CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761054Orig1s000

<u>CHEMISTRY REVIEW(S)</u>

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: **3/9/2017**
To: Administrative File, **STN 761054/0**
From: Bo Chi, Ph.D., CDER/OPQ/OPF/DMA/Branch IV
Endorsement: Patricia Hughes, Ph.D., Acting Branch Chief, CDER/OPQ/OPF/DMA/Branch IV
Subject: New 351(k) Biologic License Applications (BLA)
Applicant: Samsung Bioepis Co., Ltd.
US License: **2046**
Facility: (b) (4)
FEI: (b) (4)
Product: SB2
Dosage: Intravenous infusion, 100 mg/vial, powder for solution
Indication: Crohn's Disease, Pediatric Crohn's Disease, Ulcerative Colitis, Pediatric Ulcerative Colitis, Rheumatoid Arthritis in combination with methotrexate, Ankylosing Spondylitis, Psoriatic Arthritis, Plaque Psoriasis
BsUFA date: April 21, 2017

Recommendation: The drug substance part of this BLA is recommended for approval from quality microbiology perspective with the following post-marketing commitments:

Reevaluate and establish final in-process bioburden and endotoxin limits (b) (4) In addition, provide the qualification data of the sample for the bioburden and endotoxin tests.

Reevaluate and establish final endotoxin limits for the (b) (4)

Review Summary

Samsung has submitted this Biologics License Application (BLA) under 351(k) of the Public Health Service Act for SB2 to seek licensure for the same indications for which the reference product Remicade® is approved. The drug substance (DS) is manufactured at (b) (4) The drug product (DP) is manufactured at (b) (4) The application contains CMC information in an eCTD format.

This review contains an assessment of the SB2 drug substance section of the BLA from microbiology perspective.

36 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

Bo
Chi

Digitally signed by Bo Chi
Date: 3/29/2017 01:38:26PM
GUID: 508da71600029713f321cfd33c82d8d4

Patricia
Hughes Troost

Digitally signed by Patricia Hughes Troost
Date: 3/29/2017 03:26:11PM
GUID: 508da717000297bcbfce0919f8c09594

Recommendation: BLA Approval

BLA 761054
Review 1
March 16, 2017

Drug Name/Dosage Form	SB2 / for injection
Strength/Potency	100 mg of lyophilized infliximab in a 20 mL vial to be reconstituted in 10 mL of sterile water
Route of Administration	Intravenous infusion[1]
Rx/OTC Dispensed	Rx
Applicant/Sponsor	Samsung Bioepis Co., Ltd
US agent, if applicable	Quintiles, Inc

Product Overview

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Xianghong Jing	Division of Biotechnology Review and Research II
Drug Product	Timothy Wadkins	Division of Biotechnology Review and Research II
Immunogenicity	William Hallett	Division of Biotechnology Review and Research II
Drug Substance, Drug Product, and Immunogenicity Team Lead	Christopher Downey	Division of Biotechnology Review and Research II
Microbiology Drug Substance	Bo Chi	Division of Microbiology Assessment
Microbiology Drug Product	Jessica Hankins	Division of Microbiology Assessment
Microbiology Team Lead	Colleen Thomas	Division of Microbiology Assessment
Facilities	Wayne Seifert	Division of Inspectional Assessment
Facilities Team Lead	Peter Qiu	Division of Inspectional Assessment
Carton and Container Labeling	Jibril Abdus-Samad	Office of Biotechnology Products
Business Regulatory Process Manager	Keith Olin	Office of Program and Regulatory Operations
Application Technical Lead	Christopher Downey	Division of Biotechnology Review and Research II

[1] The recommendations of this secondary product quality review are based on evaluation of the intravenous infusion route of administration described in the proposed product labeling. The primary product quality reviews incorrectly state the route of administration as subcutaneous injection in their respective heading pages. This was the result of an error in editing a document template; the recommendations of the primary product quality reviews are also based on evaluation of the intravenous infusion route of administration.

Multidisciplinary Review Team

DISCIPLINE	REVIEWER	OFFICE/DIVISION
RPM	Christine Ford	DPARP
Cross-disciplinary Team Lead	Nikolay Nikolov	DPARP
Medical Officer	Tara Altepeter	DPARP
Pharm/Tox	Andrew Goodwin	DPARP
Clinical Pharmacology	Lei He	DCPII
Statistics	Ginto Pottackal	DBII
CMC Statistics	Yu-Ting Weng	DBVI

a. Names[2]
   i. Proprietary Name: SB2
   ii. Trade Name: Renflexis
   iii. Non-Proprietary/USAN: infliximab-abda
   iv. CAS name: 170277-31-3
   v. INN Name: pending
   vi. Compendial Name: not applicable
   vii. OBP systematic name: MAB CHIMERIC (IGG1) ANTI P01375 (TNFA_HUMAN) [SB2]

b. Pharmacologic category: Therapeutic recombinant human monoclonal antibody

Submissions Reviewed:

SUBMISSIONS REVIEWED	DOCUMENT DATE
761054/0000	March 21, 2016
761054/0011	June 24, 2016
761054/0013	July 8, 2016
761054/0014	July 22, 2016
761054/0016	August 5, 2016
761054/0017	August 19, 2016
761054/0018	August 26, 2016
761054/0020	September 9, 2016
761054/0021	September 15, 2016
761054/0026	November 8, 2016
761054/0029	December 1, 2016
761085/0033	December 14, 2016

[2] SB2 is a proposed biosimilar to US-licensed Remicade (infliximab). SB2 is the name used to refer to this product during development is used throughout this review.

Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 351(k)

2. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	DMF HOLDER	ITEM REFERENCED	LETTER OF CROSS-REFERENCE	COMMENTS
(b) (4)	Type III		(b) (4)	Yes	Not reviewed. Sufficient Leachables and Extractables data and primary stability program in BLA. DMF previously reviewed and no revision since last review.
	Type III			Yes	
	Type I			yes	

B. Other Documents: none

3. CONSULTS:

DISCIPLINE/TOPIC	DATE REQUESTED	STATUS	RECOMMENDATION	REVIEWER
Pharmacology/Toxicology safety assessment of extractables and leachables	November 18, 2016	Review dated Dec 15, 2016	No safety issues identified	Andrew Goodwin, DPARP

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

a. Recommendation[3]:

The Office of Biotechnology Products, OPQ, CDER, recommends approval of BLA 761054 for SB2 manufactured by Samsung Bioepis. The data and information submitted in this application, including the analytical similarity assessment, are adequate to support the conclusion that:

- The biological product, SB2, is highly similar to US-licensed Remicade notwithstanding minor differences in clinically inactive components.
- A sufficient analytical bridge was established to support the use of EU-approved Remicade as a comparator in clinical trials supporting this application.
- The manufacture of SB2 is well controlled and leads to a product that is pure and potent.

I recommend that this product be approved for human use under conditions specified in the package insert.

b. Action letter language:

- Manufacturing location:
  - Drug substance: (b) (4)
  - Drug product: (b) (4)
- Fill size and dosage form: 100 mg lyophilized solid in a single-use, 20 mL vial to be reconstituted in 10 mL sterile water for injection
- Dating period:
  - Drug product: 30 months; 2 to 8ºC
  - Drug substance: (b) (4) months; (b) (4) ºC
  - Stability option:

    We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating period of your Drug Substance and Drug Product under 21 CFR 601.12(d)(2)(iii).

[3] On December 15, 2016 the Division of Microbiology Assessment (DMA) classified the CMC Microbiology amendment received December 9, 2016 (761054/0031) as a major amendment to the BLA. On January 5, 2017, FDA extended the user fee goal date to April 21, 2017 to enable a full review of the submission. Preliminary review of the amendment by DMA did not identify any major issues that would preclude approval. The recommendation in this memo reflects OBP's review of CMC Product Quality information and the preliminary assessment from DMA. This recommendation is pending DMA's final review of the CMC Microbiology component of the application.

- Exempt from lot release:
    - SB2 is exempted from lot release because it is a specified product per 601.2(a).

c. Benefit/Risk Considerations:
SB2 is a proposed biosimilar to US-licensed Remicade. The analytical similarity of SB2 to US-licensed Remicade was evaluated using methods to assess physicochemical and functional properties of the products. Additionally, to establish an analytical bridge for the use of clinical data derived from European Union (EU)-approved Remicade in support of this BLA, the applicant also provided pairwise analytical comparisons between SB2 and EU-approved Remicade and between US-licensed and EU-approved Remicade.

The totality of the analytical data demonstrate that these products are highly similar in terms of protein sequence, protein structure, and biological functions linked to the mechanisms of action, as summarized below:

- Primary sequence
- TNF-α binding and neutralization (potency)
- Secondary structure
- Tertiary structure
- Afucolysated and high-mannose glycoforms
- Fc effector functions (ADCC, CDC) and Fc receptor binding
- Membrane-bound TNF-α mediated "reverse signaling"
- Regulatory macrophage function

Review of the analytical similarity assessment identified a potential difference in affinities to the FcγRIIIa receptor, as SB2 had a slightly higher affinity to this receptor than US-licensed Remicade in one of the several orthogonal assays used to evaluate this attribute. However, this difference was shown not to have significant functional impact. Binding to FcγRIIIa is linked to antibody-dependent cell-mediated cytotoxicity (ADCC) activity, and ADCC activity was similar between the products with both NK cell- and PBMC cell-based assay formats. Residual risk of this potential difference in FcγRIIIa binding affinity affecting SB2 efficacy was mitigated by implementing into routine SB2 in-process[4] testing an FcγRIIIa binding assay with limits sufficiently stringent to ensure that receptor affinity will be within the range that yielded similar ADCC activity in the similarity assessment. For more details, see Post-Marketing Commitments in Section IB and discussion of the Analytical Similarity Assessment in Section IIA of this memo.

The data submitted in this application also support the conclusion that the manufacture of SB2 is well controlled and yields a consistently high quality product. The conditions used in manufacturing have been sufficiently

[4] One of the CMC Post-marketing Commitments is to implement the FcγRIIIa binding affinity test into Drug Substance release testing

validated, and a consistent product is produced from the multiple production runs presented. From a product quality perspective, this product is approvable for human use.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Below are the draft Post-Marketing Commitments (PMCs) to be proposed to the sponsor should FDA approve this product:

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

II. Summary of Quality Assessments

A. Analytical Similarity Assessment

The totality of the analytical data provided is sufficient to conclude that SB2 is "highly similar" to US-licensed Remicade.

The applicant performed a 3-way evaluation of analytical similarity of SB2, US-licensed Remicade, and EU-approved Remicade using multiple lots of each of the three products. The expiration dates of the US-licensed Remicade and EU-approved Remicade lots was sufficiently broad and ranged over a span of approximately 3 - 4 years. For product quality attributes that were evaluated using equivalency testing and "quality range" testing, approximately 40 lots each of US-licensed and EU-approved Remicade were analyzed, and 10 lots of SB2 were analyzed, including 6 lots of Drug Product each derived from a unique lot of Drug Substance and 4 lots of Drug Substance. The applicant also provided a comparison of stability under accelerated (25 ± 2°C) and stressed (40 ± 2°C) stability conditions.

Clinical studies supporting this application used a non-US-licensed comparator product, EU-approved Remicade. To justify the use of these comparative clinical data to support a demonstration of biosimilarity of SB2 to US-licensed Remicade, the Applicant performed an analytical study to establish an adequate scientific bridge for the products. The results of these comparisons show that the three products (SB2, US-licensed Remicade, and EU-approved Remicade) met expectations for analytical similarity.

The analytical similarity assessment of SB2, US-licensed Remicade and EU-Approved Remicade used a comprehensive set of assays, as listed in Table 1 below:

Table 1. Analytical methods used in the analytical similarity assessment

Quality Attribute	Analytical Methods
Primary Structure	- Molecular weight determination by MS - Amino acid sequencing by LC-ESI-MS/MS

	- N-terminal sequencing by peptide mapping - C-terminal sequencing by peptide mapping - Peptide mapping by LC-MS - Disulfide bond location determination by peptide mapping under reducing and non-reducing conditions - Free sulfhydryl group quantification by FLR - Methionine oxidation by LC-MS - Deamidation by LC-MS - C-terminal variants analysis by LC-ESI-MS/MS
Carbohydrate structure	- Glycation by LC-MS - N-linked glycosylation site determination by LC-ESI-MS/MS - N-glycan identification by procainamide labeling and LC-ESI-MS/MS - N-glycan profile analysis by 2-AB labeling and HILIC-UPLC
High molecular weight variants/aggregates	- %HMW impurities analysis by SEC - Aggregates characterization analysis by SEC/MALLS - Aggregates characterization analysis by SV-AUC - Protein size characterization analysis by DLS
Physicochemical Properties	- Charge heterogeneity analysis by CEX - Charge heterogeneity analysis by icIEF - %IgG analysis by CE-SDS (non-reducing) - %HC+%LC analysis by CE-SDS (reducing) - Extinction coefficient determination by amino acid analysis
Physicochemical Properties (higher order structure)	- Protein secondary and tertiary structure analysis by Circular Dichroism (Far-UV/Near-UV) - Protein folding analysis by intrinsic and extrinsic fluorescence spectroscopy - Secondary structure analysis by FTIR spectroscopy - Tertiary structure analysis by HDX-MS - Tertiary structure analysis by antibody conformation array Thermal stability analysis by DSC
Protein Content	- Protein content determination by UV/VIS at 280 nm
Sub-visible particles	- Sub-visible particles analysis by micro-flow imaging (MFI)
Fab-related Biological Activity and Fab-related Target Binding Affinity	- TNF-α binding assay by FRET (potency assay) - TNF-α neutralization assay by NF-κB reporter (potency assay) - Apoptosis "reverse signaling" assay - Transmembrane TNF-α binding assay by FACS
Fc-related Biological Activity and Receptor Interactions	- Antibody-dependent Cell-mediated Cytotoxicity (ADCC) assay - ADCC assay using healthy donor PBMC - Complement-dependent Cytotoxicity (CDC) assay - FcγRIIIa binding assay by AlphaScreen - FcγRIIIa binding assay by SPR - FcγRIIIa (158F/F variant) binding assay by SPR binding assay - FcγRIIIa (158V/F variant) binding assay using NK cells from PBMC by FACS - C1q binding assay by ELISA - FcRn binding assay by AlphaScreen - FcγRIa binding assay by FRET - FcγRIIa binding assay by AlphaScreen - FcγRIIb binding assay by AlphaScreen - FcγRIIIb binding assay by SPR - FcγRIIIb binding assay using neutrophils by FACS
Additional Biological Activity Assays	- Evaluation of regulatory macrophage function by Mixed Lymphocyte Reaction (MLR) - Cytokine release inhibition activity in *in vitro* IBD model by ELISA - Inhibitory activity of apoptosis in *in vitro* IBD model

The following attributes for SB2 are similar to the US-licensed Remicade, with the exceptions described later in this section:

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

TNF-α binding and neutralization is generally regarded as the main mechanism of action by infliximab. Tier 1 statistical equivalence was performed by the CMC Statistics reviewer for the Tier 1 assays: the TNF-α binding assay by FRET and the TNF-α neutralization assay by NF-κB reporter gene. For the TNF-α binding assay by FRET, the applicant provided data for 10 lots of SB2, 41 lots of US-licensed Remicade, and 37 lots of EU-approved Remicade. For the TNF-α neutralization assay, the applicant provided data for 10 lots of SB2, 46 batches of US-licensed Remicade, and 40 batches of EU-approved Remicade. The statistical analysis using equivalence testing met the pre-determined equivalence margin of $\pm 1.5\ \sigma_R$, where σ_R is the variability of lots of US-licensed Remicade.

