ruthenylated (Ru)/sulfo-tagged-SB2 are incubated in solution to enable formation of antigen-antibody complexes that are subsequently captured on streptavidin (SA)-coated MSD plates. Clinical samples were pre-treated by acid-dissociation to reduce interference by residual circulating drug. Controls were purified monkey anti-SB2 polyclonal and human anti-Remicade monoclonal antibodies.

To detect neutralizing ADA, a cell-based assay was used in the clinical Phase I study and a ligand-binding assay was used in the clinical Phase III study.

Please refer to OBP review for more detailed information regarding assay validation.

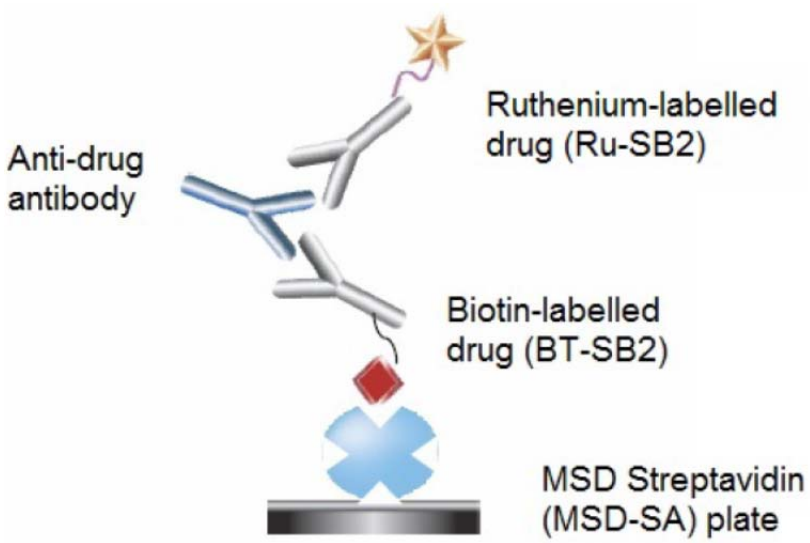

Figure 3. Overview of Electrochemiluminescent (ECL) Bridging Immunogenicity Assay for Detection of Anti-Drug Antibodies (ADAs) Using SB2-labelled Intermediates

(Source: Summary of Biopharmaceutical Studies, Figure 2.7.1.1-1)

3. Detailed Labeling Recommendations

Compared with the labeling of US-licensed Remicade, no changes have been proposed for the labeling language regarding the immunogenicity in Section 6.1 Clinical Trial Experience and PK in Section 12.3 Pharmacokinetics in the proposed labeling of SB2 (shown as below). Clinical pharmacology does not have any revision.

6.1 Clinical Trial Experience

Immunogenicity
Treatment with RENFLEXIS can be associated with the development of antibodies to infliximab. An enzyme immunoassay (EIA) method was originally used to measure antiinfliximab antibodies in clinical studies of infliximab. The EIA method is subject to interference by serum infliximab, possibly resulting in an underestimation of the rate of patient antibody formation. A separate, drug-tolerant electrochemiluminescence immunoassay (ECLIA) method for detecting antibodies to infliximab was subsequently developed and validated. This method is 60-fold more sensitive than the original EIA. With the ECLIA method, all clinical samples can be classified as either positive or negative for antibodies to infliximab without the need for the inconclusive category.

The incidence of antibodies to infliximab was based on the original EIA method in all clinical studies of infliximab except for the Phase 3 study in pediatric patients with ulcerative colitis where the incidence of antibodies to infliximab was detected using both the EIA and ECLIA methods *[see Adverse Reactions, Pediatric Ulcerative Colitis (6.1)]*.

The incidence of antibodies to infliximab in patients given a 3-dose induction regimen followed by maintenance dosing was approximately 10% as assessed through 1 to 2 years of infliximab treatment. A higher incidence of antibodies to infliximab was observed in Crohn's disease patients receiving infliximab after drug-free intervals >16 weeks. In a study of psoriatic arthritis in which 191 patients received 5 mg/kg with or without MTX, antibodies to infliximab occurred in 15% of patients. The majority of antibody-positive patients had low titers. Patients who were antibody-positive were more likely to have higher rates of clearance, reduced efficacy and to experience an infusion reaction *[see Adverse Reactions (6.1)]* than were patients who were antibody negative. Antibody development was lower among rheumatoid arthritis and Crohn's disease patients receiving immunosuppressant therapies such as 6-MP/AZA or MTX.

In the psoriasis Study II, which included both the 5 mg/kg and 3 mg/kg doses, antibodies were observed in 36% of patients treated with 5 mg/kg every 8 weeks for 1 year, and in 51% of patients treated with 3 mg/kg every 8 weeks for 1 year. In the psoriasis Study III, which also included both the 5 mg/kg and 3 mg/kg doses, antibodies were observed in 20% of patients treated with 5 mg/kg induction (weeks 0, 2 and 6), and in 27% of patients treated with 3 mg/kg induction. Despite the increase in antibody formation, the infusion reaction rates in Studies I and II in patients treated with 5 mg/kg induction followed by every 8 week maintenance for 1 year and in Study III in patients treated with 5 mg/kg induction (14.1%- 23.0%) and serious infusion reaction rates (<1%) were similar to those observed in other study populations. The clinical significance of apparent increased immunogenicity on efficacy and infusion reactions in psoriasis patients as compared to patients with other diseases treated with infliximab over the long term is not known.

The data reflect the percentage of patients whose test results were positive for antibodies to infliximab in an immunoassay, and they are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to infliximab with the incidence of antibodies to other products may be misleading.

12.3 Pharmacokinetics

In adults, single intravenous (IV) infusions of 3 mg/kg to 20 mg/kg showed a linear relationship between the dose administered and the maximum serum concentration. The volume of distribution at steady state was independent of dose and indicated that infliximab was distributed primarily within the vascular compartment. Pharmacokinetic results for single doses of 3 mg/kg to 10 mg/kg in rheumatoid arthritis, 5 mg/kg in Crohn's disease, and 3 mg/kg to 5 mg/kg in plaque psoriasis indicate that the median terminal half-life of infliximab is 7.7 to 9.5 days.

Following an initial dose of infliximab, repeated infusions at 2 and 6 weeks resulted in predictable concentration-time profiles following each treatment. No systemic accumulation of infliximab occurred upon continued repeated treatment with 3 mg/kg or 10 mg/kg at 4-or 8week intervals. Development of antibodies to infliximab increased infliximab clearance. At 8 weeks after a maintenance dose of 3 to 10 mg/kg of infliximab, median infliximab serum concentrations ranged from approximately 0.5 to 6 mcg/mL; however, infliximab concentrations were not detectable (<0.1 mcg/mL) in patients who became positive for antibodies to infliximab. No major differences in clearance or volume of distribution were observed in patient subgroups defined by age, weight, or gender. It is not known if there are differences in clearance or volume of distribution in patients with marked impairment of hepatic or renal function.

Infliximab pharmacokinetic characteristics (including peak and trough concentrations and terminal half-life) were similar in pediatric (aged 6 to 17 years) and adult patients with Crohn's disease or ulcerative colitis following the administration of 5 mg/kg infliximab.

Population pharmacokinetic analysis showed that in children with juvenile rheumatoid arthritis (JRA) with a body weight of up to 35 kg receiving 6 mg/kg infliximab and children with JRA with body weight greater than 35 kg up to adult body weight receiving 3 mg/kg infliximab, the steady state area under the concentration curve (AUCss) was similar to that observed in adults receiving 3 mg/kg of infliximab.

4. Appendix

4.1 Appendix – Individual Study Review

Study SB2-G11-NHV (3-way PK Bridge/Similarity Study in Healthy Subjects)

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

Study Phase: Phase I

Study Duration: July 13, 2013 – October 14, 2013

Objectives

Primary: to investigate and compare the pharmacokinetic (PK) profiles of SB2, US-licensed Remicade, and EU-approved Remicade in healthy subjects (SB2 to EU-approved Remicade, SB2 to US-licensed Remicade, and EU-approved Remicade to US-licensed Remicade).