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

Each protein biochemistry and biological activity attribute described in Table 1 above met the pre-determined criteria for the pairwise comparisons of SB2 to US-licensed Remicade and to EU-Approved Remicade, with the following exceptions:

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

Additionally,

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

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

In each of these cases, the impact of the slight differences in the attributes and resulting residual uncertainty is mitigated by additional information and analysis provided by the applicant:

- In the cases of FcγRIIIa binding affinity, percent basic variants, percent non-glycosylated heavy chain, percent charged glycans, and C1q binding affinity, functional assays that assess biological activity known to be influenced by the listed physicochemical attributes were evaluated in each case. The data from the functional assays all demonstrated that the modest potential differences suggested by physicochemical testing do not correspond to a change in product bioactivity or function. Basic variants were isolated, identified, characterized, and found to have no impact on function. FcγRIIIa binding affinity, percent basic variants, and percent non-glycosylated heavy chain are each controlled by in-process or lot release tests with acceptance criteria sufficiently stringent to assure that these attributes will remain in the range that yielded similar functional assay results in the analytical similarity assessment.

- In the case of high-molecular weight (HMW) species, additional characterization data support that the HMW species observed by size exclusion chromatography are non-covalent and reversible. Stability data demonstrate that the slightly higher levels for SB2 (0.6 – 0.9% versus ≤ 0.5 % for US-licensed and EU-licensed Remicade) to not impact product stability or lead to excessive sub-visible particle formation. All protein therapeutics contain HMW species at varying levels, and SB2 is a highly (>99%) pure product with respect to HWM variants.

- In the case of FcRn binding affinity, the magnitude of difference between SB2 and EU-approved Remicade was negligible. FcRn binding is linked to circulating half life *in vivo*, and there was no significant difference between the SB2 and EU-approved Remicade in pharmacokinetics studies.

In summary, the totality of analytical similarity data supports the following conclusions:

- SB2 is highly similar to US-licensed Remicade, notwithstanding minor differences in clinically inactive components.

- A sufficiently robust analytical bridge was established to support the use of EU-approved Remicade as a comparator in clinical studies.

- SB2 and US-licensed Remicade share an identical primary sequence.
- *In vitro* measures of the primary mechanism of action, TNF-α binding and TNF-α neutralization, demonstrate statistical equivalence of SB2 to US-licensed Remicade.
- An appropriate panel of functional assays measuring potential secondary mechanisms of action of anti-TNFα monoclonal antibody products yielded results meeting quality range criteria.
- The protein content of reconstituted SB2 and US-licensed Remicade is similar, demonstrating that SB2 has same total content of antibody as US-licensed Remicade. These data demonstrate that the proposed SB2 presentation (100 mg lyophilized solid in

a single-use vial) meets the statutory same strength requirement under section 351(k)(2)(A)(i)(IV) of the PHS Act.

- While some minor differences were noted in the biochemical attributes noted above, these were within the typical ranges for bioreactor-produced therapeutic monoclonal antibodies and do not preclude a determination of highly similar for SB2 relative to US-licensed Remicade. The differences were shown not to impact functional activities related to either the primary or potential secondary mechanisms of action of SB2 and US-licensed Remicade.

B. CQA Identification, Risk, and Lifecycle Knowledge Management

Table 2 below is a summary of critical quality attributes and the associated control strategies for attributes that are relevant to both Drug Substance and Drug Product. For additional information, see the primary reviews, including the Drug Substance Quality Review and Drug Product Quality Review by OBP/DBRR-II and the Drug Substance Microbiology Review and the Drug Product Microbiology Review by OPF/DMA.

Table 2: Drug Substance and Drug Product CQA Identification, Risk, and Lifecycle Knowledge Management

CQA	Risk	Origin	Control Strategy	Other
TNF-α binding and neutralization (potency)	Efficacy	Changes to protein composition during manufacture or storage	(b) (4)	
High-molecular weight (HMW) species	Efficacy, pharmacokinetics, and immunogenicity	Affected by manufacturing and storage conditions. Can form due to agitation, temperature, or light exposure.		
Fragmentation (%IgG monomer)	Efficacy, pharmacokinetics, and immunogenicity	Affected by manufacturing and storage conditions. Can form due to agitation, temperature, or light		
Fragmentation (%light chain and %heavy chain)	Efficacy, pharmacokinetics, and immunogenicity	Affected by manufacturing and storage conditions. Can form due to agitation, temperature, or light		PMC to add reducing CE-SDS to the DS and DP release specification
Charge Variant Profile (deamidation, C-terminal and N-terminal variants and oxidation)	Efficacy, pharmacokinetics, and immunogenicity	(b) (4) manufacture and storage		Originally proposed only for DS release and stability specifications, added to DP release and stability specifications at FDA request
Glycosylation	Efficacy and pharmacokinetics	(b) (4) process		PMC to add reducing CE-SDS to the DS and DP release and stability specification. Assay is sensitive to %non-glycosylated heavy chain
Protein content	Efficacy, pharmacokinetics, safety	Manufacturing process		

CQA	Risk	Origin	Control Strategy	Other
FcRn binding	Efficacy Pharmacokinetics	(b) (4) process	(b) (4)	
ADCC	Efficacy	(b) (4) process		PMC to add a FcγRIIIa binding affinity test to DS release specification
CDC	Efficacy	(b) (4) process		
Apoptosis (signaling via mTNF-α)	Efficacy	(b) (4) process		
pH	Safety, efficacy	Manufacturing process		
Endotoxin	Safety	Contamination during the manufacturing process		Review recommendation by OPF/DMA is pending

C. Drug Substance Quality Summary

CQA Identification, Risk and Lifecycle Knowledge Management

Table 3 below summarizes the critical quality attributes and their control strategy that are relevant specifically to the Drug Substance. For additional information, see the primary reviews, including the Drug Substance Quality Review and Drug Product Quality Review by OBP/DBRR-II and the Drug Substance Microbiology Review and the Drug Product Microbiology Review by OPF/DMA.

Table 3: Drug Substance CQA Identification, Risk, and Lifecycle Knowledge Management

CQA	Risk	Origin	Control Strategy	Other
Bioburden	Safety; product quality (potential degradation or modification of product)	Contamination during manufacturing process	(b) (4)	Review recommendation by OPF/DMA is pending
Appearance (color and clarity)	Safety	Manufacturing process		
Host Cell Proteins	Safety and immunogenicity	Process-related impurity introduced by expressing in host cell line		
Host Cell DNA	Safety	Process-related impurity introduced by expressing in host cell line		
(b) (4)	Safety and immunogenicity	Process-related impurity (b) (4)		
Virus Contamination	Safety	Contamination during manufacture		
(b) (4)	Safety, stability	Manufacturing process		

[1]Not considered a CQA by the applicant.

1. Description:
   SB2 is a recombinant chimeric IgG1κ monoclonal antibody that binds human TNF-α. The amino acid sequence of the variable domain is of murine origin and that of the constant region is of human origin. SB2 consists of 4 polypeptide chains (2 identical heavy chains and 2 identical light chains) comprised of a total 1328 amino acids, and SB2 has a molecular weight of approximately 149 kDa. The SB2 expression construct was reverse engineered from published Remicade sequences and is expressed in a CHO cell line. Amino acid sequencing and tryptic peptide mapping with mass spectrometry analysis confirms the correct amino acid sequence. (b) (4)

2. Mechanism of action:
   SB2 binds specifically to TNF-α and blocks its interaction with TNF receptors. TNF-α is a naturally occurring cytokine with stimulatory activities for most cells of the immune system and is involved in normal inflammatory and immune responses. TNF-α is also involved in a variety of cellular processes, including apoptosis, differentiation, and proliferation. Elevated levels of TNF-α are found in the synovial fluid of patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. TNF-α plays an important role in both the pathologic inflammation and the joint destruction that are characteristic of these diseases. TNF-α occurs both as a membrane bound (mTNF-α) form and a soluble form (sTNF-α). SB2 binds to both the soluble and membrane bound forms. SB2 functions primarily by binding and neutralizing and sequestering excess sTNF-α produced in local tissue sites in inflammatory disease states.

   Other possible clinically relevant SB2 activities include mediating antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) towards mTNF-α-positive inflammatory T-cells or other cells associated with inflammatory disease. Additionally, SB2 may induce "reverse signaling" in mTNF-α-positive cells or induce regulatory macrophages. These activities have been suggested to contribute to inflammatory bowel disease indications, although the significance of the contribution of any of these individual mechanisms not well established (based on literature review).

3. Potency Assays:
   There are two *in vitro* potency assays for SB2. The first assay measures the binding affinity for soluble TNF-α in a competitive inhibition format. The assay measures the loss of fluorescence resonance energy transfer (FRET) between fluorescently labeled infliximab and TNF-α upon competition by unlabeled SB2. SB2 causes a dose-dependent loss in fluorescence signal, and the relative competitive binding activity is reported as a percentage of the activity of the reference standard.

   The second assay measures neutralization of soluble TNF-α using a reporter gene assay. The assay uses a reporter cell line with a luciferase gene encoded downstream of NF-κB binding DNA sequences. Binding of TNF-α to its receptor

activates NF-κB, which induces luciferase expression, and luciferase enzymatic activity results in a luminescence signal. SB2 sequesters TNF-α, preventing it from binding the receptor to induce the downstream luminescence signal. The loss of fluorescence signal from this neutralization activity is SB2 dose-dependent and is reported as a relative percentage of the activity of the reference standard.

4. Reference material(s):
   A well characterized primary reference standard was derived from a clinical batch. The applicant plans to qualify a working reference standard against this primary reference standard. Samsung provided an acceptable qualification protocol for future working reference standards. The two-tiered reference standard approach will ensure sufficient inventory of working reference standard for routine release and stability testing while minimizing drift by linking working reference standard activity to a single primary reference standard.

5. Critical starting materials or intermediates:
   (b) (4)

6. Manufacturing process summary:
   (b) (4)

7. Container closure:
   (b) (4)

(b) (4)

8. Dating period and storage conditions:
   The sponsor conducted real-time, accelerated, and stressed stability studies on 3 intended-for-commercial lots, 1 clinical lot, and 1 pilot scale lot to support a proposed dating period of (b) (4) months when stored at (b) (4) °C.

D. Drug Product Quality Summary

Table 4 provides a summary of the identification, risk, and lifecycle knowledge management for critical quality attributes specifically related to Drug Product manufacture and testing. See Table 1 for CQAs related to both the Drug Substance and Drug Product.

Table 4: Drug Product CQA Identification, Risk, and Lifecycle Knowledge Management

CQA	Risk	Origin	Control Strategy	Other
Sterility	Safety, Efficacy (degradation or modification of the product by contaminating microorganisms)	Contamination may be introduced during manufacture or through a container closure integrity failure	(b) (4)	Review recommendation by OPF/DMA is pending
Visible Particles	Safety	Product- or process-related impurities, contamination		
Appearance (lyophilized cake)	safety	Manufacturing process		
Appearance (color and clarity)	safety	Manufacturing process		
Sub-visible particles	Safety	Manufacturing process, product degradation		
Identity	Safety and efficacy	N/A		
Reconstitution time	Safety, efficacy	Manufacturing process, storage conditions		
Moisture content	Stability	Manufacturing process, loss of container closure integrity		
Osmolality	Safety, stability	Manufacturing process		

1. Potency:
   Potency of SB2 is considered, for the purposes of this review, as the percent TNF-α binding or TNF-α neutralizing activity relative to the current reference standard. The potency assays are the same as those described in the Drug Substance section of this review.

2. Strength:
   SB2 is supplied as a 100 mg lyophilized solid in a single-use vial. The lyophilized powder in the vials is to be reconstituted in 10 mL sterile water for injection, yielding a 100 mg/10 mL solution.

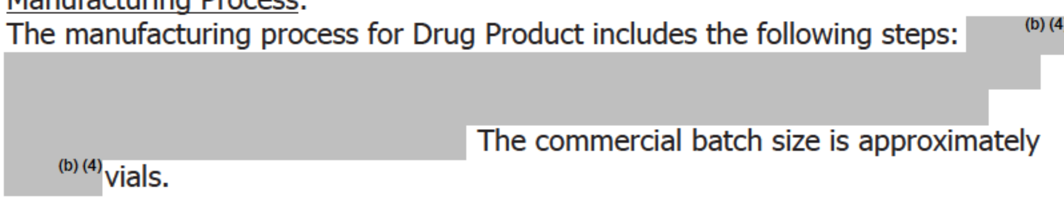
   Comparative data for protein concentration demonstrate that SB2 (100 mg lyophilized solid in a single-use vial) has the same total content of therapeutic antibody and the same concentration of antibody upon reconstitution as US-licensed Remicade. The proposed SB2 presentation (100 mg lyophilized solid in a single-use vial) meets the statutory same strength requirement under section 351(k)(2)(A)(i)(IV) of the PHS Act.

3. Summary of Product Design:
   SB2 will be supplied as a sterile, preservative-free lyophilized powder in vials. The lyophilized powder is to be reconstituted in sterile water for injection and further diluted into 0.9% sodium chloride solution in an infusion bag. Because of the potential formation of visible particles, the draft labeling for SB2 states that an in-line filter must be incorporated during infusion.

4. List of Excipients:
   Excipients include monobasic sodium phosphate monohydrate, dibasic sodium phosphate heptahydrate, sucrose, and polysorbate 80. Except for the antibody itself, all ingredients meet compendial requirements (USP/NF, Ph. Eur. and/or JP) and are commonly used for formulation of biopharmaceuticals. No excipients are of human or animal origin.

5. Reference material(s):
   The same reference standard is used for Drug Product as for Drug Substance. Refer to the Drug Substance reference standard section above.

6. Manufacturing Process:
   The manufacturing process for Drug Product includes the following steps: (b) (4)

   The commercial batch size is approximately (b) (4) vials.

   Three Drug Product batches at the commercial scale were manufactured and analyzed to validate the manufacturing process. Manufacturing process parameters were within pre-specified parameters, and product quality attributes were within specification limits. These data support a well controlled process that will

consistently produce a high quality product and that is adequate from a product quality review perspective. Microbial control was also assessed for these validation batches, and media fill simulations were also performed; a review recommendation on these data from the Division of Microbiology Assessment is pending. Additionally, shipping validation studies support that the product is maintained at the 2 to 8°C storage condition and the physical integrity of the containers is maintained when SB2 shipped to distribution centers.

7. Container Closure:
   The primary packaging material for SB2 Drug Product consists of a (b) (4) 20 mL (b) (4) glass vial (b) (4), stoppered with a (b) (4) rubber stopper (b) (4)) and sealed with an aluminum crimping cap (b) (4)).

8. Expiration Date & Storage Conditions:
   The sponsor conducted real-time, accelerated, and stressed stability studies on 3 commercial Drug Product lots, 3 clinical Drug Product lots, and 1 pilot scale Drug Product lot. These data support a dating period of 30 months when stored at 2 to 8°C.

9. List of co-packaged components:
   None.

E. Novel Approaches/Precedents

None.

F. Any Special Product Quality Labeling Recommendations

None.

G. Establishment Information

There are no outstanding inspection or facility issues. The Division of Inspectional Assessment recommends approval of the BLA. The manufacturing and testing facilities, their responsibilities in SB2 production, and inspectional outcomes are summarized in the table below.

OVERALL RECOMMENDATION: Approve				
DRUG SUBSTANCE				
Site Name and Address	**FEI Number**	**Responsibilities**	**Inspection Outcome**	**Final Recommendation from OPF/DIA**
(b) (4)	(b) (4)	-Manufacturing and packaging -QC release testing (appearance, protein concentration, endotoxin, and microbial enumeration) -Stability testing for clinical batch (all tests) -In-process testing (IPT) testing (b) (4)	PAI (b) (4) VAI	Approve based on inspection assessment
	(b) (4)	-DS storage	PAI (b) (4) NAI	Approve based on inspection assessment
	(b) (4)	-In-proess test (IPT) testing ((b) (4)	Waived	Approve based on profile
Samsung Bioepis Co., Ltd.[1] 107, Cheomdan-daero, Yeonsu-gu, Incheon, Republic of Korea	3010031951	-In-process test (IPT) testing (b) (4)	PAI Aug 16–19, 2016 VAI	Approve based on inspection assessment

Site Name and Address	FEI Number	Responsibilities	Inspection Outcome	Final Recommendation from OPF/DIA
(b) (4)		-QC release testing (all tests excluding appearance, protein concentration, endotoxin, and microbial enumeration) -Stability testing for the PVR batches (all tests except endotoxin and microbial enumeration) and commercial batches (all tests)	waived	Approve based on profile
		-Stability testing for the PVR batches (TNF-α neutralization assay by NF-κB reporter gene)	Waived	Approve based on profile
		-Stability testing for the PVR batches (endotoxin and microbial enumeration)	Waived	Approve based on profile
		-MCB and WCB manufacturing -MCB and WCB storage	Waived	Approve based on profile
		-MCB and WCB storage	Waived	No evaluation needed based on low GMP risk
DRUG PRODUCT				
Site Name and Address	**FEI Number**	**Responsibilities**	**Inspection Outcome**	**Final Recommendation from OPF/DIA**
(b) (4)		-Manufacturing and Packaging -QC release testing (sterility) -Stability testing for clinical batch (container closure integrity, CCIT) -In-process test (IPT) testing	PAI (b) (4) VAI	Approve based on inspection assessment
		-QC release testing (alternative site for all tests excluding uniformity of dosage units, sterility, endotoxin, and CCIT) -Stability testing for clinical batches (all tests excluding sterility and CCIT)	PAI (b) (4) VAI	Approve based on inspection assessment

(b) (4)			
	-QC release testing (all tests excluding endotoxin and sterility) -Stability testing (all tests excluding endotoxin and -sterility)	waived	Approve based on profile
	-Stability testing for the clinical and PVR batches -(TNF-α neutralisation assay by NF-κB reporter gene)	Waived	Approve based on profile
	-QC release testing (endotoxin) -Stability testing (endotoxin and sterility)	Waived	Approve based on profile

[1] Samsung Bioepis is the site where the analytical similarity data were collected and analyzed. Similarity activities were evaluated during the PAI of that facility.

H. Lifecycle Knowledge Management

a. Drug Substance

i. Protocols approved:
- annual stability protocol (may be used to extend shelf life)
- qualification of new working reference standard
- concurrent validation of (b) (4)

ii. Outstanding review issues/residual risk:
- See Post-marketing Commitments in section IB (page 5)

iii. Future inspection points to consider
- Follow up on 483 observations
- Evaluate trending of release and in-process tests results

b. Drug Product

i. Protocols approved:
- annual stability protocol (may be used to extend shelf life)

ii. Outstanding review issues/residual risk:
- See Post-marketing Commitments in section IB (page 5)

iii. Future inspection points to consider
- Follow up on 483 observations
- Evaluate trending of release and in-process tests results

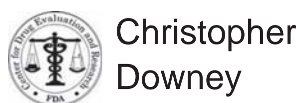
Quality Assessment Summary Table

Noteworthy Elements of the Application

#	Checklist	Yes	No	Comment
Product Type				
1.	Recombinant Product	x		
2.	Naturally Derived Product		x	
3.	Botanical		x	
4.	Human Cell Substrate/Source Material		x	
5.	Non-Human Primate Cell Substrate/Source Material		x	
6.	Non- Primate Mammalian Cell Substrate/Source Material	x		
7.	Non-Mammalian Cell Substrate/Source Material		x	
8.	Transgenic Animal Sourced		x	

9.	Transgenic Plant Sourced			x	
10.	New Molecular Entity			x	
11.	PEPFAR Drug			x	
12.	PET Drug			x	
13.	Sterile Drug Product		x		
14.	Other_________________				
	Regulatory Considerations				
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application (#________________)			x	
16.	Comparability Protocol(s)			x	
17.	End of Phase II/Pre-NDA Agreements)			x	
18.	SPOTS (Special Products On-line Tracking System			x	
19.	USAN Name Assigned			x	
20.	Other		x		Biosimilar Product to Remicade
	Quality Considerations				
21.	Drug Substance Overage			x	
22.	Design Space	Formulation		x	
23.		Process		x	
24.		Analytical Methods		x	
25.		Other		x	
26.	Other QbD Elements		x		Design of experiments used in manufacturing process development (e.g. lyophilization cycle)
27.	Real Time Release Testing (RTRT)			x	
28.	Parametric Release in lieu of Sterility Testing			x	

29.	Alternative Microbiological Test Methods			x	
30.	Process Analytical Technology in Commercial Production			x	
31.	Non-compendial Analytical Procedures	Drug Product	x		
32.		Excipients		x	
33.		Drug Substance	x		
34.	Excipients	Human or Animal Origin		x	
35.		Novel		x	
36.	Nanomaterials			x	
37.	Genotoxic Impurities or Structural Alerts			x	
38.	Continuous Manufacturing			x	
39.	Use of Models for Release			x	
40.	Other ________________			x	



Christopher Downey

Digitally signed by Christopher Downey
Date: 3/16/2017 09:48:50AM
GUID: 508da6d9000264ed71c49d80cfe4e31a

Juhong Liu

Digitally signed by Juhong Liu
Date: 3/23/2017 04:30:20PM
GUID: 508da6da000265f64de5224635a510aa

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

REVIEWER: Jessica Hankins, Ph.D.
ACTING QAL: Dupeh Palmer, Ph.D.
ACTING BRANCH CHIEF: Patricia Hughes, Ph.D.

BLA:	761054
Applicant:	Samsung Bioepis Co, Ltd.
US License Number:	2046
Submission Reviewed:	351(k) BLA
Product:	Proposed biosimilar to infliximab
Indication:	Crohn's disease, Pediatric Crohn's disease, Ulcerative Colitis, Pediatric Ulcerative Colitis, Rheumatoid Arthritis in combination with methotrexate, Ankylosing Spondylitis, Psoriatic Arthritis, Plaque Psoriasis
Dosage Form:	100 mg lyophilized in vials (single use vial) for intravenous infusion.
Manufacturing Sites:	Drug product: (b) (4) (FEI: (b) (4))
FDA Receipt Date:	21 March 2016
Action Date:	21 April 2017

Conclusion and Approvability Recommendation

The BLA, as amended, was reviewed from a product quality microbiology and sterility assurance perspective and is recommended for approval. There are four post-marketing commitments:

1. Qualify an in-process (b) (4) method and establish an in-process (b) (4) limit for the (b) (4) of the SB2 drug product manufacturing process. Submit the proposed limit as a CBE-30 supplement described under 21 CFR 601.12 (c).
2. Conduct two additional (b) (4) determination studies for post-use integrity testing of the (b) (4) using two additional lots of SB2 drug product.

3. Conduct endotoxin, bioburden, and sterility test method qualification study using one additional batch of SB2 Drug Product manufactured according to the commercial drug product manufacturing processes.
4. Repeat the container closure integrity test (CCIT) validation for the SB2 drug product using a positive control with a defect size of no more than 20 microns. Submit the CCIT validation study report as a CBE30 described under 21 CFR 601.12 (c).

Product Quality Microbiology Assessment: Drug Product

Drug Product Quality Microbiology Information Reviewed

Sequence number	Date	Description
0000	03/21/2016	Original BLA
0031	12/09/2016	Information request response
0039	02/08/2017	Information request response
0040	03/08/2017	Information request response
0041	03/10/2017	Information request response
0042	03/17/2017	Information request response

Module 3.2

P.1 Description and Composition of the Drug Product

The drug product (DP) is a sterile, white, lyophilized concentrate for injection for intravenous use. The lyophilized DP is reconstituted in 10 mL sterile water for injection (WFI), yielding a single dose formulation of 10 mg/mL at pH 6.2. The reconstituted DP is then diluted in 0.9% sodium chloride for infusion.

(b) (4) The table below describes the active ingredient and excipients for the DP.

Table 3.2.P.1–1. Composition of SB2 DP

Component	Nominal Quantity/Vial	Function	Quality Standard
Infliximab	100 mg	Active substance	In-house[a]
Monobasic sodium phosphate monohydrate	5.55 mg	(b) (4)	USP-NF
Dibasic sodium phosphate heptahydrate	2.60 mg		USP-NF
Sucrose	500 mg		Ph. Eur./USP-NF
Polysorbate 80	0.5 mg		Ph. Eur./USP-NF
Water for Injection[b]	*q.s.*		Ph. Eur./USP-NF

[a] Specification of SB2 DS (infliximab) is provided in Section 3.2.S.4.1 Specification.
[b] WFI evaporates during SB2 DP manufacturing process.

DESCRIPTION IS SATISFACTORY

P.2 Pharmaceutical Development

Microbiological Attributes

Container closure integrity testing (CCIT) is performed using the methylene blue dye ingress test. CCIT, instead of sterility testing, is performed annually and upon expiry during the stability program and is listed as a testing parameter in the proposed shelf life specification; however, CCIT is not conducted at release.

Reviewer comment: The DP is preservative-free and is tested for sterility and endotoxin upon release and during the stability program. CCIT is performed annually and upon expiry in lieu of sterility testing during the stability program. CCIT is not conducted at release. The method validation for CCIT is reviewed in section 3.2.P.8.3.

SATISFACTORY

P.3 Manufacture

55 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

Digitally signed by Jessica Hankins
Date: 4/18/2017 12:06:36PM
GUID: 57640ae700ea29dfdaa5ef6b52b35c55

Digitally signed by Dupeh Palmer-Ochieng
Date: 4/18/2017 12:08:25PM
GUID: 508da70b00028e31283d148af9660733

Digitally signed by Patricia Hughes Troost
Date: 4/18/2017 01:45:48PM
GUID: 508da717000297bcbfce0919f8c09594

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Biotechnology Products

LABEL AND LABELING REVIEW

Date:	April 3, 2017
Reviewer:	Jibril Abdus-Samad, PharmD, Labeling Reviewer Office of Biotechnology Products (OBP)
Through:	Timothy Wadkins, PhD, Quality Reviewer OBP/Division of Biotechnology Review and Research II
Application:	BLA 761054/0
Product:	Renflexis (infliximab-abda*)
Applicant:	Samsung Bioepis Co., Ltd.
Submission Dates:	March 21, 2016; January 17, 2017

Executive Summary:

The revisions to the container label and carton labeling submitted on January 17, 2017 for Renflexis (infliximab-abda*) for Injection 100 mg in a single-dose vial are acceptable. However, DPARP will communicate three pending items during labeling negotiations:

1. OBP PI recommendations.
2. Revision of references to the nonproprietary name for Renflexis to "infliximab-abda*" throughout all labeling.
3. Revision of " (b) (4) " on the carton labeling preparation instructions to include the dosage form so that it reads "0.9% Sodium Chloride Injection, USP".

Background and Summary Description:

The Applicant, Samsung Bioepis Co., Ltd., submitted BLA 761054/0 Renflexis (SB2**) on March 21, 2016 as a proposed biosimilar to US-licensed Remicade (infliximab). Table 1 lists the proposed characteristics of Renflexis (SB2**). This review evaluates the proposed label and labeling submitted on March 21, 2016 (Application 761054 - Sequence 0000 - 1.14 Labeling -).

* Renflexis has been developed as a proposed biosimilar to US-licensed Remicade (infliximab). Subsequent to submission of the 351(k) BLA, the nonproprietary name for Renflexis was determined to be infliximab-abda.

** At the time of the original submission, the Agency generally referred to Samsung's proposed product by Samsung's descriptor "SB2." Subsequently, the nonproprietary name for Renflexis was determined to be infliximab-abda.

Table 1: Proposed Product Characteristics of Renflexis (SB2**).

Proprietary Name:	Renflexis
Proper Name:	SB2**
Indication:	Tumor necrosis factor (TNF) blocker indicated for Crohn's Disease, Pediatric Crohn's Disease, Ulcerative Colitis, Pediatric Ulcerative Colitis[1], Rheumatoid Arthritis, Ankylosing Spondylitis, Psoriatic Arthritis Plaque Psoriasis
Dose:	Crohn's Disease: 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. Pediatric Crohn's Disease: 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. Ulcerative Colitis: 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. Pediatric Ulcerative Colitis: 5 mg/kg at 0, 2, and 6 weeks, then every 8 weeks. Rheumatoid Arthritis: 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. Ankylosing Spondylitis: 5 mg/kg at 0, 2 and 6 weeks, then every 6 weeks. Psoriatic Arthritis and Plaque Psoriasis: 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.
Route of Administration:	Intravenous infusion
Dosage Form:	for Injection
Strength and Container-Closure:	100 mg lyophilized powder in a single-dose vial.
Storage and Handling:	Refrigerate at 2°C to 8°C (36°F to 46°F). RENFLEXIS infusion should begin within 3 hours of reconstitution and dilution.

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

Materials Reviewed:

- Container Label
  \\cdsesub1\evsprod\bla761054\0000\m1\us\mockup-vial.pdf
- Carton Labeling
  \\cdsesub1\evsprod\bla761054\0000\m1\us\mockup-carton.pdf
- Prescribing Information (PI) and Medication Guide (MG)
  \\cdsesub1\evsprod\bla761054\0000\m1\us\draft-labeling-text-redline.pdf

---

Start of Sponsor Material

Container Label

End of Sponsor Material

Subpart G-Labeling Standards
Subpart A-General Labeling Provisions

I. Container

A. 21 CFR 610.60 Container Label

(a) Full label. The following items shall appear on the label affixed to each container of a product capable of bearing a full label; *This product has a partial label (see below). However, there is space on the label to allow for placement of some of the items recommended for the full label.*

(b) Package label information. If the container is not enclosed in a package, all the items required for a package label shall appear on the container label; *not applicable*.

(c) Partial label. If the container is capable of bearing only a partial label, the container shall show as a minimum:

- the name (expressed either as the proper or common name);
  does not conform.

DMEPA found the nonproprietary name "infliximab-abda", conditionally acceptable for the proposed product.[2] Should this 351(k) BLA be approved during this review cycle, infliximab-abda will be the proper name designated in the license for this 351(k) BLA. During PI labeling negotiations, DPARP will request the Applicant revise references to the nonproprietary name for Renflexis throughout all the proposed label and labeling.

- the lot number or other lot identification; *conforms. However, the lot and expiration are duplicated*.

  OBP Request: Remove the duplicate lot and expiration dates on the right-side panel to create space on this partial label.

  Applicant's Response January 17, 2017: The Applicant has considered deleting the multiple lot and expiration dates, but as the Applicant was able to secure space to accommodate all labeling recommendations by the Agency, and as the Applicant believes that including multiple lot and expiration dates which can be peeled off and attached onto, for example infusion bags, can reduce medication errors, the Applicant has decided to maintain this information.
  The Applicant's response is acceptable.

- the name of the manufacturer; *conforms. However, the license number requires revision.*

  OBP Request: Revise the " (b) (4) " to read "US License No. XXXX."
  The Applicant's revision is acceptable.

- in addition, for multiple dose containers, the recommended individual dose; *not applicable*.

- Containers bearing partial labels shall be placed in a package which bears all the items required for a package label; *conforms*.

(d) No container label. If the container is incapable of bearing any label, the items required for a container label may be omitted, provided the container is placed in a package which bears all the items required for a package label; *not applicable*.

[2] Mena-Grillasca C. Nonproprietary Name Suffix Memo for Renflexis (BLA 761054). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 JAN 06.

(e) Visual inspection. When the label has been affixed to the container, a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents; *insufficient data submitted*.

OBP Request: Indicate how the label is affixed to the vial and where the visual area of inspection is located per 21 CFR 610.60(e)

Applicant's Response January 17, 2017: The label is affixed to the vial with a sufficient area of the vial uncovered as per 21 CFR 610.60(e). The visual area of inspection is located as shown in Figure 1.

*Note the intent of image above is to show the visual area of inspection after the label is affixed to the vial. However, the image does not show the proposed labeling content for this 351(k) BLA 761054.
The Applicant's response is acceptable.

B. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located at the top of the label. [See 21 CFR 207.35]; *conforms*.

C. 21 CFR 201.5 Drugs; adequate directions for use; *conforms*.

D. 21 CFR 201.6 Drugs; misleading statements; *conforms*.

E. 21CFR 201.10 Drugs; statement of ingredients; placement and prominence; *conforms*.

F. 21 CFR 201.15 Drugs; prominence of required label statements; *does not conform*.

OBP Request: Re-locate the 'Rx only' statement to be placed after the statements "Single-dose vial. Discard unused portion."
The Applicant's revision is acceptable.

G. 21 CFR 201.17 Drugs; location of expiration date; *conforms*.

H. 21 CFR 201.25 Bar code; *not applicable because bar codes are not required on partial labels.* However, OBP concurs with DMEPA's recommendation to add a barcode if space permits. To create space on the partial label (21 CFR 610.60(c), consider deleting the following information that is not required:

- (b) (4)
-
-

The Applicant's revision is acceptable.

I. 21 CFR 201.50 Statement of identity; *conforms*.

J. 21 CFR 201.51 Declaration of net quantity of contents; *does not conform*.

OBP Request: Revise the prominent "(b) (4)" in the green background color to read "100 mg per vial" or "100 mg/vial".
The Applicant's revision is acceptable.

K. 21 CFR 201.55 Statement of dosage; *conforms*.

L. 21 CFR 201.100 Prescription drugs for human use; *does not conform*.

OBP Request: Revise "(b) (4)" to read "For Intravenous Infusion Only."
The Applicant's revision is acceptable.

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

II. Carton

A. 21 CFR 610.61 Package Label:

a) The proper name of the product [see 21 CFR 600.3 (k) and section 351 of the PHS Act]; *does not conform.*

DMEPA found the nonproprietary name "infliximab-abda", conditionally acceptable for the proposed product.[3] Should this 351(k) BLA be approved during this review cycle, infliximab-abda will be the proper name designated in the license for this 351(k) BLA. During PI labeling negotiations, DPARP will request the Applicant to revise references to the nonproprietary name for Renflexis throughout all the proposed labels and labeling.

b) The name, addresses, and license number of manufacturer; *conforms*.

c) The lot number or other lot identification; *conforms*.

d) The expiration date; *conforms*.

e) The preservative used and its concentration, if no preservative is used and the absence of a preservative is a safety factor, the words "no preservative"; *conforms*.

f) The number of containers, if more than one; *not applicable*.

g) The amount of product in the container expressed as (1) the number of doses, (2) the volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable; *conforms*.

h) The recommended storage temperature; *conforms*.

i) The words "Do not Freeze" or the equivalent, as well as other instructions, when indicated by the character of the product; *conforms*.

j) The recommended individual dose if the enclosed container(s) is a multiple-dose container; *not applicable*.

---

[3] Mena-Grillasca C. Nonproprietary Name Suffix Memo for Renflexis (BLA 761054). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 JAN 06.

k) The route of administration recommended, or reference to such directions in an enclosed circular; *does not conform.*

> OBP Request: Revise "[redacted] (b) (4)" to read "For Intravenous Infusion Only."
> *The Applicant's revision is acceptable.*

l) Known sensitizing substances, or reference to enclosed circular containing appropriate information; *not applicable*.

m) The type and calculated amount of antibiotics added during manufacture; *not applicable*.

n) The inactive ingredients when a safety factor, or reference to enclosed circular containing appropriate information; *not applicable*.

o) The adjuvant, if present; *not applicable*.

p) The source of the product when a factor in safe administration; *not applicable*.

q) The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information; *not applicable*.

r) Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words "No U.S. standard of potency"; *conforms*.

s) The statement "Rx only" for prescription biologicals; *conforms*.

- Note: If product has a medication guide, a statement is required on the package label if it is not on the container label (see above). *It is recommended the statement be present on both labels.*

B. 21 CFR 610.62 Proper name; package label; legible type [Note: Per 21 CFR 601.2(c)(1), certain regulations including 21 CFR 610.62 do not apply to the four categories of "specified" biological products listed in 21 CFR 601.2(a)]; *Exempt. Renflexis (SB2**) is a monoclonal antibody and is exempt*.

C. 21 CFR 610.63 Divided manufacturing responsibility to be shown; *not applicable*.

D. 21 CFR 610.64 Name and address of distributor; *conforms*.

The name and address of the distributor of a product may appear on the label provided that the name, address, and license number of the manufacturer also appears on the label and the name of the distributor is qualified by one of the following phrases: "Manufactured for ______". "Distributed by ______", "Manufactured by ______ for ______", "Manufactured for ______ by _______", "Distributor: ______", or 'Marketed by ______". The qualifying phrases may be abbreviated.

E. 21 CFR 610.67 Bar code label requirements; *conforms*.

Biological products must comply with the bar code requirements at §201.25 of this chapter;

F. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located on top of the label [See 21 CFR 207.35]; *conforms*. *We concur with DMEPA's request for the Applicant to replace the placeholder with the actual numbers*.

G. 21 CFR 201.5 Drugs; adequate directions for use; *conforms*.

H. 21 CFR 201.6 Drugs; misleading statements; *conforms*.

I. 21 CFR 201.10 Drugs; statement of ingredients [Placement and Prominence]; *conforms*.

J. 21 CFR 201.15 Drugs; prominence of required label statements; *conforms*.

K. 21 CFR 201.17 Drugs; location of expiration date; *conforms*.

L. 21 CFR 201.25 Bar code label requirements; *conforms*.

M. 21 CFR 201.50 Statement of identity; *conforms*.

N. 21 CFR 201.51 Declaration of net quantity of contents; *does not conform*.

OBP Request: Revise the prominent "100 mg" in the green background color to read "100 mg per vial" or "100 mg/vial".
The Applicant's revision is acceptable.

O. 21 CFR 201.55 Statement of dosage; *conforms*.

P. 21 CFR 201.100 Prescription drugs for human use; *conforms*. *However, we recommend revising the inactive ingredients to appear in alphabetical order (per USP General Chapters <1091> Labeling of Inactive Ingredients). Additionally, we concurred with DMEPA's recommendation to revise the reconstitution instructions as well.*

OBP Request: To ensure the proper preparation of the product and to comply with USP General Chapters <1091> Labeling of Inactive Ingredients, revise the statement on the side panel, "Reconstitute each vial with 10 mL Sterile Water for Injection, USP. Each mL contains…" to as follows:

> "Reconstitute each vial with 10 mL Sterile Water for Injection, USP. Do NOT shake reconstituted solution. Must further dilute with 0.9% Sodium Chloride, USP. Once reconstituted, each mL contains 10 mg infliximab-xxxx***, dibasic sodium phosphate heptahydrate (0.26 mg), monobasic sodium phosphate monohydrate (0.56 mg), polysorbate 80 (0.05 mg), and sucrose (50 mg)."

On April 3, 2017 OBP noted the omission of the dosage form "Injection" from "0.9% Sodium Chloride, USP." OBP will request the Applicant to include the dosage form "Injection" so that it reads "Sodium Chloride Injections, USP."

Additional Labeling Recommendations

We provided the following labeling recommendations.

Confirm there is no text on the ferrule and cap overseal of the vials to comply USP General Chapters: <1> Injections, Packaging, Labeling on Ferrules and Cap Overseals.

The Applicant confirmed there is no text on the ferrule and cap.

Prescribing Information

We provided the following revisions to the PI. DPARP will communicate our recommendations during labeling negotiations. OBP edits appear in tracked changes.

A. Highlights of Prescribing Information

1. Product Title

   We updated the product title with the dosage form per 21 CFR 201.57(a)(2). The dosage form for this product is "for Injection" per USP General Chapters: <1> Injections, Nomenclature and Definitions.

   RENFLEXIS (infliximab-xxxx*)** (b) (4) **-for Injection, for Intravenous Use**

2. Dosage Forms and Strengths

   We revised this section to include the dosage form per 21 CFR 201.57(a)(8). The dosage form for this product is "for Injection" per USP General Chapters: <1> Injections, Nomenclature and Definitions.

*** At the time of this request, the suffix had not been not determined. FDA used "-xxxx" as a placeholder for the suffix.

For injection: 100 mg of lyophilized infliximab-xxxx*** in a 20 mL vial for intravenous infusion. (3)

B. Full Prescribing Information

1. Dosage and Administration

We added the concentration of the reconstituted solution to comply with 21 CFR 201.57(c)(3)

Allow the reconstituted solution to stand for 5 minutes. The reconstituted solution concentration is 10 mg/mL.

2. Dosage Forms and Strengths

We revised this section to include the dosage form per 21 CFR 201.57(a)(8). The dosage form for this product is "for Injection" per USP General Chapters: <1> Injections, Nomenclature and Definitions.

For injection: 100 mg vial: 100 mg of lyophilized infliximab-xxxx*** in a 20 mL vial for intravenous infusion. (3)

3. Description

We added the dosage form to comply with 21 CFR 201.57(c)(12).

RENFLEXIS for Injection is supplied as a sterile, white, lyophilized powder for intravenous infusion.

4. How Supplied/Storage and Handling

We added the dosage form and a description of the identifying characteristics to comply with 21 CFR 201.57(c)(17).

Each RENFLEXIS (infliximab-xxxx***) for Injection 100 mg vial is individually packaged in a carton.

NDC XXXXX-XXX-XX 100 mg vial

Each single dose vial contains 100 mg of lyophilized infliximab-xxxx*** for final reconstitution volume of 10 mL.

C. Manufacturing Information

1. We revised the country of origin statement to align with our best labeling practice.

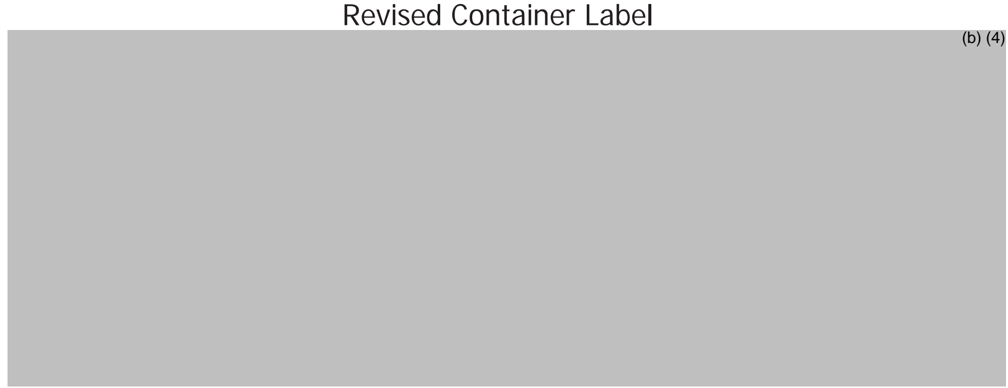
(b) (4) -Product of Denmark

Conclusions:

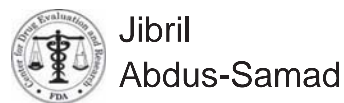
The revisions to the container label and carton labeling submitted on January 17, 2017 for Renflexis (infliximab-abda*) for Injection 100 mg in a single-dose vial are acceptable (see below). However, DPARP will communicate three pending items during labeling negotiations:

1. OBP PI recommendations.
2. Revision of references to the nonproprietary name for Renflexis to "infliximab-abda*" throughout all labeling.
3. Revision of " (b) (4) " on the carton labeling preparation instructions to include the dosage form so that it reads "0.9% Sodium Chloride Injection, USP".

Revised Container Label



1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page



Digitally signed by Jibril Abdus-Samad
Date: 4/03/2017 03:26:12PM
GUID: 50814c7000007a3754a457f037f74915

Digitally signed by Timothy Wadkins
Date: 4/03/2017 03:32:10PM
GUID: 55919d6600e16c43f14b0f7f7c1732bc

BLA STN 761054
Product name: SB2
Samsung Bioepis Co., Ltd

Review of Drug Substance Product Quality and of the Analytical Similarity Assessment

Xianghong Jing, Ph.D.
Drug Substance and Similarity Assessment Reviewer

Christopher Downey, Ph.D., ATL

Office of Biotechnology Products
Division of Biotechnology Review and Research II

OBP CMC Review Data Sheet

1. **BLA#:** STN 761054

2. **REVIEW DATES:** November 15, 2016

3. **PRIMARY REVIEW TEAM:**

CDTL:	Nikolay Nikolov
Medical Officer:	Tara Altepeter
Product Quality Team:	Xianghong Jing (DS quality)
	Timothy Wadkins (DP quality)
	Christopher Downey (Application Technical Lead)
Immunogenicity:	William Hallett
Microbiology Drug Substance:	Bo Chi
Microbiology Drug Product:	Jessica Hankins
Facilities:	Wayne Seifert
CMC Statistics:	Yu-Ting Weng
Clinical Pharmacology:	Lei He
OBP Labeling:	Jibril Abdus-Samad
RPM:	Christine Ford
	Keith Olin

4. **MAJOR 21st Century Review DEADLINES**

Filing 74 Day letter:	June 3, 2016
Mid-Cycle Meeting:	August 30, 2016
Primary Review Due:	December 15, 2016
Secondary Review Due:	December 22, 2016
CDTL Review Due:	December 29, 2016
Wrap-Up Meeting:	December 12, 2016
BSUFA Action Date:	January 21, 2017

5. **COMMUNICATIONS WITH APPLICANT:**

SUBMISSION(S) REVIEWED	DOCUMENT DATE	IR sending date	DISCIPLINE(S) AFFECTED
761054/0000	March 21 2016		OBP, DMA, DIA
761054/0011	June 24 2016	May 13 2016	OBP (similarity methods)
761054/0013	July 8 2016	July 1 2016	OBP (my 1st IR

			response)
761054/0014	July 22 2016	PAI	OBP ((b) (4))
761054/0016	August 5 2016	May 13 2016	OBP (additional lots for similarity)
761054/0017	August 19 2016	August 11 2016	DMA DIA
761054/0018	August 26 2016	August 11 2016	DMA DIA
761054/0020	September 09 2016	July 29 2016	OBP
761054/0021	September 15 2016	July 29 2016	OBP
761054/0026	November 8 2016	October 15 2016	OBP
761054/0029	December 1 2016	November 30 2016	OBP
761085/0033	December 14 2016	December 9 2016	OBP

6. **DRUG PRODUCT NAME/CODE/TYPE:**

a. Code Name: SB2
b. Trade Name: Renflexis
c. Non-Proprietary/USAN: infliximab-xxxx (pending)
d. CAS name: 170277-31-3
e. INN Name: N/A
f. Compendial Name: not applicable
g. OBP systematic name:
MAB CHIMERIC (IGG1) ANTI P01375 (TNFA_HUMAN) [SB2]

7. **PHARMACOLOGICAL CATEGORY:** Therapeutic recombinant human monoclonal antibody
8. **DOSAGE FORM:** Injection
9. **STRENGTH:** 100 mg of lyophilized infliximab in a 20 mL vial for intravenous infusion
10. **ROUTE OF ADMINISTRATION:** Subcutaneous injection
11. **REFERENCED MASTER FILES:**

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)
(b) (4)			Yes	DMF is current and will comply with all statements made in it.
			Yes	
			Yes	

12. **INSPECTIONAL ACTIVITIES:**

A PAI was conducted from (b) (4). Information about the facility and FDA personnel involved is described below:

Firm: (b) (4)
Location:
FEI:

Dates of inspection:

Days in the facility: (b) (4)
FDA Participants: CDER/OPQ/OPF/DIA
CDER/OPQ/OPF/DIA
CDER/OPQ/OBP/DBRRII
CDER/OPQ/OBP/DBRRII

This pre-license inspection of the drug substance manufacturing facility at (b) (4) was conducted on (b) (4) following a request by Branch IV of Division of Inspectional Assessment, Office of Process and Facilities, Office of Pharmaceutical Quality, CDER. The inspection was conducted to support the approval of Samsung Bioepis's BLA STN761054/0 for SB2. This inspection was system-based and covered Quality, Laboratory, Raw Materials, Facilities and Equipment and Production Systems. This inspection was limited to the manufacturing of SB2 drug substance.
No refusals were encountered during the inspection. No sample collection was needed.
A 1-item Form FDA 483 (Attachment 1) was issued to the firm at the end of the inspection on (b) (4) containing the observations summarized below.