Secondary: to investigate the safety, tolerability, and immunogenicity data of SB2, EU-approved Remicade and US-licensed Remicade in healthy subjects.

Study Population

Healthy male and female subjects, aged 18-55 years, n=159 (53/arm)

Test Formulation

The final formulation, which will be used for the commercial batches, was used in this study.

Table 1. Test Products

Active pharmaceutical ingredient: infliximab			
	SB2	EU sourced Remicade®	US sourced Remicade®
Formulation	Vial of 100 mg lyophilised powder	Vial of 100 mg lyophilised powder	Vial of 100 mg lyophilised powder
Batch number	P49203A	2RMA69101	CKS83013P1

(Source: Study SB2-G11-NHV report, Table 9-1)

Study Design

This study was a single-blind, 3-arm, parallel group, single-dose study. A total of 159 healthy subjects aged 18-55 years (inclusive) were to be 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, or EU-approved

Remicade, or US-licensed Remicade by intravenous (IV) infusion for 120 minutes on the first day of study and then followed for 10 weeks during which the PK, safety, tolerability and immunogenicity measurements were made. To avoid infusion-related reaction, premedication with IV hydrocortisone (100 mg), oral acetaminophen (1000 mg), and oral loratadine (10 mg) were administered 30 minutes to 1 hour prior to the infusion of SB2, EU-approved Remicade and US-licensed Remicade. The scheme of study design is shown in Figure 1.

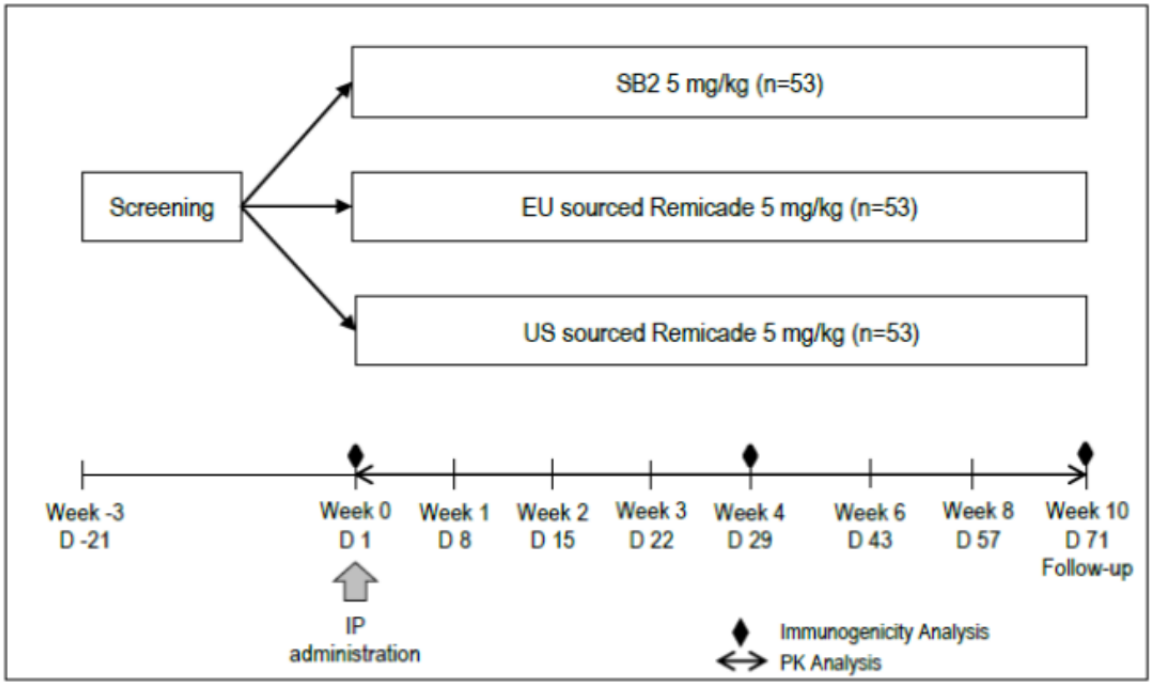

Figure 1. Study design of Study SB2-G11-NHV

(Source: Study SB2-G11-NHV report, Figure 9-1)

PK Assessment

PK sample**:** Blood samples for PK analysis were collected on Day 1 at 0 hour (predose), 1, 2 (end-of-infusion), 3, 4, 6, 12, 24, 48 and 72 hours after start of infusion; and on Days 6, 8, 15, 22, 29, 43, 57 and 71 (after start of infusion). The serum concentration of infliximab was measured using an enzyme-linked immunosorbent assay for the detection and quantification of infliximab.

Primary endpoints: Cmax, AUC0-t, AUC0-inf

Secondary endpoints: time to Cmax (Tmax), volume of distribution during terminal phase (Vz), terminal elimination rate constant (kel), terminal half-life (T1/2), total body clearance (CL), area under the concentration-time curve extrapolated from time zero to infinity as a percentage of total AUC (%AUCextrap)

Immunogenicity Assessment

Blood samples for immunogenicity assessment were collected on Day 1 (predose), Day 29, and Day 71.

Results

Demographics

A total of 319 subjects were screened, of which 159 subjects were randomized. No subjects discontinued from the study. The demographics of all randomized subjects are shown in Table 2 and the demographics of three treatment arms are comparable. The subject's inclusion/exclusion in data analysis was shown in Table 3. According to the PK and immunogenicity results, subjects were also included in PK population, ADA negative, and ADA positive population in data analysis (Table 4).

Table 2. Demographics Profile of All Randomized Subjects in Study SB-G11-NHV

Treatment	SB2 N=53	EU sourced Remicade® N=53	US sourced Remicade® N=53	Total N=159
Age (years)				
Mean	40.7	40.3	39.4	40.1
SD	9.67	9.72	9.87	9.71
Median	42	42	41	42
Min	19	19	23	19
Max	55	55	55	55
Gender, n (%)				
Male	49 (92.5)	51 (96.2)	50 (94.3)	150 (94.3)
Female	4 (7.5)	2 (3.8)	3 (5.7)	9 (5.7)
Race, n (%)				
White	51 (96.2)	52 (98.1)	52 (98.1)	155 (97.5)
Asian	1 (1.9)	0 (0.0)	1 (1.9)	2 (1.3)
Black or African American	1 (1.9)	0 (0.0)	0 (0.0)	1 (0.6)
Other	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.6)
Ethnicity, n (%)				
Not Hispanic or Latino	53 (100.0)	52 (98.1)	53 (100.0)	158 (99.4)
Hispanic or Latino	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.6)
Height (cm)				
Mean	178.5	178.1	178.6	178.4
SD	7.65	6.04	7.20	6.96
Median	179	179	178	179
Min	158	164	163	158
Max	191	188	194	194
Weight (kg)				
Mean	78.38	80.48	79.10	79.32
SD	8.709	7.506	8.304	8.183
Median	79.2	80.1	79.6	79.7
Min	60.2	63.9	62.9	60.2
Max	93.2	94.3	94.2	94.3
BMI (kg/m^2)				
Mean	24.56	25.39	24.79	24.91
SD	2.078	2.092	2.058	2.092
Median	24.6	25.0	24.8	24.8
Min	20.8	20.9	20.8	20.8
Max	29.1	29.8	30.0	30.0

N = number of subjects in the safety set; SD = standard deviation; BMI = Body Mass Index (BMI was calculated with weight at baseline [Day -1] and height at Screening).
Percentages were based on the number of subjects in the safety set.
Source: Table 14.1.3.1

(Source: Study SB2-G11-NHV report, Table 11-2)

Table 3. Inclusion or exclusion information in Study SB-G11-NHV data analysis

Subject ID./ Random ID	Treatment	Inclusion/exclusion in data analysis (Sponsor)	Inclusion/exclusion in data analysis (Reviewer)
32193/1234	SB2	Subjects got inpatient hospitalization to treat adverse events, Concussion and Borrelia infection, respectively, during the study periods. According to the concomitant medication records, the medication received included: Subject 1234: Novaminsulfon Subject 1256: Pantozol, Ibuhexal, Unacid, Novaminsulfon, Clexane, Paracetamol, Doxycyclin However, the exact records for infused fluid during the hospitalization could not be collected. Considering the possible influence of plasma dilution on PK due to fluid infusion and the primary objective of this PK similarity study, these two subjects were excluded in data analysis.	All data analysis was conducted with and without data from this subject.
70570/1256	SB2		

Table 4. Summary of study population

	SB2	**EU-approved Remicade**	**US-licensed Remicade**	**Total**
All Randomized Subject	53 (100%)	53 (100%)	53 (100%)	159 (100%)
PK Population	53/53 (100%)	53/53 (100%)	53/53 (100%)	159 (100%)
ADA-positive Population	26/53 (49.1%)	23/53 (43.4%)	23/53 (43.4%)	72/159 (45.3%)
ADA-negative Population	27/53 (50.9%)	30/53 (56.6%)	30/53 (56.6%)	87/159 (54.7%)

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

PK Results

The infliximab serum concentration vs time profiles and PK similarity analysis are shown in Figure 2 and Tables 5 and 6. Results indicated the infliximab PK profiles following a single IV infusion (5 mg/kg) of SB2, EU-approved Remicade, or US-licensed Remicade in healthy subjects are similar. In the pairwise comparisons, the 90% CI of the geometric mean ratio of AUC0-inf, AUC0-last, and Cmax are all within the PK similarity criteria limits of 80-125%.

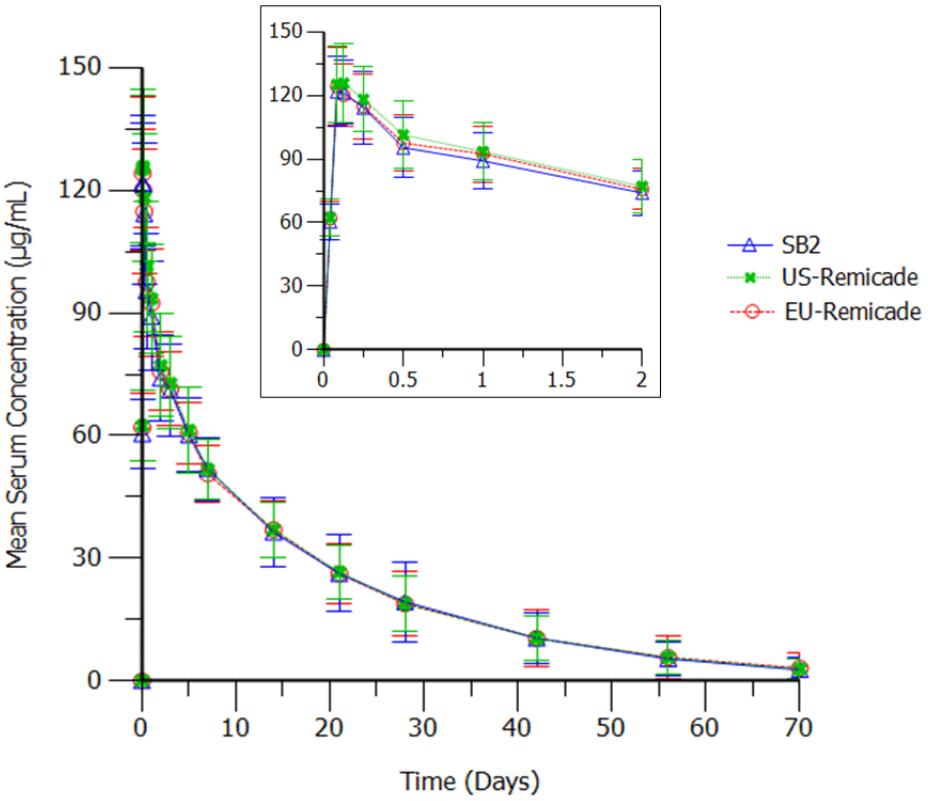

Figure 2. Infliximab PK profiles following a single IV dose (5 mg/kg) of SB2, EU-approved Remicade, or US-licensed Remicade in healthy subjects (Study SB-G11-NHV)

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

Table 5. Summary of PK parameters

PK Parameter	Statistics	SB2 N=51	EU sourced Remicade® N=53	US sourced Remicade® N=53
AUC_{inf} (h·µg/mL)	n	51	53	53
	Mean	38702.8145	39359.7493	39270.1707
	SD	11113.62172	12332.41615	10064.08853
	Median	36762.200	36671.595	39830.173
	Min	15814.809	24009.474	18724.040
	Max	71278.687	80096.460	71320.685
AUC_{last} (h·µg/mL)	n	51	53	53
	Mean	36862.4180	37022.3524	37367.5577
	SD	9132.75342	9398.42182	8332.05331
	Median	35386.266	35731.589	38413.331
	Min	15802.891	23983.183	18689.294
	Max	60722.367	63795.826	59882.300
C_{max} (µg/mL)	n	51	53	53
	Mean	126.9975	126.2377	129.1508
	SD	16.89586	17.88151	18.75573
	Median	124.900	125.100	127.700
	Min	89.870	94.370	90.370
	Max	178.800	189.400	180.100
T_{max} (h)	n	51	53	53
	Mean	2.9294	2.5824	2.7591
	SD	1.11529	0.95950	1.03184
	Median	3.000	2.067	2.967
	Min	2.033	2.017	2.017
	Max	6.033	6.100	6.050
Vz (mL)	n	51	53	53
	Mean	4586.6308	4846.4691	4806.2983
	SD	1583.28395	1286.70908	1215.53183
	Median	4863.005	4887.124	4774.498
	Min	1334.332	1764.489	2217.910
	Max	8768.506	7572.070	7054.409
k_{el} (1/h)	n	51	53	53
	Mean	0.0031	0.0026	0.0025
	SD	0.00279	0.00141	0.00139
	Median	0.002	0.002	0.002
	Min	0.001	0.001	0.001
	Max	0.015	0.008	0.008
$t_{1/2}$ (h)	n	51	53	53
	Mean	324.0859	339.4503	339.7093
	SD	148.70388	155.43045	135.64835
	Median	329.856	312.547	341.451
	Min	46.456	82.834	89.203
	Max	641.849	724.307	667.381
CL (mL/h)	n	51	53	53
	Mean	10.8980	11.0550	10.6992
	SD	3.17422	3.04419	2.86050
	Median	10.537	10.574	10.079
	Min	6.229	4.963	6.471
	Max	22.748	17.510	20.589
$\%AUC_{extrap}$ (%)	n	51	53	53
	Mean	3.8475	4.5713	4.0792
	SD	3.93668	5.00777	3.84646
	Median	2.851	2.214	2.814
	Min	0.056	0.084	0.069
	Max	16.438	20.351	16.038

N = number of subjects in the PK population; n = number of subjects who contributed to summary statistics.
Subjects 1234 and 1256 were excluded from the PK population due to major protocol deviations.
Source: Table 14.2.2.1

(Source: Study SB2-G11-NHV report, Table 11-3)

Table 6. PK similarity among SB2, EU-approved Remicade, and US-licensed Remicade in Study SB-G11-NHV (PK population)

Average Bioequivalence Approach						
Parameter	**LSM (T)**	**N**	**LSM (R)**	**N**	**GMR (%)**	**90% CI (%)**
SB2 (T) vs US-licensed Remicade (R)						
Cmax	125.3	53	127.8	53	98.01	(93.77, 102.52)
AUC0-t	36023	53	36965	53	97.45	(89.58, 106.02)
AUC∞	37463	53	38552	53	97.18	(88.52, 106.67)
SB2 (T) vs EU-approved Remicade (R)						
Cmax	125.3	53	125.05	53	100.23	(95.96, 104.69)
AUC0-t	36023	53	36501	53	98.69	(90.61, 107.48)
AUC∞	37463	53	38288	53	97.85	(88.82, 107.79)
EU-approved Remicade (T) vs US-licensed Remicade (R)						
Cmax	125.05	53	127.8	53	97.82	(93.48, 102.36)
AUC0-t	36501	53	36965	53	98.74	(91.52, 106.53)
AUC∞	38288	53	38552	53	99.31	(90.97, 108.42)

The units of Cmax and AUC are µg/mL and µg*h/mL, respectively.