(b) (4)

Eleven discussion items were made to the firm during the inspection. The recommendations are provided in the General discussion with management section of the Establishment Inspection Report.

13. ENVIRONMENTAL ANALYSIS

Pursuant to 21 CFR 25.31, Samsung Bioepis Co. Ltd., claims a categorical exclusion from the requirement of an Environmental Analysis (EA) for SB2 in accordance with 21 CFR 25.31(g), which as cited below states that the class of action, comparability determination for a biological product subject of licensing, is categorically excluded and, therefore, ordinarily does not require the preparation of an EA.

SB2 has been developed as a proposed biosimilar product to United States (US)-licensed Remicade® based on a series of similarity assessments against the reference product in terms of structural, physiochemical characteristics, biological activities and clinical profiles. Since

assessing biosimilarity between a proposed biosimilar product to a reference product is a similar concept to determining comparability between pre- and post-change products, the Applicant believes that a categorical exclusion from the requirement of an EA under 21 CFR 25.31(g) is applicable to SB2.

Reviewer note: The sponsor's environmental analysis and claim of categorical exclusion are adequate.

14. CONSULTS REQUESTED BY OBP:

N/A

15. QUALITY BY DESIGN ELEMENTS

The following was submitted in the identification of QbD elements (check all that apply):

	Design Space
x	Design of Experiments
	Formal Risk Assessment / Risk Management
	Multivariate Statistical Process Control
	Process Analytical Technology
	Expanded Change Protocol

16. PRECEDENTS:

None

17. ADMINISTRATIVE

Recipient	Date
Clinical Division BLA RPM	
Division of Biotechnology Review and Research II File/BLA STN 761054	

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation:

We recommend approval of the BLA. The data submitted in this Biologics License Application support the conclusion that the manufacture of SB2 is well controlled and leads to a product that is pure and potent. The product is free of endogenous and adventitious infectious agents sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product has been manufactured from multiple production runs. It is recommended that SB2 be approved for human use (under conditions specified in the package insert).

We recommend an expiration dating period of (b) (4) months for SB2 drug substance when stored at (b) (4) °C.

We recommend an expiration dating period of 30 months for SB2 drug product when stored at 2 – 8°C.

We recommend approval of the proposed release and shelf-life specifications for SB2 drug substance and drug product.

The similarity assessment performed support that:

- SB2 is highly similar to US-licensed Remicade notwithstanding minor differences in clinically inactive components;
- A sufficiently robust analytical bridge was established to support the use of EU-Approved Remicade as a comparator in the clinical study.

II. List Of Deficiencies To Be Communicated:

There are no CMC-Product Quality deficiencies precluding approval of this BLA.

III. List Of Post-Marketing Commitments/Requirement:

There are two Product Quality-related Post-Marketing Commitments, which will include due dates negotiated with the sponsor:

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

IV. Primary Container Labeling Review

The primary container labeling was reviewed separately by Jibril Abdus-Samad with concurrence by Xianghong Jing and Christopher Downey

V. Review Of Common Technical Document - Quality Module 3.2

CTD Modules 3.2.S, 3.2.R, and 3.2.A are reviewed in this document. Module 3.2.P was reviewed separately by Timothy Wadkins and Christopher Downey.

VI. Review Of Immunogenicity Assays – Module 5.3.1.4

The immunogenicity assays were reviewed separately by William Hallett and Christopher Downey.

3 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

Drug Substance
3.2.S.1 General Information
3.2.S.1.1 Nomenclature

The following is the provided nomenclature for SB2 (reproduced directly from the submission).

International Non-proprietary Name (INN)	Infliximab
United States Adopted Name (USAN)	Infliximab
Chemical name(s)	Immunoglobulin G, (human-mouse monoclonal cA2 heavy chain), (anti-human tumour necrosis factor), disulphide with human-mouse monoclonal cA2 light chain, dimer
Company or laboratory code	SB2 (current code) (b) (4) (previous code) (b) (4) (current CMO code) (b) (4) (previous CMO code)
Chemical Abstracts Service (CAS) registry number	170277-31-3

3.2.S.1.2 Structure
SB2 (infliximab) is a chimeric human/mouse monoclonal antibody, which is typically a "Y"-shaped large glycoprotein consisting of four polypeptide chains (two identical heavy chains (HC) and two identical light chains (LC)), connected by disulphide bonds. Each chain presents constant and variable regions whereby in both chains, the variable region is murine whereas the constant region is of human origin (IgG1 and human kappa origins for the HC and LC, respectively). Infliximab consists of 1328 amino acids and has a molecular weight of approximately 149 kDa.

Structural characterization was performed to confirm the primary structure of SB with respect to amino sequence and post translational modification, as showed below (directly from the submission).

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

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

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

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

Analytical tests for structural characterization of SB2 included:

- Molecular weight determination by LC-MS
- Amino acid sequencing using liquid chromatography, coupled to electrospray ionization and tandem mass spectrometry (LC-ESI-MS/MS)
- N- and C-terminal sequencing using LC-ESI-MS/MS
- Peptide mapping by LC-MS
- Identification of disulfide bonds by peptide mapping and quantification of free sulfhydryl groups by fluorescence spectroscopy
- Analysis and quantification of PTMs by LC-MS: Methionine oxidation, deamidation, and N- and C-terminal modifications

3.2.S.1.3 General Properties

Molecular Weight (MW): Approximately 149 kDa (glycosylated form)

Isoelectric point (pI): The calculated isoelectric point (pI) is 7.6. The apparent pI of the main isoform is 7.5, which was determined by imaged capillary isoelectric focusing (icIEF).

Extinction coefficient: 1.4 $(mg/mL)^{-1} \cdot cm^{-1}$

Glycosylation: One N-linked glycosylation site is located at asparagine (Asn) 300 on each heavy chain. There are no O-linked glycosylation sites.

Biological activity: Infliximab is known to neutralize the biological activities of tumor necrosis factor alpha (TNF-α) by binding with high affinity to the soluble and transmembrane forms of

TNF-α, which are located on the outer membranes of T cells and similar immune cells. This inhibits or prevents effective binding of TNF-α with its receptors, thereby blocking the inflammatory effects of TNF- α. In addition, infliximab has the capability of lysing cells involved in the inflammatory process. In detail, the antigen-binding fragment (Fab) domain of infliximab specifically binds to TNF-α. Direct binding of the Fab domain to cells results in signal cascades inducing apoptosis. It is known that binding of the crystallizable fragment (Fc) domain to the complement component C1q complex and Fc receptors leads to cell lysis by complement-dependent cytotoxicity (CDC) and antibody-dependent cell mediated cytotoxicity (ADCC).

SB2 drug substance (DS) is a clear to opalescent and colorless to slightly yellowish solution of (b) (4) mg/mL infliximab, with pH at 6.2 (b) (4)

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

SB2 drug substance (DS) is manufactured, packaged, stability and quality-control tested, in accordance with good manufacturing practice (GMP), at the following sites provided in Table 3.2.S.2.1–1.

105 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

3.2.R.4 Analytical Similarity

Reviewer Comment:

The data provided in this section support the following conclusions:

- *The SB2 biological product is highly similar to US-licensed Remicade;*
- *The data demonstrate an analytical bridge between US-licensed Remicade and EU-Approved Remicade*
- *For attributes where minor potential differences between SB2 and US-licensed Remicade are detected, the data support that there are no impacts on function, activity, or stability in vitro. Therefore, there is little risk of clinically meaningful differences between the SB2 and the reference product in terms of the safety, purity, and potency of the product;*
- *Method qualification results for methods used in the analytical similarity assessment are adequate to support that the methods are scientifically sound and suitable probe the intended quality attributes;*
- *The sponsor's proposed quality ranges based on a 3 standard deviation range are appropriate acceptance criteria for each Tier 2 attribute.*

The biosimilarity of SB2 clinical, process validation run (PVR), and commercial batches to Remicade® from US and EU was assessed using a range of state-of-the-art orthogonal analytical tests in line with guidelines ICH Q6B and FDA guidance for industry.

The characterization for the similarity assessment between SB2 and Remicade involved the determination of:

1) Physiochemical properties including primary and higher-order structure, post-translational modifications (PTMs) and associated heterogeneities, glycosylation, charge variants, purity/impurities, and quantity;
2) Biological activities including, soluble TNFα-mediated, membrane-associated TNFα-mediated, and Fab- and Fc-related activities;
3) Comparative stability studies conducted to compare the degradation profiles of SB2 DP with those of Remicade

Each attribute was assessed in a three-way bridge approach to demonstrate the analytical similarity between SB2 and US-licensed Remicade® as a reference product in support of a 351(k) application and to establish an analytical bridge between US Remicade® and European Union (EU) Remicade, the latter of which was used in clinical studies in support of this application. Quality attributes were classified into three tiers for similarity assessment based on a criticality risk assessment and amenability to statistical analysis. The scheme of the similarity assessment including tiering system is shown in Figure 3.2.R4-1. Tier 1 is evaluated by statistical equivalence criteria, tier 2 by ≥90% of lots tested were within a

"quality range" defined by a multiple of the SD of the comparator product, and tier 3 is a visual, semi-qualitative comparison of graphical data.

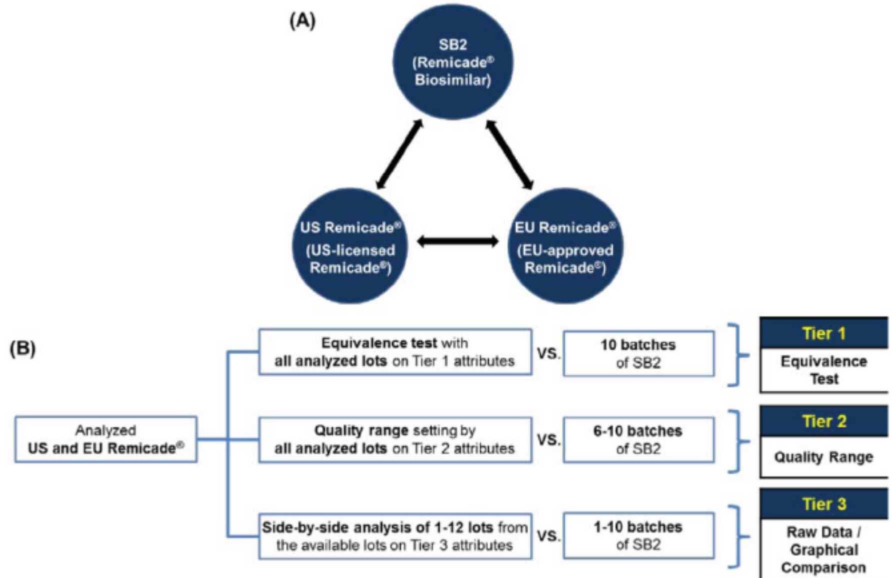


Figure 3.2.R.4–1. Overview of Similarity Assessment
(A) Three-way bridge approach for similarity assessment (B) Scheme for the tier dependent assessment

The following ten batches of SB2 material were used in the similarity assessment. In total, 46 lots of US- Remicade and 43 lots EU-Approved Remicade were used in the similarity assessment.

Table 1: SB2 DS and DP lots used for similarity assessment in BLA 761054

# of SB2 Lots for similarity assessment	DS Batch #	DP batch #	DP Manufacturing Site	DP Manufacture Date	Use of batch
1	HP5-13-603-001	P49202A	(b) (4)	Feb 2013	Clinical studies
2	HP5-13-603-002	P49208A		Nov 2013	Clinical studies
3	HP5-14-603-004	SB2-DP-14001		July 2014	Process Validation
4	HP5-14-603-005	SB2-DP-14002		July 2014	Process Validation
5	HP5-14-603-006	SB2-DP-14003		July 2014	Process Validation

6	HP5-15-603-005	PA0703	(b) (4)	Mar 2016	Commercial
7	HP5-15-603-001	N/A		May 2015	Intended for filling into commercial DP lots
8	HP5-15-603-003	N/A		May 2015	
9	HP5-15-603-007	N/A		July 2015	
10	HP5-15-603-009	N/A		July 2015	

Reviewer Comment:

1) *The initial BLA submission included data for 5 lots of SB2 drug product in the analytical similarity assessment. To alleviate the risk that 5 lots may be insufficient for a robust statistical analysis, on May 13, 2016 FDA requested that the sponsor provide, for all Tier 1 and Tier 2 attributes and for SPR methods orthogonal to the FcγRIIIa receptor affinity method, data derived from the additional 5 commercial DS lots that had been manufactured to that point but not included in the analysis. To assure independence of that data points, FDA agreed in a July 29, 2016 communication that the sponsor could provide results from the one available DP lot manufactured solely from one DS lot and from the additional four available DS lots. FDA agreed to this strategy of including independent DS lots in the similarity assessment rather than including data from DP lots derived from pooled DS lots or multiple DP lots derived from the same DS lot, because use of independent DS lots is more likely to represent the variability of DS manufacture. The sponsor provided the requested data in Amendment eCTD0011 submitted date June 24, 2016.*

   DP manufacture consists of (b) (4) *Therefore, the only attributes expected to be significantly affected by DP manufacture are the levels aggregates and particulates and attributes specific to the drug product such as protein content per vial, sterility, residual moisture, and reconstitution time. Comparison of available data for DP lots and the DS lots from which they were derived support that critical attributes such as TNFα binding, TNFα neutralization, glycoforms, and charge variants do not differ significantly between a DS lot and its resulting DP lot.*

2) *The July 29, 2016 FDA communication to the sponsor also requested data for C1q binding for the 5 new lots to added to the similarity assessment to bolster a Tier 2 assessment. FDA also requested the sponsor provide data from all of the additional SB2*

lots and from any available additional reference product lots for, at minimum, the assays below:

- *ADCC assay using healthy donor PBMC*
- *FcγRIIIa binding assay (158V/V) by SPR*
- *FcγRIIIa binding assay (158F/F) by SPR*
- *Transmembrane TNF-α binding by FACS*
- *Evaluation of regulatory macrophage function by MLR*
- *Regulatory macrophage induction activity*
- *T cell anti-proliferation*

The sponsor provided the information requested in items in Amendment eCTD0020, submitted on September 9, 2016.

3) *SB2 is formulated to be at the same concentration and content of protein per vial as US-Remicade. The formulation of SB2 differs slightly from US-Remicade in that SB2 is at pH 6.2 whereas US-Remicade is 7.2. Both products use monobasic and dibasic phosphate* (b)(4) *The formulation of a biosimilar is not required to be identical to the reference product, and the minor differences here pose little risk of complicating the similarity analysis. The comparative stability and stressed stability data discussed below support similarity of degradation profiles between the products in the two formulations, and formulation development data (see 3.2.P.2.2) and long term stability data (see 3.2.P.8) support that the SB2 formulation results in stable product.*

A summary of the analytical similarity results prepared by the reviewer are presented in the following table 2.