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

Immunogenicity Results

A validated electrochemiluminescent (ECL) bridging immunogenicity assay using SB2-labelled intermediates and a cell-based assay was used for detection of ADAs and nAbs in Studies SB2-G11-NHV, respectively.

In Study SB2-G11-NHV, serum samples were collected at baseline, Day 29, and the end-of-study visit (Day 71) for assessment of the ADA and nAb of SB2, EU-approved Remicade and US-licensed Remicade. Overall, following a single 5 mg/kg IV dose of study drug, the incidence of ADAs was similar between all three treatment arms throughout the study (Table 7).

Note that the ADA incidence has been originally reported to be 25/53 (47.2%), 20/53 (37.3%) and 20/53 (37.7%) for SB2, EU-approved Remicade and US-licensed Remicade, respectively, in the study report. After the bioanalytical inspection, the ADA incidence was updated as shown

below and there was no update regarding the nAb incidence. Please refer to OBP review for more detailed information regarding the ADA incidence update.

Table 7. Immunogenicity results of Study SB-G11-NHV in healthy subjects

Immunogenicity	The number (%) of subjects at different visit	SB2 (N=53)	EU-approved Remicade (N=53)	US-licensed Remicade (N=53)
ADA+	Day 1 (Baseline)	0/53 (0)	0/53 (0)	0/53 (0)
	Day 29	2/53 (3.8%)	0/53 (0)	1/53 (1.9%)
	Day 71	26/53 (49.1%)	23/53 (43.4%)	23/53 (43.4%)
nAb+/ADA+*	Day 1 (Baseline)	0/0 (0)	0/0 (0)	0/0 (0)
	Day 29	1/2 (50%)	0/0 (0)	0/1 (0)
	Day 71	14/26 (53.8%)	14/23 (60.9%)	7/23 (30.4%)

*The reported incidence of nAb/ADA for Study SB2-G11-NHV was considered inaccurate due to the assay limitation and bioanalytical inspection issue.

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

Additional analyses according to subject antibody (ADA) status were also conducted. The magnitude of the impact of ADAs on the PK parameters was comparable between three treatments as reflected in the tables below.

Table 8. Statistical analysis of PK parameters (Study SB-G11-NHV) (ADA negative population)

SB2 (T) vs US-licensed Remicade (R)						
Parameter	**LSM (T)**	**N**	**LSM (R)**	**N**	**GMR**	**90% CI**
Cmax	127.50	27	126.31	30	100.95	(94.69, 107.62)
AUC0-t	41523	27	40632	30	102.19	(93.68, 111.48)
AUC∞	44232	27	43168	30	102.46	(92.76, 113.19)
SB2 (T) vs EU-approved Remicade (R)						

Parameter	T	N	R	N	GMR	90% CI
Cmax	127.50	27	125.67	30	101.46	(94.86, 108.53)
AUC0-t	41523	27	41655	30	99.68	(91.32, 108.81)
AUC∞	44231	27	44973	30	98.35	(88.56, 109.23)
EU-approved Remicade (T) vs US-licensed Remicade (R)						
Parameter	**T**	**N**	**R**	**N**	**GMR**	**90% CI**
Cmax	125.66	30	126.31	30	99.49	(93.20, 106.21)
AUC0-t	41655	30	40632	30	102.52	(93.92, 111.90)
AUC∞	44973	30	43168	30	104.18	(93.99, 115.48)

The units of Cmax and AUC are µg/mL and µg*h/mL, respectively.

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

Table 9. Statistical analysis of PK parameters (Study SB-G11-NHV) (ADA positive population)

SB2 (T) vs US-licensed Remicade (R)						
Parameter	**LSM (T)**	**N**	**LSM (R)**	**N**	**GMR**	**90% CI**
Cmax	123.13	26	129.87	23	94.81	(88.98, 101.03)
AUC0-t	31081	26	32674	23	95.12	(83.82, 107.96)
AUC∞	31529	26	33265	23	94.78	(83.08, 108.12)
SB2 (T) vs EU-approved Remicade (R)						
Parameter	**T**	**N**	**R**	**N**	**GMR**	**90% CI**
Cmax	123.13	26	124.26	23	99.09	(93.80, 104.68)
AUC0-t	31081	26	30725	23	101.16	(89.91, 113.82)
AUC∞	31529	26	31038	23	101.58	(89.99, 114.66)
EU-approved Remicade (T) vs US-licensed Remicade (R)						
Parameter	**T**	**N**	**R**	**N**	**GMR**	**90% CI**
Cmax	124.26	23	129.87	23	95.68	(89.80, 101.95)

AUC0-t	30725	23	32674	23	94.03	(85.66, 103.22)
AUC∞	31038	23	33265	23	93.30	(84.60, 102.91)

The units of Cmax and AUC are µg/mL and µg*h/mL, respectively.

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

Conclusions

- The infliximab PK profiles following a single IV infusion (5 mg/kg) of SB2, EU-approved Remicade, or US-licensed Remicade in healthy subjects are similar. In the pairwise comparisons, the 90% CI of the geometric mean ratio of AUC0-inf, AUC0-last, and Cmax are all within the PK similarity criteria limit of 80-125%.
- Overall, following a single 5 mg/kg IV dose of study drug, the incidence of ADAs was similar between all three treatment arms.

Study SB2-G31-RA (Comparative Clinical Study in RA Patients)

Title: A Randomised, Double-blind, Parallel Group, Multicentre 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

Study Phase: Phase III

Study Duration: August 12, 2013– August 25, 2015

Objectives

Primary: to demonstrate the equivalence of SB2 to Remicade® at Week 30, in terms of 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:

- to evaluate efficacy of SB2 compared to Remicade using relevant efficacy endpoints other than ACR20 at Week 30 in subjects with moderate to severe RA despite MTX therapy
- to evaluate safety and tolerability of SB2 compared to Remicade in subjects with moderate to severe RA despite MTX therapy
- to evaluate pharmacokinetics of SB2 compared to Remicade in subjects with moderate to severe RA despite MTX therapy
- to evaluate immunogenicity of SB2 compared to Remicade in subjects with moderate to severe RA despite MTX therapy

- to evaluate the safety, tolerability, immunogenicity and efficacy in subjects with RA who transitioned to SB2 from Remicade® compared to subjects who maintained Remicade from the randomised, double-blind period

Study Population

584 subjects with moderate to severe RA

Test Formulation

The final formulation, which will be used for the commercial batches, was used in this study.

Test Products

Table 10. Test products

Investigational Product	Batch Numbers
SB2	P49203A, P49204A, P49205A, P49208A
EU Sourced Remicade®	2RMA66904, 2RMA68401, 3RMA60401, 3RMKA82703, 3RMA61507, 3RMA66502

(Source: Study SB2-G31-RA report, Table 9-1)

Study Design

Randomised, Double-blind Period

This was a randomised, double-blind, parallel group, multicentre clinical study to evaluate the efficacy, safety, PK and immunogenicity of SB2 compared with Remicade in subjects with moderate to severe RA despite MTX therapy. The study consisted of 6 weeks of Screening period and 54 weeks of active treatment.

At Randomisation, eligible subjects with moderate to severe RA (who were diagnosed at least 6 months prior to study entry), who have had an inadequate response to MTX and who have been on a stable dose of MTX 10–25 mg/week given orally or parenterally for at least 4 weeks prior to Screening, were randomised at Week 0. Subjects were randomised in a 1:1 ratio to receive either SB2 3 mg/kg or Remicade 3 mg/kg via a 2 hour 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.