1. *A pairwise comparison was performed between all three of SB2, US-licensed Remicade, and EU-approved Remicade. These are presented in the far right column in the format of SB2 compared to criteria derived from US-licensed Remicade/SB2 compared to criteria derived from EU-approved Remicade/EU-approved Remicade compared to criteria derived from US-licensed Remicade.*
    a. *"Pass" denotes that the comparison met criteria for statistical equivalence to the comparator for Tier 1 attributes, ≥ 90% of lots were within the quality range of the comparator for Tier 2 attributes, or that our analysis of the distribution of results or visual comparison of graphical data concluded that Tier 3 attributes were similar.*
    b. *"OOR" denotes Out of Range and means that <90% of lots did met the quality range for a Tier 2 attribute or that we noted potential difference between the product under consideration and the comparator product for a Tier 3 attribute. These out of range results are reviewed in detail in the following sections of this review.*
2. *Throughout the table, the number of lots analyzed and reviewer comments will be represented with the format of SB2:US-Licensed Remicade:EU-Approved Remicade. For example, in the first row, 5 lots of SB2, 3 lots of US-Remicade, and 3 lots of EU Remicade were analyzed for primary structure, and this is represented by 5:3:3 in the "number of lots" column.*
3. *The ranges for SB2 in the table represent the range of the minimum and maximum result observed. The ranges for US-Remicade and EU-Remicade in the table represent the quality range determined by the sponsor. The sponsor determined quality ranges for many of the Tier 3 attributes by similar methodology to that used for Tier 2 attributes.*
4. *For the Tier 3 attributes where the applicant provided quantitative quality ranges, the conformance to the provided ranges was considered in our analysis, but our conclusions of similarity were also based on an assessment of the risk for the attributes, the nature and precision of the assay, and in several cases the limitations of statistically comparing relatively few lots (the lots required for Tier 3 attributes are less stringent than Tier 1 or 2).*
5. *We evaluated some attributes (e.g. acidic and basic product-related variants) using a different tier than the applicant. In those cases, the tier used by FDA is provided in the table.*
6. *For Tier 2 criteria such as CEX-HPLC and SEC where chromatographic or other graphical data are available, I visually compared the chromatograms in addition to reviewing the quantitative data derived from the chromatograms. All attributes that met quantitative criteria for similarity were also similar by a visual comparison of representative chromatograms or other graphical data.*

Table 2: SB2 Similarity Assessment Results

Category	Test		Tier	Number of Lots (SB2: US- Licensed Remicade: EU-Approved Remicade)	US-Licensed Remicade Quality Range	SB2 min – max Range	EU-Approved Remicade Quality Range	US Remicade vs SB2 / SB2 vs EU-Approved Remicade / US-Licensed Remicade vs EU-Approved Remicade
Primary Structure	Molecular weight	Deconvoluted molecular weight (Intact and Reduced)	3	5:3:3	Visually Similar to SB2 and EU-Approved Remicade	Visually Similar to US-Licensed Remicade and EU-Approved Remicade	Visually Similar to US-Licensed Remicade and SB2	Pass/Pass/Pass
		Deglycosylated Mass (Reduced and non-reduced)	3	5:3:3	Visually Similar to SB2 and EU-Approved Remicade	Visually Similar to US-Licensed Remicade and EU-Approved Remicade	Visually Similar to US-Licensed Remicade and SB2	Pass/Pass/Pass
		Peptide Fragments and Experimental Masses	3	2:1:1	Visually Similar to SB2 and EU-Approved Remicade	Visually Similar to US-Licensed Remicade and EU-Approved Remicade	Visually Similar to US-Licensed Remicade and SB2	Pass/Pass/Pass (No new peptides observed)
		N-terminal/C-terminal Variants	3	5:3:3	Visually Similar to SB2 and EU-Approved Remicade	Visually Similar to US-Licensed Remicade and EU-Approved Remicade	Visually Similar to US-Licensed Remicade and SB2	Pass/Pass/Pass
		Peptide mapping(Trypsin or Lys-C treatment)	3	2:1:1	Visually Similar to SB2 and EU-Approved Remicade	Visually Similar to US-Licensed Remicade and EU-Approved Remicade	Visually Similar to US-Licensed Remicade and SB2	Pass/Pass/Pass
		Disulfide Bond Analysis	3	2:1:1	Visually Similar to SB2 and EU-Approved Remicade	Visually Similar to US-Licensed Remicade and EU-Approved Remicade	Visually Similar to US-Licensed Remicade and SB2	Pass/Pass/Pass
		Free Thiol Group /Methionine Oxidation / Deamidation/Glycati	3	5:3:3	Visually Similar to SB2 and EU-Approved Remicade	Visually Similar to US-Licensed Remicade and EU-Approved Remicade	Visually Similar to US-Licensed Remicade and SB2	Pass/Pass/Pass

Category	Test		Tier	Number of Lots (SB2: US- Licensed Remicade: EU-Approved Remicade)	US-Licensed Remicade Quality Range	SB2 min – max Range	EU-Approved Remicade Quality Range	US Remicade vs SB2 / SB2 vs EU-Approved Remicade / US-Licensed Remicade vs EU-Approved Remicade
		on						
	Glycan Map	N-Glycan Species	3	2:1:1	Visually Similar to SB2 and EU-Approved Remicade	Visually Similar to US-Licensed Remicade and EU-Approved Remicade	Visually Similar to US-Licensed Remicade and SB2	Pass/Pass/Pass
		% Gal and % Charged Glycans	3 3	5:3:3 5:3:3	36.7-59 5.3-10.2	40.5-42.4 1.2-1.5	42.6-61.2 5.6-10.4	Pass/Pass/Pass Pass/OOR[a]/Pass (SB2 % charged glycans are at a lower level) Note: The marginal difference on charged glycans shows no difference on the functional tests, ADCC, FcRn, & FcγRIIIa, under the conditions of w/, w/o sialidase. So, the slightly higher % of charged glycan on SB2 lots does not likely have impact on the efficacy of infliximab.
		N-Glycan profile (%Afucose + %HM)	2	10:46:43	6.7-13.5%	6.6-9.5%	6.0-13.5%	Pass/Pass/Pass
Higher Order Structure	Far-UV CD & Near-UV CD		3	2:1:1	Visually Similar to SB2 and EU-Approved Remicade	Visually Similar to US-Licensed Remicade and EU-Approved Remicade	Visually Similar to US-Licensed Remicade and SB2	Pass/Pass/Pass
	Intrinsic & Extrinsic fluorescence Spectroscopy		3	2:1:1	Visually Similar to SB2 and EU-Approved Remicade	Visually Similar to US-Licensed Remicade and EU-Approved Remicade	Visually Similar to US-Licensed Remicade and SB2	Pass/Pass/Pass
	Fourier Transform infrared (FTIR) spectroscopy		3	2:1:1	Visually Similar to SB2 and EU-	Visually Similar to US-Licensed	Visually Similar to US-Licensed	Pass/Pass/Pass

Category	Test	Tier	Number of Lots (SB2: US- Licensed Remicade: EU-Approved Remicade)	US-Licensed Remicade Quality Range	SB2 min – max Range	EU-Approved Remicade Quality Range	US Remicade vs SB2 / SB2 vs EU-Approved Remicade / US-Licensed Remicade vs EU-Approved Remicade
				Approved Remicade	Remicade and EU-Approved Remicade	Remicade and SB2	
	Antibody Conformation Array	3	3:0:2	N/A	Visually Similar to EU-Approved Remicade	N/A	pass
	Differential Scanning Calorimeter (DSC)	3	2:1:1	Visually Similar to SB2 and EU-Approved Remicade	Visually Similar to US-Licensed Remicade and EU-Approved Remicade	Visually Similar to US-Licensed Remicade and SB2	Pass/Pass/Pass
	SV-AUC (%monomer, LMW%, % other aggregates)	3	2:1:1	41 0.9 0.8	43-43 0-0.7 0-1.3	39 0.0 1.9	Pass (Orthogonal method for aggregates)
	Extinction Coefficient	3	1:1:1 (triplicate)	1.44-1.67 (ave. 1.55)	1.47-1.64 (ave. 1.57)	1.51-1.69 (ave. 1.60)	Pass/Pass/Pass
Particles and Aggregates	MFI: ≥ 5 µm particles/mL	3	2:1:1	3799	3615-3970	8299	Pass/OOR/OOR (see section on subvisible particles below)
	MFI: ≥ 25 µm particles	3	2:1:1	Visually Similar to SB2 and EU-Approved Remicade	Visually Similar to US-Licensed Remicade and EU-Approved Remicade	Visually Similar to US-Licensed Remicade and SB2	Pass/Pass/Pass
	DLS: Submicron particles	3	2:1:1	Visually Similar to SB2 and EU-Approved Remicade	Visually Similar to US-Licensed Remicade and EU-Approved Remicade	Visually Similar to US-Licensed Remicade and SB2	Pass/Pass/Pass
Product Related	SEC: % HMW	2	10:46:41	≤ 0.5 %	0.6-0.9%	≤ 0.5 %	OOR/OOR/Pass Note: Overall, the level of (0.6-0.9%) HMW from SB2 lots is

Category	Test		Tier	Number of Lots (SB2: US- Licensed Remicade: EU-Approved Remicade)	US-Licensed Remicade Quality Range	SB2 min – max Range	EU-Approved Remicade Quality Range	US Remicade vs SB2 / SB2 vs EU-Approved Remicade / US-Licensed Remicade vs EU-Approved Remicade
Impurties								still low (< 1%). Since SEC method only catches irreversible HMW agg. The sponsor conducted SV-AUC to characterize both reversible and irreversible HMW, showing no difference among US, EU and SB2 lots.
	rCESDS:	% HC+ LC	2	10:46:41	≥ 98.4%	97.3-98.6%	≥ 98.3%	Pass/Pass/Pass
		% NGHC	2	10:3:3[b]	0.5-0.7%	0.8-1.4%	0.3-0.7%	OOR (6 of 10 lots)/ OOR (6 of 10 lots)/Pass
	nrCESDS:	% Main peak	2	10:46:41	≥ 93.8%	94.3-95.8%	≥ 93.5%	Pass/Pass/Pass
		% Pre peaks	2	10:3:3	0.8-2.3%	1.3-3.2%	1.4%-2.7%	Pass/Pass/Pass
	CEX-HPLC after CpB:	% Acidic peaks	2	5:3:3	27-32.7	29.9-34.5	24.6-29.8	Pass/Pass/Pass
		% Main peak	2	5:43:41	63.9-69.5	59.8-63.6	66.9-72	OOR (3 of 5 lots)/OOR (3 of 5 lots)/OOR (see comment for %basic peaks below)
		% Basic peaks	2	5:43:41	3.4-4.3	4.8-6.9	3.2-3.4	OOR (5 of 5 lots)/ OOR (5 of 5 lots)/Pass Higher basic variants caused by c-lys and alpha amidation of c term proline residue. No functional impact on TNF binding and FcgRIIIa binding.
	iCIEF after CpB	% Acidic peaks	2	5:43:41	29.6-33.7	30.1-34.5	26.9-31.7	Pass/Pass/Pass
		% Main peak	2	5:43:41	64.2-68.1	59.9-63.9	66.3-71	Fail/Fail/Fail (consistent with CEX-HPLC data)

Category	Test		Tier	Number of Lots (SB2: US- Licensed Remicade: EU-Approved Remicade)	US-Licensed Remicade Quality Range	SB2 min – max Range	EU-Approved Remicade Quality Range	US Remicade vs SB2 / SB2 vs EU-Approved Remicade / US-Licensed Remicade vs EU-Approved Remicade
		% Basic peaks	2	5:43:41	2.0-2.4	5.5-6.4	1.8-2.1	OOR (5 of 5 lots)/ OOR (5 of 5 lots)/Pass (consistent with CEX-HPLC data)
General Properties	Quantity (mg/Vial)		2	6:41:18	87-106	94-96	90-103	Pass/Pass/Pass
Biological Activity-Fab related	TNF-alpha neutralization assay by NF-kB reporter gene		1	10:46:40	88-117%	93-101%	86-116%	Pass(Equivalency testing)
	TNF alpha binding assay by FRET		1	10:41:37	89-108%	91-102%	85-109%	Pass (Equivalency Testing)
	Apoptosis		2	10:42:28	81-115%	89-105%	79-122%	Pass/Pass/Pass
Biological Activity-Fc related	ADCC		2	10:46:30	59-141%	115-135%	48-156%	Pass/Pass/Pass
	CDC		2	10:32:26	84-110%	93-107%	85-116%	Pass/Pass/Pass
	FcRn Binding Assay		2	10:40:32	69-132%	113- 120%	78-118%	Pass/OOR (2 of 10 lots)/Pass (see comments in FcRn section below)
	FcγRIIIa binding on NK cells		2	10:41:34	75-130%	88-133%	70-128%	OOR (3 of 10 lots)/OOR (3 of 10 lots)/Pass (see comments in FcγRIIIa section below)
	FcγRIIIa binding (158V/V) by SPR		2	11:14:13	1.01E-06 - 1.57E-06	1.21E-06 to 1.39E-06	9.82E-07 - 1.44E-06	Pass/Pass/Pass
	FcγRIa binding		3	5:3:3	94-103%	85-104%	106-112%	Pass/Pass/Pass
	FcγRIIa binding		3	3:3:3	101-104%	115%-123%	104-120%	Pass/Pass/Pass
	FcγRIIb binding		3	3:3:3	99-101%	115%-122%	99-104%	Pass/Pass/Pass
	FcγRIIIb binding (SPR)		3	3:3:3	9.99E-06 to	9.61E-06 to 1.23E-	9.09E-	Pass/Pass/Pass

Category	Test	Tier	Number of Lots (SB2: US- Licensed Remicade: EU-Approved Remicade)	US-Licensed Remicade Quality Range	SB2 min – max Range	EU-Approved Remicade Quality Range	US Remicade vs SB2 / SB2 vs EU-Approved Remicade / US-Licensed Remicade vs EU-Approved Remicade
				1.10E-05	05	06 to 1.12E-05	
	FcγRIIIb binding(neutrophils)	3	2:1:1	95%	97-99%	96%	Pass/Pass/Pass
	C1q binding by ELISA	2	10:42:31	81-112 %	103 to 114%	76-116 %	OOR (2 of 10 lots/Pass/Pass (see discussion of C1q data below)
Additional Biological Assays	TNF-beta binding	3	2:1:1	No signal response	No signal response	No signal response	Pass/Pass/Pass
	tmTNF-alpha binding	3	10:12:6	101-114%	100-108%	94-109%	Pass/Pass/Pass
	ADCC using PBMC	3	10:6:6	115-153%	108-137%	89-136%	Pass/Pass/Pass
	FcγRIIIa binding (158F/F)	3	5:3:3	8.48E-07 to 1.43E-06	1.21E-06 to 1.61E-06	9.67E-07 to 1.36E-06	Pass/Pass/Pass
	FcγRIIIa binding (158V/F) using NK cells from PBMC	3	5:6:6	90-110%	85-100%	88-103%	Pass/Pass/Pass
	Inhibition of Cytokines Release in vitro IBD model	3	5:6:6	68-119%	85%-107%	64-118%	Pass/Pass/Pass
	Inhibition of apoptosis in IBD model	3	5:6:6	90-94%	85%-97%	89-97%	Pass/Pass/Pass
	Regulatory of Macrophages Induction	3	10:12:6	74-120%	81-113%	83-125%	Pass/Pass/Pass

a. OOR: Out of Quality Range. For Tier 2 attributes OOR means >10% of lots are outside the comparator quality range; for Tier 3 attributes OOR means quantitative results a significant of lots are outside the comparator quality range, a visual comparison of the results suggest a potential difference, or both.

b. Quality range for %NGHC by rCE-SDS was not determined. To have a tight control over the purity of (%HC + %LC) by rCE-SDS, the sponsor committed to add rCE-SDS as a release for DS and DP upon the completion of method validation.

3.2.R.4.2.1 Similarity Assessment Overview

The characterization for the similarity assessment involved the determination of physicochemical properties and biological activities of SB2 and Remicade®. Physiochemical properties include primary and higher-order structure, post-translational modifications (PTMs) and associated heterogeneities, glycosylation, charge variants, purity/impurities, and quantity. Biological activities include Fab- and Fc-related activities. Each attribute was assessed in a three-way bridge approach to demonstrate the similarity between SB2 and US Remicade® as a reference product in support of a 351(k) application and to establish a quality bridge between US Remicade® and European Union (EU) Remicade®.

In addition, comparative stability studies were conducted to compare the degradation profiles of SB2 DP with those of Remicade®. The stability studies include comparative stability studies under stress conditions, forced degradation stability studies, and photostability studies in commercial product packaging.

Reviewer comment*: There were only five DP lots included for similarity assessment in the original BLA submission. Upon our request on May 13, 2016, the sponsor provided the analytical data (for Tier 1 and Tier 2 quality attributes, and some of the Tier 3 quality attributes) for five intended-commercial batches of drug substance (DS) as well as one batch of drug product (DP) subsequently produced using one of the DS batches in the amendment eCTD0016 08/05/2016. For the analytical similarity assessment, the data from the new DP lot and 4 additional commercial DS lots for which a DP lot had not yet been manufactured were combined with the data from five DP lots initially included in the initial BLA submission.*

The review below reflects the most recent data update with a total of 10 SB2 lots for analytical similarity assessment.

3.2.R.4.2.2 Similarity Assessment for Tier 1 (Equivalence Test)

3.2.R.4.2.2.1 TNF-α Binding Assay by FRET (SB2:US:EU = 10:41:37 lots)

The TNF-α binding activity was measured as a percent relative to the Research Reference Standard (RRS), where increasing percent binding activity represents increasingly tight binding to TNF-α. Equivalence testing was performed using SB2, US Remicade®, and EU Remicade® in a three way assessment: SB2 vs US Remicade®, SB2 vs EU Remicade®, and US Remicade® and EU Remicade®. The sponsor concluded that as the 1-2α confidence intervals fall within the corresponding equivalence acceptance criterion, the relative TNF-α binding activity of SB2 is statistically equivalent to US Remicade® and EU Remicade®, and that the relative TNF-α binding activity of EU Remicade® is statistically equivalent to US Remicade®.

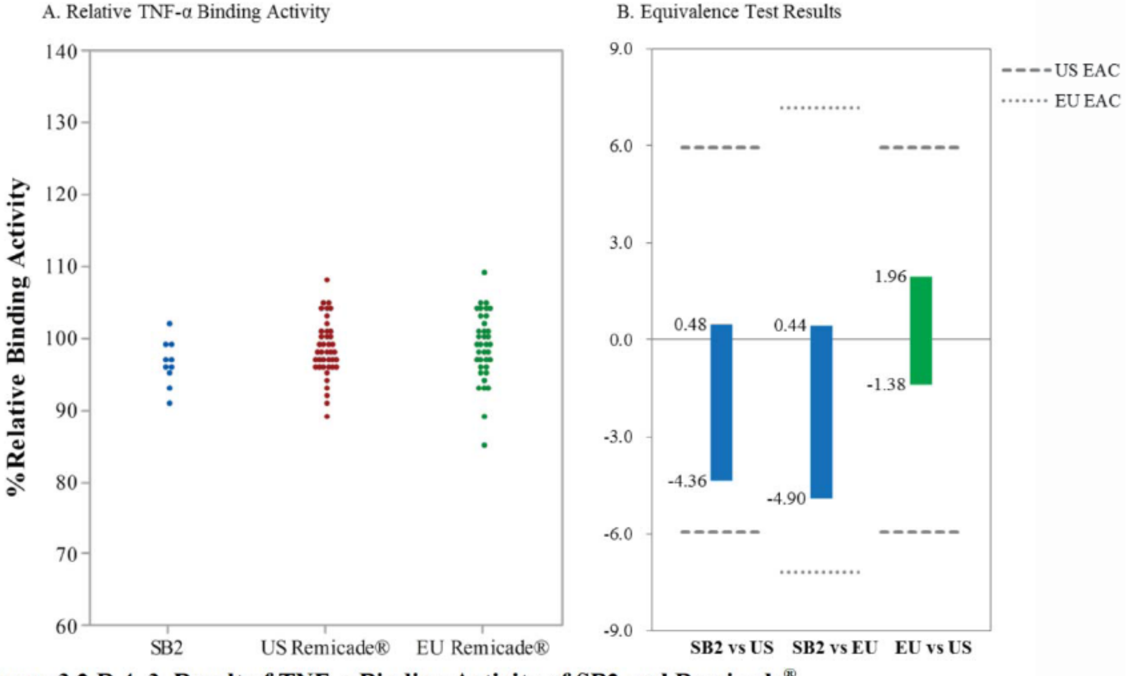


Figure 3.2.R.4–3. Result of TNF-α Binding Activity of SB2 and Remicade®
* EAC: Equivalence acceptance criterion

***Reviewer comment**: Data distribution of the 10 SB2 lots gives a tighter standard deviation compared to those of US and EU lots. Figure 1B above showed the US and EU Equivalence Acceptance Criteria (EAC), and the pairwise comparison results with 90% confidence interval, indicating a pass result for equivalence test.*

Overall, from the product quality and assay qualification perspective, the results of the two tier 1 assays are acceptable. However, statistical equivalence for TNFα binding activity and neutralization activity were reviewed by the CMC statistics reviewer based on the data analysis.

Assay qualification: The assay for the SB2 TNFα binding activity was developed in a competitive inhibition format with FRET detection. The sponsor provided assay qualification results showing that it is suitable for measuring activity in a linear range between 50- 150% relative to reference standard. Specifically, the assay linear range study was conducted to measure the accuracy, precision and linearity of the binding assay. Samples were prepared at 50%, 75%, 100%, 125%, and 150% relative potency levels and tested in the assay. Data showed that the average recovery was 100.6% (range 94.9 to 106.0%) for ED-REM-CEN sample (innovator DP) with binding activities ranging from 50% to 150%. Within the assay range of 50-150%, the average intra-assay precision was found to be 2.2% RSD (range 1.5% to 3.1%), and the inter-assay precision was 4.3% RSD.

This assay is a release test. Refer to section 3.2.S.4 for review of method validation.

3.2.R.4.2.2.2 TNF-α Neutralization Assay by NF-κB Reporter Gene (SB2:US:EU = 10:46:40 lots)

The TNF-α neutralizing activity was measured in percent relative to the RRS. The assay measures inhibition of TNF-α-induced expression of NF-κB via a NF-κB-dependent luciferase reporter gene. Equivalence testing was performed using SB2, US Remicade, and EU Remicade in a three way assessment as previously described in the TNF- α binding assay. Similarly, as the 1-2α confidence intervals fall within the corresponding equivalence acceptance criterion, the sponsor concluded that the relative TNF-α neutralization activity of SB2 is statistically equivalent to US Remicade® and EU Remicade®, and that the relative TNF-α neutralization activity of EU Remicade® is statistically equivalent to US Remicade®.

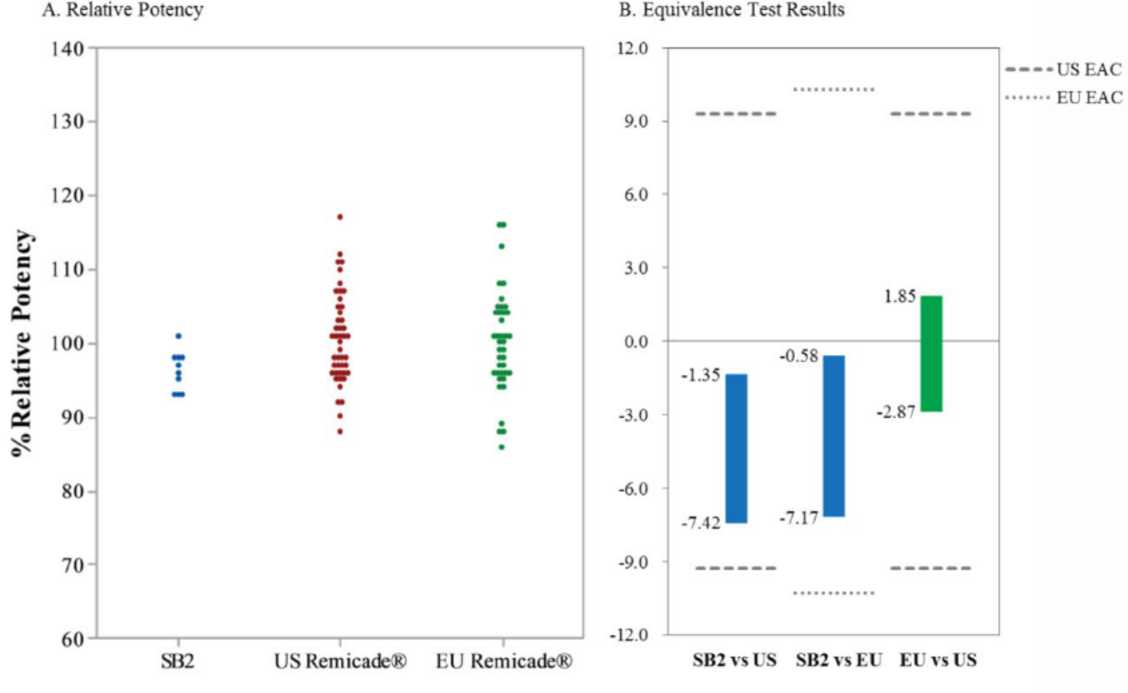


Figure 3.2.R.4–2. Result of TNF-α Neutralization Activity of SB2 and Remicade®

Reviewer comment*: Statistical equivalence for TNFα neutralizing activity was confirmed by the CMC statistics reviewer.*

Assay Qualification (Doc# 09090): Qualification work determined that the assay is linear within the 50-150% relative potency (RP) range. In linearity studies, the assay performed with an accuracy of 102.0% and an intermediate precision of 1.5% relative standard deviation (RSD). Assay accuracy and precision was qualified as well. Specificity was demonstrated that two additional IgG1 antibodies, anti-LINGO-1 and IDEC152, failed to inhibit luciferase reporter gene expression. The final relative potency for a sample is

calculated as the geometric mean from at least three of the four blocks that have passed assay acceptance criteria.

This assay is a release test. Refer to section 3.2.S.4 for review of method validation.

***Reviewer comment**: The Tier 1 attributes directly probing the primary mechanism of action are similar between SB2 and US-Remicade and EU-Remicade. The CMC Statistics reviewer concluded that TNF-α binding and neutralization are statistically equivalent for all pair-wise comparisons. A sufficient number of US and EU lots were subjected for similarity analysis with the 10 SB2 lots. Both the TNF-α binding assay and neutralization assays are also drug substance and drug product release tests for identity and potency measurement, and were fully validated with SB2 reference standard as a control. Assay accuracy, precision, and specificity were demonstrated. Of note, as the commercial reference standard was not yet available at the time of assay development, the innovator (ED-REM-CEN) drug product was used throughout the assay development work, including for the analytical similarity assessment.*

3.2.R.4.2.3 Similarity Assessment for Tier 2 (Quality Range Approach)

Tier 2 quality attributes are those of moderate to high risk for impact on quality for which quantitative data can be obtained. For these attributes, statistical similarity is discussed based on a quality range approach with the quality range for each comparator defined as the average ± 3 standard deviations unless otherwise noted. A result is considered passing when at least 90% of the lots of the product under consideration is within the quality range of the comparator.

***Reviewer comment**: To enable cross-reference to the source document (3.2.R.4), the sections in this review are presented in the same order in which they were discussed in that document. However, in some cases, such as main peak, acidic, and basic variants measured by CEX-HPLC, FDA considered an attribute to be Tier 2 instead of the Tier 3 used by the sponsor. In those cases, the attributes will be discussed in the Tier 3 section of the review below but will be highlighted as being considered a Tier 2 attribute.*

In some cases in this section, the Tier 3 results related to a Tier 2 result are discussed to provide additional context. In those cases, the Tier 3 result will be highlighted as such.

3.2.R.4.2.3.1 N-Glycan Profile Analysis (SB2:US:EU = 10:46:43 lots)

N-glycan profiles of SB2 and US Remicade® are categorized into three different groups according to structural compositions: sum of afucosylated glycans (%Afucose) and mannosylchitobiose core without L-fucose (%High Mannose (HM)), neutral galactosylated glycans (%Gal), and charged glycans (%Charged). Based on scientific literature,

afucosylated glycans and high mannose glycans can impact FcγRIIIa binding and ADCC activities.

Reviewer notes*: The neutral galactosylated glycans (%Gal) and % charged glycans were assessed as tier 3 attributes, and review details refer to section 3.2.R.4.2.4.2 Carbohydrate Structure.*

Similarity for %Afucose + %HM is discussed as a Tier 2 attribute based on quality range approach, with the quality range for each comparator defined as the average ± 3 standard deviations.

The level of the %Afucose + %HM was 8.3-9.5% for SB2. The relative contents of SB2 were within both the US and EU quality ranges (6.7-13.5% and 6.0-13.5%, respectively) and those of EU Remicade® (Min: 7.3%, Max: 12.8%) were also within the US quality range. Therefore, the level of the %Afucose + %HM of SB2 is considered to be similar to that of US Remicade®.

Assay Qualification: Hydrophilic interaction ultra-performance liquid chromatography (HILIC-UPLC) was used to determine the relative quantity of N-glycan species, including N-Glycan identification using Procainamide Labeling and LC-ESI-MS/MS after PNGase-F treatment, the structure of N-glycans, and N-glycan profile analysis. This method was developed and qualified for determination of relative content of each glycan moieties. This method is defined as a quantitative test according to ICH Q2 (R1) guideline. Qualification was performed on specificity, linearity, precision, accuracy and solution stability to confirm suitability of this method for its intended purposes. Qualification report confirmed that the results of specificity, linearity, precision, accuracy and solution stability met all acceptance criteria. Therefore, it is concluded that the present analytical method is suitable for quantifying the released N-glycan of SB2 material.

Reviewer comment*: The SB2 level of the %Afucose + %HM, which potentially has an impact on Fc effector function on ADCC, was within the quality ranges of US and EU Remicade. The qualified assay is adequate to support the testing results.*

3.2.R.4.2.3.2 Reducing CE-SDS (SB2:US:EU = 10:46:41 lots)

Capillary electrophoresis-sodium dodecyl-sulphate (CE-SDS) is a current technique in the biotechnology industry used to determine the purity of protein. CE-SDS involves heat denaturing of a specified concentration of protein in the presence of SDS. Once denatured, the sample is separated in a capillary containing a replaceable SDS polymer matrix, which provides the sieving selectivity for the separation. This method was developed and qualified for determination of main peak content.

The result of the analysis was that the percent of the main peak (%Main) of SB2 (results ranged from 97.3-98.6%) was within in the US-Remicade and EU-Remicade quality ranges (≥ 98.4 and ≥ 98.3%, respectively) for all lots except one and that all EU Remicade® lots

(Min: 98.6%, Max: 99.7%) were also within the US-Remicade quality range. The sponsor attributed the slight difference of SB2 to the higher level of non-glycosylated heavy chain (%NGHC) of SB2 (0.8-0.9%) compared that of Remicade® (0.3-0.7%). SB2 passes the Tier 2 quality range criteria and is considered similar to that of US Remicade® in terms of purity.
Assay qualification: The reducing CE-SDS method was validated following ICH guidelines, and assay specificity, linearity, precision, accuracy, working range, robustness were validated with pass results at Samsung Bioepis. Acceptance criteria for system suitability are determined that there must be no interfering peaks detected after 10 kDa peak in blank injection(s).
Reviewer comment: *The %main of one lot SB2 (97.3%) falls outside of the US and EU quality range (≥ 98.4 and ≥ 98.3%, respectively); 90% (9 of 10) of SB2 lots fall within the respective quality ranges. This is partly attributable to the slightly higher level of %NGHC (non-glycosylated HC). The percent of SB2 NGHC (0.8-1.4%) was slighter higher than the US and EU quality ranges (0.5-0.7% and 0.3-0.7%, respectively). It is known that the N-glycosylation at Fc region of antibodies associated with Fc-related functional activities. However, the total levels of %NGHC are quite low (<1%) both for SB2 and the reference product. The ADCC and CDC functional assays support the products have similar Fc-mediated function and that the difference of 0.6% in NGHC poses a low risk of affecting potency.*

This attribute was not originally part of the control strategy for SB2. Typically, monoclonal antibody products include a release test to control the purity of(%HC+%LC). To assure that the level of %NGHC are controlled and that the %NGHC cannot not drift upward to a level that may pose a greater risk to impact potency, we requested that the sponsor include specifications for reducing CE-SDS in the DS and DP release. The sponsor agreed to add the reducing CE-SDS test (b) (4) *to the DS and DP specifications post-approval upon completion of method validation.*

3.2.R.4.2.3.3 Non-Reducing CE-SDS(SB2:US:EU = 10:46:41 lots)
CE-SDS under non-reducing condition was performed to determine the purity levels of intact immunoglobulin G (IgG) expressed as 2H2L. It may be also used to determine the impurity levels of misassembled antibody species such as free light chain, free heavy chain, half of IgG (HL) or a variant with one missing LC (expressed as 2H1L). This method was developed and qualified for determination of main peak content.