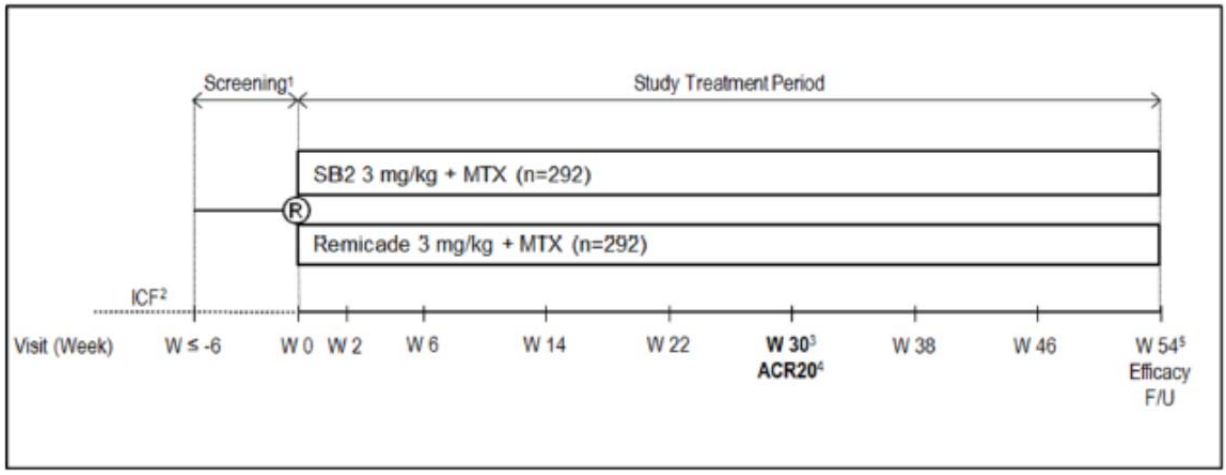

Figure 3. Graphical study design of Study SB2-G31-RA

(Source: Study SB2-G31-RA report, Figure 9-1)

Transition-Extension period

The transition-extension period was conducted from Week 54 to Week 78 and consisted of 24 weeks of active treatment. It was a randomised, double-blind period to investigate the safety, tolerability, immunogenicity, and efficacy of SB2 in subjects who transitioned from the Remicade treatment group to the SB2 treatment group, subjects who maintained Remicade treatment after Week 54, and subjects who continued in the SB2 treatment group after Week 54.

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

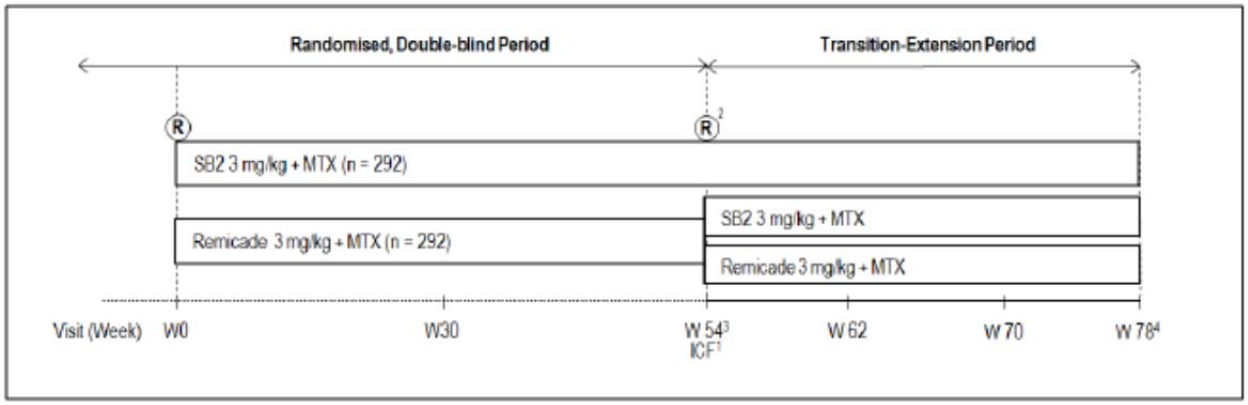

Figure 4. Graphical study design including the transition-extension period

(Source: Study SB2-G31-RA 78-week Clinical Study report, Figure 9-2)

Efficacy Assessment

The primary efficacy endpoint was the ACR20 response at Week 30.

PK Assessment

PK samples were collected in a subset of patients (the first 50% of the enrolled subjects, ~ 292 subjects) at baseline and prior to dosing at Weeks 2, 6, 14, 22 and 30 during the study for Ctrough measurement.

Immunogenicity Assessment

Immunogenicity samples were collected at Weeks 0 (baseline), 2, 6, 14, 22, 30, 38, 46, 54, 62, 70, and 78.

Results

Demographics

A total of 584 subjects were randomized: 291 subjects were randomised to the SB2 treatment group and 293 subjects were randomised to the Remicade treatment group.

At Week 54, 201 subjects from the SB2 treatment group and 195 subjects from the Remicade treatment group were enrolled and re-randomised to the transition-extension period. Of 195 subjects who received Remicade during the randomised, double-blind period, 94 subjects were transitioned to SB2 (Remicade/SB2) and 101 subjects continued on Remicade (Remicade/ Remicade). The 201 subjects who received SB2 during the randomised, double-blind period continued to receive SB2 (SB2/SB2).

Table 11. Demographic characteristics for the randomised, double-blind period (Randomised Set)

	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)

BMI = Body Mass Index; SD = standard deviation
Percentages were based on the number of randomised subjects.
Source: 54-week CSR Table 14.1-3.1

(Source: Study SB2-G31-RA 78-week Clinical Study report, Table 11-2)

Efficacy Results

The primary analysis of ACR20 response with the number of subjects who achieved ACR20 response at Week 30 is presented in Table 12.

At Week 30, the proportion of subjects achieving ACR20 response was similar between the SB2 (64.1% (148/231)) and Remicade (66.0% (163/247)) treatment groups. The time-response

curves of SB2 and Remicade up to Week 30 showing the ACR20 response over time were also estimated to be similar (Figure 5).

For detailed information regarding efficacy comparison, refer to the medical review and statistical review.

Table 12. Primary Analysis of ACR20 Response Rate at Week 30

Treatment	n/n'	(%)	Adjusted Difference Rate[a]	95% CI
SB2 (N=231)	148/231	(64.1)	−1.88%	(−10.26%, 6.51%)
Remicade® (N=247)	163/247	(66.0)		

CI = confidence interval; N = number of subjects in the PPS1; n' = number of subjects with an assessment; n = number of responders

[a]The adjusted treatment difference and its 95% CI were analysed by non-parametric method using NParCov with Baseline CRP as a covariate, and stratified by region.

Source 54-week CSR Table 14.2-2.1

(Source: Study SB2-G31-RA 78-week Clinical Study report, Table 11-7)

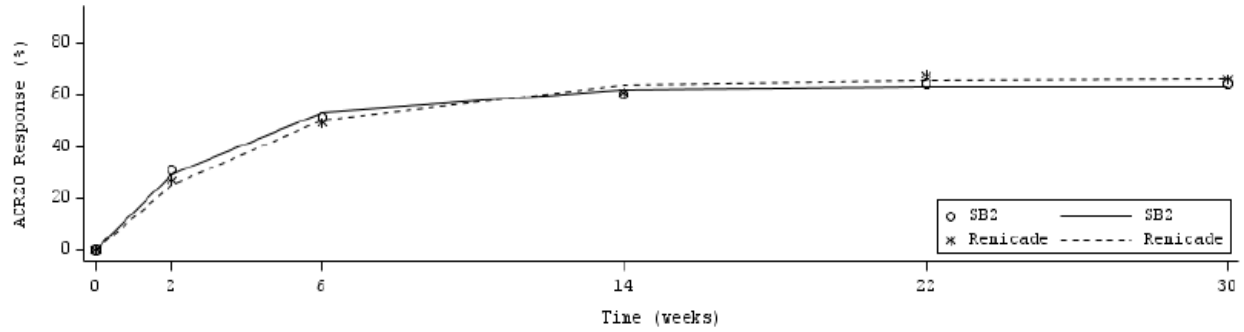

Figure 5. Time-Response Model for ACR20 Response up to Week 30

(Source: Study SB2-G31-RA 78-week Clinical Study report, Figure 11-1)

PK Results

PK samples 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. It was noted that since only trough PK sample were collected, serum concentrations were undetectable in ~36% patients at Week 30 (59 out of 139 and 42 out of 143 in SB2 and EU-approved Remicade treatment, respectively). Overall, the serum trough concentrations (Ctrough) of infliximab are highly variable and the range of Ctrough appears comparable between SB2 and EU-approved Remicade in RA patients (Table 13).

Table 13. Summary of serum trough concentration (µg/mL) (PK Population)

Timepoint	Statistics	SB2 N=165	Remicade® N=160
Week 0	n	160	149
	Mean (SD)	0.000 (0.0000)	0.000 (0.0000)
	CV%	NC	NC
	Min, Max	0.00, 0.00	0.00, 0.00
Week 2	n	161	156
	Mean (SD)	17.965 (8.6612)	16.954 (6.0218)
	CV%	48.2125	35.5191
	Min, Max	0.00, 90.08	0.00, 34.79
Week 6	n	155	153
	Mean (SD)	13.374 (11.1216)	12.039 (7.1710)
	CV%	83.1586	59.5654
	Min, Max	0.00, 73.32	0.00, 35.87
Week 14	n	153	143
	Mean (SD)	3.593 (6.0938)	3.380 (3.6535)
	CV%	169.6090	108.0864
	Min, Max	0.00, 54.66	0.00, 23.24
Week 22	n	146	147
	Mean (SD)	3.538 (10.6475)	2.390 (2.6090)
	CV%	300.9453	109.1630
	Min, Max	0.00, 110.54	0.00, 12.90
Week 30	n	139	143
	Mean (SD)	1.915 (2.8055)	2.224 (4.7326)
	CV%	146.5085	212.7572
	Min, Max	0.00, 19.33	0.00, 50.71

CV% = coefficient variation; NC = not calculated; SD = standard deviation
Source: 54-week CSR Table 14.2-7.1

(Source: Study SB2-G31-RA 78-week Clinical Study report, Figure 11-18)

Immunogenicity Results

In Study SB2-G31-RA, immunogenicity samples were collected at Weeks 0 (baseline), 2, 6, 14, 22, 30, 38, 46, 54, 62, 70, and 78 for assessment of the ADA and nAb of SB2 and EU-approved Remicade. Overall, following multiple 3 mg/kg IV dose of study drug, the incidence of ADAs was comparable between SB2 and EU-approved Remicade throughout the study, including the transition-extension period (Tables 14 and 15).

Table 14. Incidence of anti-drug antibodies and neutralising antibodies to infliximab (Safety Set)

		SB2			Remicade®			Total		
		N=290			N=293			N=583		
Timepoint	Parameter	n'	n	(%)	n'	n	(%)	n'	n	(%)
Week 0	ADA	290	5	(1.7)	293	7	(2.4)	583	12	(2.1)
	NAb	5	0	(0.0)	7	0	(0.0)	12	0	(0.0)
Week 2	ADA	286	10	(3.5)	291	14	(4.8)	577	24	(4.2)
	NAb	10	4	(40.0)	14	4	(28.6)	24	8	(33.3)
Week 6	ADA	282	21	(7.4)	286	16	(5.6)	568	37	(6.5)
	NAb	21	11	(52.4)	16	7	(43.8)	37	18	(48.6)
Week 14	ADA	274	73	(26.6)	280	63	(22.5)	554	136	(24.5)
	NAb	73	70	(95.9)	63	60	(95.2)	136	130	(95.6)
Week 22	ADA	268	121	(45.1)	273	108	(39.6)	541	229	(42.3)
	NAb	121	113	(93.4)	108	96	(88.9)	229	209	(91.3)
Week 30	ADA	251	133	(53.0)	264	116	(43.9)	515	249	(48.3)
	NAb	133	129	(97.0)	116	109	(94.0)	249	238	(95.6)
Week 30 overall	ADA	287	158	(55.1)	292	145	(49.7)	579	303	(52.3)
	NAb	158	146	(92.4)	145	130	(89.7)	303	276	(91.1)
Week 38	ADA	243	123	(50.6)	255	115	(45.1)	498	238	(47.8)
	NAb	123	114	(92.7)	115	103	(89.6)	238	217	(91.2)
Week 46	ADA	237	121	(51.1)	231	99	(42.9)	468	220	(47.0)
	NAb	121	113	(93.4)	99	87	(87.9)	220	200	(90.9)
Week 54	ADA	223	118	(52.9)	222	89	(40.1)	445	207	(46.5)
	NAb	118	99	(83.9)	89	78	(87.6)	207	177	(85.5)
Week 54 overall	ADA	287	179	(62.4)	292	168	(57.5)	579	347	(59.9)
	NAb	179	166	(92.7)	168	147	(87.5)	347	313	(90.2)

ADA = anti-drug antibody; NAb = neutralising antibody; n': number of subjects with available ADA/NAb results against SB2 at each timepoint
ADA was determined as positive if at least 1 ADA positive result was obtained up to the timepoint regardless of the ADA result at Week 0.
Percentages were based on n'.
Source: 54-week CSR Table 14.3-3.1

(Source: Study SB2-G31-RA 78-week Clinical Study report, Table 12-20)

Table 15. Incidence of anti-drug antibodies and neutralising antibodies to infliximab for the transition-extension period (Extended Safety Set)

		SB2			Remicade®									Total		
					Overall			SB2			Remicade®					
		N=201			N=195			N=94			N=101			N=396		
Timepoint	Parameter	n'	n	(%)	n'	n	(%)	n'	n	(%)	n'	n	(%)	n'	n	(%)
Week 0 (St-BL)	ADA	201	4	(2.0)	195	3	(1.5)	94	3	(3.2)	101	0	(0.0)	396	7	(1.8)
	NAb	4	0	(0.0)	3	0	(0.0)	3	0	(0.0)	0	0	(0.0)	7	0	(0.0)
Week 54 (Ex-BL)	ADA	198	101	(51.0)	193	75	(38.9)	92	31	(33.7)	101	44	(43.6)	391	176	(45.0)
	NAb	101	82	(81.2)	75	66	(88.0)	31	28	(90.3)	44	38	(86.4)	176	148	(84.1)
Week 62	ADA	193	92	(47.7)	195	79	(40.5)	94	35	(37.2)	101	44	(43.6)	388	171	(44.1)
	NAb	92	82	(89.1)	79	69	(87.3)	35	33	(94.3)	44	36	(81.8)	171	151	(88.3)
Week 70	ADA	188	89	(47.3)	191	76	(39.8)	91	34	(37.4)	100	42	(42.0)	379	165	(43.5)
	NAb	89	80	(89.9)	76	71	(93.4)	34	32	(94.1)	42	39	(92.9)	165	151	(91.5)
Week 78	ADA	187	88	(47.1)	182	70	(38.5)	88	32	(36.4)	94	38	(40.4)	369	158	(42.8)
	NAb	88	84	(95.5)	70	63	(90.0)	32	28	(87.5)	38	35	(92.1)	158	147	(93.0)
Week 78 overall*	ADA	201	133	(66.2)	195	120	(61.5)	94	59	(62.8)	101	61	(60.4)	396	253	(63.9)
	NAb	133	126	(94.7)	120	104	(86.7)	59	49	(83.1)	61	55	(90.2)	253	230	(90.9)
Week 78 overall**	ADA	194	104	(53.6)	195	94	(48.2)	94	43	(45.7)	101	51	(50.5)	389	198	(50.9)
	NAb	104	95	(91.3)	94	83	(88.3)	43	38	(88.4)	51	45	(88.2)	198	178	(89.9)

ADA = anti-drug antibody; Ex-BL = Extended Baseline; NAb = neutralising antibody; n': number of subjects with available ADA/NAb results against SB2 at each timepoint; St-BL = Study Baseline
Percentages were based on n'.
*Overall ADA (or NAb) results were defined as "Positive" for subjects with at least one ADA (or NAb) positive up to Week 78 after Week 0, otherwise results were determined as "Negative".
**Overall ADA (or NAb) results were defined as "Positive" for subjects with at least one ADA (or NAb) positive up to Week 78 after Week 54, otherwise results were determined as "Negative".
Source: Table 14.3-3.1

(Source: Study SB2-G31-RA 78-week Clinical Study report, Table 12-21)

Impact of immunogenicity on efficacy

Overall, the ACR20 response rate in the ADA positive subgroup was lower compared to ADA negative subgroup. However, among the subjects who had an overall post-dose positive ADA or negative ADA up to Week 30, the ACR20 response rate was similar between the SB2 and Remicade treatment groups at Week 30 (Table 16).

Table 16. ANCOVA for ACR20 response at week 30 by 30-week ADA result and treatment

30-week ADA Result	Treatment	Responder n'	n	(%)	Adjusted Difference Rate (SE)	95% CI	P value
Positive	SB2 (N=127)	127	72	(56.7)	−0.88% (5.966%)	(−12.63%, 10.87%)	
	Remicade® (N=126)	126	74	(58.7)			
							0.989
Negative	SB2 (N=104)	104	76	(73.1)	−1.57% (5.914%)	(−13.23%, 10.08%)	
	Remicade® (N=121)	121	89	(73.6)			

ACR = American College of Rheumatology; ADA = anti-drug antibodies; ANCOVA = analysis of covariance; CI = confidence interval; N = number of subjects in the per-protocol set 1; n' = number of subjects with available assessment results; n = number of responders; SE = standard error
The p- value is for the interaction term.
Source: 54-week CSR Table 14.2-2.6
(Source: Study SB2-G31-RA 78-week Clinical Study report, Table 11-17)

The ACR20 response rates at Week 78 by 78-week overall ADA status for the transition-extension period are summarized in Table 17. Overall, the ACR20 response rate at Week 78 were generally similar between the Remicade/SB2 and Remicade/Remicade treatment groups as well as the SB2/SB2 treatment group in each of ADA negative and ADA positive subgroups. Please also refer to medical review for further details.

Table 17. Summary of ACR20 response by 78-week ADA result, visit, and treatment

		SB2	Remicade			Total
			Overall	SB2	Remicade	
Timepoint	ADA result against SB2	N=201 n' n (%)	N=195 n' n (%)	N=94 n' n (%)	N=101 n' n (%)	N=396 n' n (%)
Week 78	Positive	117 76 (65.0)	107 66 (61.7)	54 31 (57.4)	53 35 (66.0)	224 142 (63.4)
	Negative	63 47 (74.6)	71 52 (73.2)	31 23 (74.2)	40 29 (72.5)	134 99 (73.9)
	Positive after Week 54*	96 60 (62.5)	85 53 (62.4)	41 26 (63.4)	44 27 (61.4)	181 113 (62.4)
	Negative after Week 54*	84 63 (75.0)	93 65 (69.9)	44 28 (63.6)	49 37 (75.5)	177 128 (72.3)

SOURCE: Listings 16.2.6-1.3 and 16.2.9-1.6
- ADA: anti-drug antibody
- n': number of subjects with available assessment results at each timepoint; percentages were based on n'.
- ADA results were defined as "Positive" for subjects with at least one ADA positive up to Week 78 after Week 0, otherwise results were determined as "Negative".
- *: ADA results were defined as "Positive" for subjects with at least one ADA positive up to Week 78 after Week 54, otherwise results were determined as "Negative".

(Source: Study SB2-G31-RA 78-week Clinical Study report, Table 14.2-1.4)

Impact of immunogenicity on PK

In patients with RA, additional analyses according to subject antibody (ADA) status showed that Ctrough of SB2 or EU-approved Remicade in RA patients who were antibody-positive were highly variable and also lower as compared to those in patients who were antibody-negative. The numerical difference observed in the comparison of concentrations between the SB2 and EU-approved Remicade treatment in each ADA subgroup analysis was likely due to the high inter-subject variability of trough serum concentrations, especially in ADA positive subgroups (CV is 252% and 352% for SB2 and EU-approved Remicade treatment, respectively) (Table 18).

It was also noted that since only trough PK sample were collected, serum concentrations were undetectable in ~36% RA patients at Week 30 (59 out of 139 (42%) and 42 out of 143 (29%) in SB2 and EU-approved Remicade treatment, respectively), especially in ADA-positive subgroups (56 out of 75 (75%) and 34 out of 69 (49%) in SB2 and EU-approved Remicade treatment, respectively).

Table 18. Mean (%CV) serum trough concentrations of infliximab at Week 30

Parameter	SB2	N	EU-approved Remicade	N
ADA- Population				
Cmin,ss	3.682 (86.51)	64	2.604 (85.89)	74
ADA+ Population				
Cmin,ss	0.407 (252.22)	75	1.818 (352.63)	69

The unit of serum concentration is µg/mL.

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

Impact of immunogenicity on Safety

The immunogenicity does not appear to affect the safety comparison between SB2 and EU-approved Remicade. Overall, the incidence of infusion-related reactions was higher in the ADA-positive subgroup than the ADA-negative subgroup, but was comparable between 2 treatment groups within each ADA subgroup. Please also refer to medical review for further details.

Conclusions:

- 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, following multiple 3 mg/kg IV dose of study drug, the incidence of ADAs was comparable between SB2 and EU-approved Remicade throughout the study, including the transition-extension period.

Appendix 4.2 Office of Clinical Pharmacology Filing Memo

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA/BLA Number	761054	**SDN**	1
Applicant	Samsung	**Submission Date**	03/21/2016
Generic Name	Infliximab	**Brand Name**	Renflexis
Drug Class	Anti-TNFalpha		
Indications	▪ Rheumatoid Arthritis (RA) ▪ Ankylosing Spondylitis (AS) ▪ Crohn's Disease (CD) ▪ Pediatric Crohn's Disease ▪ Ulcerative Colitis (UC) ▪ Pediatric Ulcerative Colitis ▪ Plaque Psoriasis (Ps) ▪ Psoriatic Arthritis (PA)		
Dosage Regimen	▪ RA: 3mg/kg at week 0, 2, 6, and q8w; ▪ AS: 5mg/kg at week 0, 2, 6, and q6w; ▪ CD, Pediatric CD, UC, Pediatric UC, Ps, and PA: 5mg/kg at week 0, 2, 6, and q8w		
Dosage Form	Lyophilized powder for IV infusion	**Route of Administration**	IV infusion
OCP Division	DCP2	**OND Division**	Pulmonary, Allergy, and Rheumatology Products

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
Division	Lei He, PhD	Anshu Marathe, PhD
Pharmacometrics		
Genomics		

Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	5/20/2016	**74-Day Letter Date**	6/3/2016
Review Due Date	12/15/2016	**PDUFA Goal Date**	1/21/2017

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

☑ Yes

☐ No

If yes explain

Study SB-G11-NHV has been conducted as a single-dose 3-way bridging PK study involving SB2, US-licensed Remicade® and EU-approved Remicade®. It was conducted at a single center and the pharmacokinetic and immunogenicity assays for this study were conducted in one bioanalytical laboratory. The results of this pivotal study serve as the basis to provide an acceptable bridge in order to support the SB2 BLA. Therefore, we request that both the clinical site and analytical site be inspected for this study.

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type	Count	Comment(s)
In Vitro Studies		
☐ Metabolism Characterization		
☐ Transporter Characterization		
☐ Distribution		
☐ Drug-Drug Interaction		
In Vivo Studies		
Biopharmaceutics		
☐ Absolute Bioavailability		
☐ Relative Bioavailability		
☐ Bioequivalence		
☐ Food Effect		
☑ Other		Bioanalytical reports: 1) Validation of an ELISA Method for the Quantitation of Infliximab (SB2) in Human Serum (by (b) (4) 2) ELISA Analysis of Infliximab in Human Serum Samples from Samsung Study SB2-G 11-NHV (by (b) (4) 3) ELISA Analysis of Infliximab in Human Serum Samples from Samsung Study SB2-G31-RA (by (b) (4) 4) Validation of an ELISA Method for the Quantitation of Infliximab in Human Serum - Methotrexate Interference and SB2 and EU Remicade® Accuracy and Precision in RA Serum (by (b) (4)

Human Pharmacokinetics			
Healthy Subjects	☑ Single Dose		Study SB2-G 11-NHV
	☐ Multiple Dose		
Patients	☐ Single Dose		
	☑ Multiple Dose		Study SB2-G31-RA
☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☐ Sex			
☐ Geriatrics			
☐ Pediatrics			
☐ Hepatic Impairment			
☐ Renal Impairment			
☐ Genetics			
Extrinsic Factors			
☐ Effects on Primary Drug			
☐ Effects of Primary Drug			
Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
Pharmacokinetics/Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
☐ QT			
Pharmacometrics			
☐ Population Pharmacokinetics			
☐ Exposure-Efficacy			
☐ Exposure-Safety			

Total Number of Studies	**In Vitro**	4	**In Vivo**	2
Total Number of Studies to be Reviewed				

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☐No ☑N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☐Yes ☐No ☑N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 351(k) application?	☑Yes ☐No ☐N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☐Yes ☐No ☑N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	An IR (dated 4/21/2016) has been sent requesting individual PK and immunogenicity data in .xpt format. The requested datasets were provided by sponsor on 4/27/2016.
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☑Yes ☐No ☐N/A	
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	

Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☐Yes ☐No ☑N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐Yes ☐No ☑N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☐Yes ☐No ☑N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☑No ☐N/A	

Filing Memo
See Attachment: Presentation slides in filing meeting.

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BLA 761054
SB2 (a proposed biosimilar to Remicade (Infliximab)
Samsung

Filing Meeting

Clinical Pharmacology

Lei He, Anshu Marathe

May 06, 2016

1

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Clinical Pharmacology Summary

- Application is fileable from a clinical pharmacology perspective.
- IR has been sent requesting individual PK and immunogenicity data as SAS transport files.
- Topline results
  - Phase I study SB2-G11-NHV in healthy subjects:
    - ❑ PK similarity was demonstrated between SB, US-Remicade and EU-Remicade in healthy subjects
    - ❑ OSI inspection
  - Phase III study SB2- G31-RA in RA
    - ❑ SB2 PK was similar to EU-Remicade in RA patients

2

Clinical Development Program

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Study	Objective	Population	Dose	Product Comparison
SB2-G11-NHV	Phase I, 3-way PK bridging	Healthy subjects	5 mg/kg SD	SB2 vs US-Remicade SB2 vs EU-Remicade US-Remicade vs EU-Remicade
SB2-G31-RA	Phase III, supportive PK	RA patients	3 mg/kg MD	SB2 vs EU-Remicade

Study SB2-G11-NHV

Pivotal 3-way PK Bridging Study in HS

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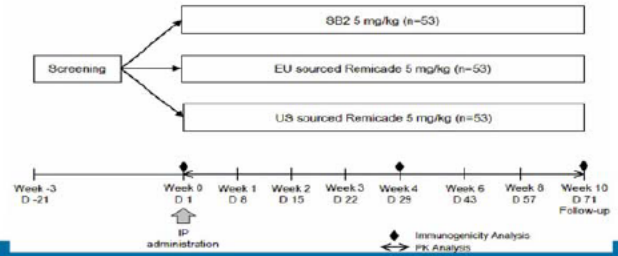
- **Study design**: R, single-blind, three arm, parallel group, single-dose, Phase 1 study in HS (n=159, 53/arm)
- **Objectives**:
  - Primary: PK similarity b/w SB2, EU-Remicade and US-Remicade
  - Secondary: safety, tolerability, immunogenicity
- **Dose**: single dose (5 mg/kg) 2hr IV infusion
- **Endpoints**:
  - Primary: C_{max}, AUC_{last}, AUC_{inf}
  - Secondary: PK, safety and tolerability, immunogenicity



Study SB2-G11-NHV : Results

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❖ PK similarity was demonstrated between SB2 (n=51), EU-Remicade (n=53), and US-Remicade (n=53) in healthy subjects.

	PK Parameter	GMR (90%CI)
SB2 *vs* US	Cmax	0.98 (0.94, 1.03)
	AUClast	0.98 (0.90, 1.06)
	AUCinf	0.98 (0.89, 1.07)
SB2 *vs* EU	Cmax	1.01 (0.96, 1.05)
	AUClast	0.99 (0.91, 1.08)
	AUCinf	0.99 (0.90, 1.09)
EU *vs* US	Cmax	0.98 (0.94, 1.02)
	AUClast	0.98 (0.91, 1.07)
	AUCinf	0.99 (0.91, 1.09)

5

Study SB2-G11-NHV: Immunogenicity

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- Immunogenicity by treatment

	Time	SB2	EU-Remicade	US-Remicade
ADA+	Day 1 (baseline)	0/53 (0)	0/53 (0)	0/53 (0)
	Day 29	2/53 (3.8%)	0/53 (0)	1/53 (1.9%)
	Day 71	25/53 (47.2%)	20/53 (37.7%)	20/53 (37.7%)
nAb+	Day 1 (baseline)	0	0	0
	Day 29	1/2 (50%)	0	0/1 (0)
	Day 71	14/25 (56.0%)	14/20 (70.0%)	7/20 (35.0%)

- PK is similar between treatments in ADA+ and ADA- subjects

6

Study SB2-G31-RA

Supportive steady-state PK in RA

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- **Study design**: R, DB, MC, parallel-group, Phase 3 study in RA patients despite MTX therapy (n=584, 291 with SB2, 293 with EU-Remicade)
- **Objective:**
  - Primary: efficacy,
  - Secondary: efficacy, safety/tolerability, PK and immunogenicity
- **Dosing:**
  - 3 mg/kg 2 hr IV infusion at Weeks 0, 2, 6 and then Q8W up to 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
- **Endpoint:**
  - Primary: ACR20 response rate at week 30
  - Secondary: efficacy, PK (Ctrough), and safety
- **PK analyses** were performed in a subset of 325 (55.7%) subjects, comprising the PK population (SB2: n= 165; EU Remicade: n= 160) up to week 30.
  - Blood samples were collected within 30 minutes prior to administration of the products at Weeks 0, 2, 6, 14, 22 and 30.

7

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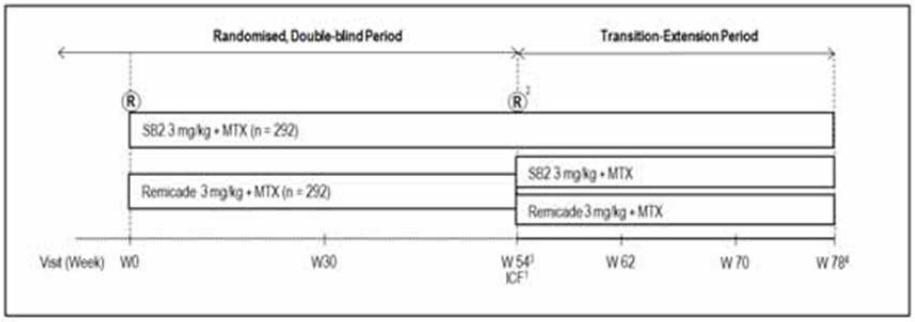
Study SB2-G31-RA



8

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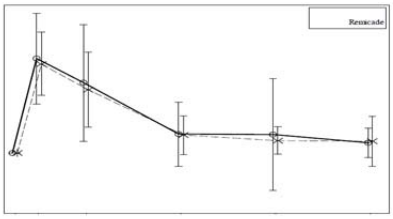
Study SB2-G31-RA Results

- PK is similar between SB2 and EU-Remicade in RA patients



Mean serum Ctrough from week 0 to 30

- Immunogenicity by treatment over time

Time	SB2 (N=290)		EU (n=293)	
	ADA+	Nab+	ADA+	Nab+
wk 0	1.7%	0	2.4%	0
wk2	3.5%	40%	4.8%	28.6%
wk6	7.4%	52.4%	5.6%	43.8%
wk14	26.6%	95.9%	22.5%	95.2%
wk22	45.1%	93.4%	39.6%	88.9%
wk30 overall	55.1%	92.4%	49.7%	89.7%
wk38	50.6%	92.7%	45.1%	89.6%
wk46	51.1%	93.4%	42.9%	87.9%
wk54 overall	62.4%	92.7%	57.5%	87.5%
Wk78 overall	66.2%	94.7%	EU/SB: 62.8% EU/EU: 60.4%	EU/SB: 83.1% EU/EU: 90.2%

- PK (Ctrough), efficacy (ACR20), and safety (TEAE) are comparable between treatments in subgroup (ADA+ or ADA-)analysis.

9

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Proposed Draft Labeling

- Clinical Pharmacology (12.3) contains the same information as Remicade labeling.

10

Midcycle Deliverables

- PK Results
  - Confirmation of all results

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/s/

LEI HE
12/15/2016

ANSHU MARATHE
12/15/2016