For the result, the %IgG of all lots of SB2 (94.3-95.0%) were within both the US and EU quality ranges (≥ 93.8% and ≥ 93.5%, respectively) and all lots of EU Remicade® (Min: 94.4%, Max: 97.3%) were within the US quality range. In addition, the electrophoretic patterns of SB2 on the CE-SDS non-reduced were similar to those of US and EU Remicade®. Therefore, SB2 was considered similar to US Remicade® in terms of purity.

Assay qualification: Samsung Bioepis validated the nrCE-SDS method following ICH guideline Q2 (R1), which include validation parameters, specificity, linearity and range, accuracy, repeatability, intermediate precision, quantitation limit, and robustness.
***Reviewer comment**: The %IgG of SB2 in nrCE-SDS was within both the US and EU quality ranges. Qualified assay is adequate to support the testing results. This method is proposed for DS and DP release. See section 3.2.S.4.3 for method validation.*

3.2.R.4.2.3.4 Size-exclusion Chromatography (SEC) (SB2:US:EU = 10:46:41 lots)
Aggregates may, in principle, enhance immunogenicity and affect safety and efficacy. Size-exclusion chromatography (SEC) under native conditions separates monomeric mAbs from other variants of lower or higher molecular weight by differential exclusion from the pores of the packing material. This method was developed and qualified for detection of aggregates in SB2. The early eluting peak (high molecular weight species, HMW) eluted at about 6.5 minutes, while the monomer (main peak) and low molecular weight (LMW) eluted at about 7.6 minutes and 8.3 minutes.
SEC analysis results for %HMW in SB2 DS and DP ranged from 0.6% to 0.9%, which were slightly higher than the quality ranges of US Remicade® (≤ 0.5%) and EU Remicade® (≤ 0.5%).

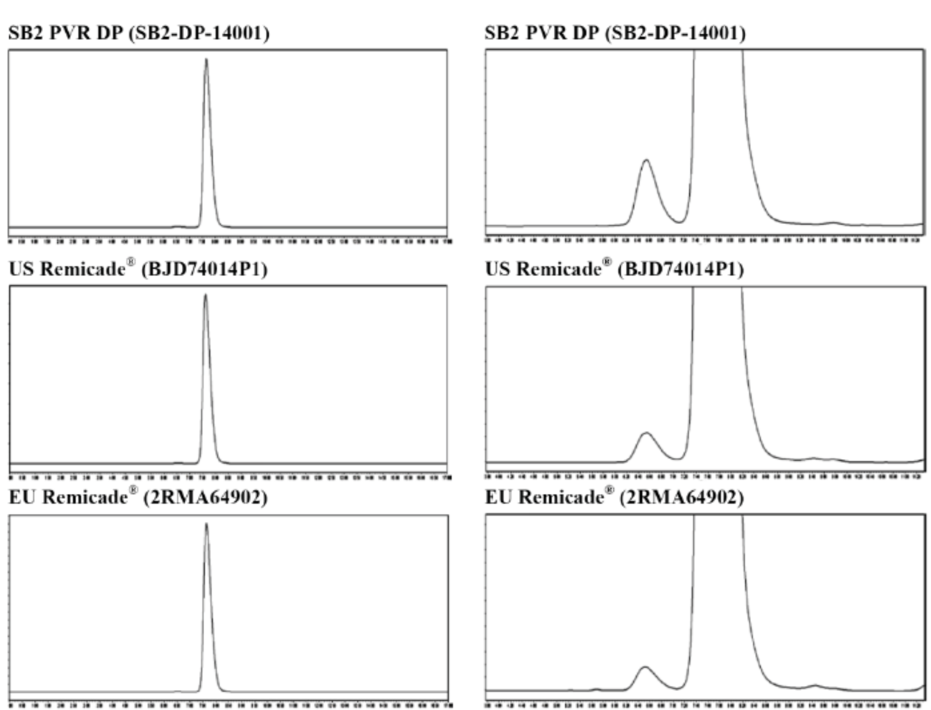
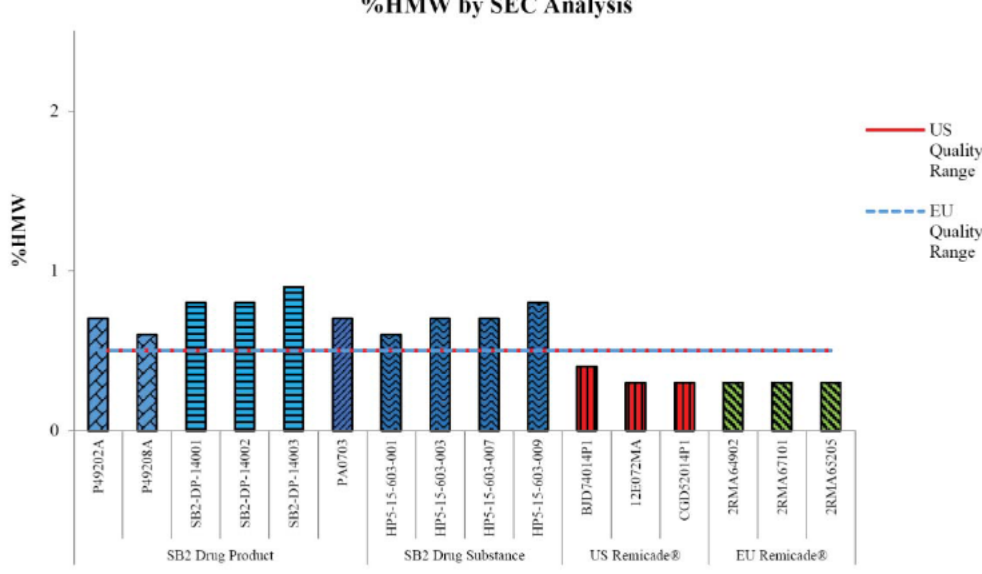


Figure 3.2.R.4–13. SEC Profiles of Representative SB2 and Remicade®
(Left: Full Chromatogram, Right: Zoom-in)



igure 3.2.R.4–15. Similarity of %HMW between SB2 and Remicade® by SEC

Note that this graph contains the data from one set of experiments run side-by-side, i.e. 5 SB2:3 US:3 EU lots in this case. However, the quality ranges for this and all the tier 2 attributes (unless otherwise noted) were actually determined based on a higher number of US and EU lots, e.g. data from 46 US lots and 41 EU lots are used to determine the quality ranges for %HMW.

As one of the two orthogonal methods, SEC/MALLS (Tier 3 attribute) was used to determine the relative contents of high molecular weight (HMW), monomer, and low molecular weight (LMW). Based on the SEC/MALLS results (Table 3.2.R.4-56), SB2 was similar to US Remicade® in terms of scattering profiles, the calculated mass of the monomer and dimer, and peak percentage from UV detection. The average dimer level of SB2 ranged from 0.56 to 0.70%. For US and EU Remicade, the average level of dimer was 0.30% and 0.22%, respectively.

Additionally, Sedimentation velocity - analytical ultracentrifugation (SV-AUC; Tier 3 attribute) was used as an orthogonal method to SEC/MALLS to investigate the monomer content, the presence of aggregates and fragments. %HMW from SEC analysis includes only irreversible aggregates and dimers, while that from SV-AUC includes reversible and non-reversible aggregates. These findings indicate that over a half of protein existed as reversible dimer and the irreversible aggregates existed in a very low level (<1.0%) in both SB2 and Remicade.

Table 3.2.R.4–56. Summary of Peak Percentage Data by SEC/MALLS from UV-detection of SB2 and Remicade®

Sample			Value	Area (%)		
				HMW	Monomer	LMW
SB2 Clinical DP		P49202A	Mean	0.57	99.37	0.06
			SD	0.02	0.02	0.00
SB2 PVR DP		SB2-DP-14001	Mean	0.70	99.25	0.05
			SD	0.00	0.00	0.00
Remicade®	US	BJD74014P1	Mean	0.30	99.65	0.05
			SD	0.00	0.01	0.01
	EU	2RMA64902	Mean	0.22	99.73	0.05
			SD	0.01	0.00	0.00

Assay Qualification: The SEC validation (doc# 09696) parameters, specificity, linearity, precision (repeatability and intermediate precision), accuracy, quantitation limit, range and robustness were evaluated according to ICH guideline Q2 (R1). At least one blank (MP) injection was performed after the system suitability standards to evaluate carryover. A series of analyses was made according to the method to establish and confirm system suitability. The acceptance criteria for testing of system suitability include: 1) Evaluate results against the method system suitability criteria. 2) Evaluate the blank injection(s) for carryover. There should be no interfering peaks in the blank. All the validation results from all analytical runs met the criteria. The SEC/MALLS and SV-AUC assays were also qualified and demonstrated to be suitable for their use in the similarity assessment, but the qualification results are not discussed in detail here.

***Reviewer comment**: Although %HMW in SB2 was higher than in US and EU Remicade, the relative contents of HMW were very low (< 1.0%) across SB2, US and EU Remicade, and the monomer contents of the three products were more than 99%. The SEC peak profile was similar between all the products, with no peaks present in SB2 that were not also present in the Remicade comparators. In addition, the results of orthogonal analysis using size exclusion chromatography coupled to multi-angle laser light scattering (SEC/MALLS) and sedimentation velocity analytical ultracentrifugation (SV-AUC) demonstrate similarity of SB2 with US and EU Remicade in terms of size heterogeneity, type, and quantity for aggregates. Half of the aggregates determined by SEC are reversible dimers based on SEC/MALLS measurement.*

HMW species may pose a risk of nucleating formation of additional aggregates or particulates. Available 30 months SB2 drug product stability data for clinical DP lots, 24 months data for PV lots, and 6 month accelerated stability data for all of these lots of SB2 showed no changes of %HMW or significant trends in formation of particulate matter over the storage period, indicating the stability of SB2 DP. The comparative stability assessment between SB2 and Remicade discussed below showed no significant differences in the rates of formation of HMW species.

The <1% levels of HMW species in SB2 are well within the normal ranges typically observed for modern monoclonal antibody products, indicative of a well controlled

manufacturing process and adequately formulated product. The Clinical Pharmacology review of clinical trial data found that there was not a significant difference in immunogenicity between SB2 and EU-Remicade. SB2 is a highly pure product with respect to HMW species, many of the HMW species that are present appear to reversible, and there is no evidence for impact on product stability or immunogenicity. Therefore, the slight difference observed in the content of %HMW compared to Remicade is not considered significant.

3.2.R.4.2.3.5 Quantity (SB2:US:EU = 6:41:18 lots)

The protein content of SB2 and Remicade® was determined by ultraviolet/visible spectroscopy (UV/VIS) at 280 nm. Results for protein content in SB2 DP ranged from 94 mg/vial to 96 mg/vial, which were within the quality ranges of US Remicade® (87-106 mg/vial) and EU Remicade® (90-103 mg/vial). The content of EU Remicade® (Min: 91 mg/vial, Max: 99 mg/vial) was also within the US quality range. Method qualification data were provided and are acceptable but are not reviewed in detail here; UV absorbance is the standard method for determining protein content and is well suited to this purpose.

Reviewer comment*: There are batch release data for 2 additional DP lots available in 3.2.P.5.4. These lots also fell within the quality ranges of US-Remicade and EU-Remicade. In general, the SB2 lots are at the low end of the Remicade quality ranges. However, risk of the protein content differing is mitigated by the SB2 release specification limit of* (b) (4) *mg/vial, which is tighter than the quality range and therefore sufficiently tight to assure all future commercial lots will fall within the quality range of US-Remicade.*

3.2.R.4.2.3.6 Apoptosis Assay for Signaling Mediated by Membrane-Bound TNF-α (SB2:US:EU = 10:42:28 lots)

This assay is sensitive to "Reverse Signaling" mediated by engagement of TNF-α in cell membranes, which transmits a signal into the cells and leads to apoptosis. This signaling is a potential mechanism of action for inflammatory bowel disease (IBD) indications. The relative apoptosis activity of SB2 and Remicade® was determined by measuring the induced caspase activity in Jurkat cells expressing membrane TNF-α. In brief, Jurkat cells expressing membrane TNF-α were incubated with sample (SB2 or Remicade®) for 24 hours in a 37°C/5% CO2 incubator. By adding Caspase-Glo®, the relevant luminescence signal which was induced by caspase acting on a luminogenic peptide substrate, showed intensities proportional to the apoptosis activity.

Results for apoptosis activity in SB2 DS and DP ranged from 89% to 105%, which were within the quality ranges of US Remicade® (81-115%) and EU Remicade® (79-122%). The activity of EU Remicade® (Min: 78%, Max: 111%) was also within the quality range of US Remicade® except one lot (Lot No. 9CU3301302) that was slightly lower than the US quality range.

Assay qualification: Samsung Bioepis validated the SB2 apoptosis assay following ICH guideline Q2 (R1), which include validation parameters, specificity, linearity, working range, repeatability, and accuracy.

***Reviewer comment**: The SB2 apoptosis measurement was within both the US and EU quality ranges. Qualified assay is adequate to support the testing results. This established similarity on apoptosis supports the conclusion that infliximab reverse signaling mediated by tmTNF-α expressed on cell surface is similar for all pairwise comparisons between SB2, US-Remicade, and EU-Remicade.*

3.2.R.4.2.3.7 FcγRIIIa Binding Assay on NK cells (SB2:US:EU = 10:41:34 lots)
The Fc receptor called CD16a or FcγRIIIa on natural killer (NK) cells recognizes IgG which is bound to the surface of a target cell. Crosslinking and activation of FcγRIIIa by IgG causes the release of cytokines such as IFN-γ that signal to other immune cells, and release of cytotoxic mediators like perforin and granzyme that promote cell death of target cell. This process is known as antibody-dependent cell-mediated cytotoxicity (ADCC). The FcγRIIIa receptor has a polymorphism at amino acid 158 with a Val (V) or Phe (F) residue. It has been suggested that the IgG binding affinity of Val variant (158V/V) receptor is higher than that of the Phe variant (158F/F).

The FcγRIIIa (158V/V) binding activity was determined by an amplified luminescence proximity homogeneous assay screen (AlphaScreen®), which is based on FcγRIIIa competitive inhibition binding to the Fc region of infliximab.

Assay qualification (Doc. #:01512) : The FcγRIIIa competitive inhibition binding assay uses AlphaScreen® Technology as a detection method for binding of FcγRIIIa to the Fc portion of SB2. AlphaScreen® is a beads-based chemistry consisting of a donor bead and an acceptor bead that can be used to study biomolecular interactions in a microplate format. The AlphaScreen® acceptor beads are coated with hIgG1, Alphascreen® donor beads are coated with GSH (reduced glutathione) and FcγRIIIa is tagged with GST (Glutathione-STransferase). In this assay, molecules captured on the bead surface leads to an energy transfer from the donor beads to the acceptor beads, ultimately producing a luminescent signal. Signal is generated only when GSH-coated donor beads and hIgG1-coated acceptor beads are close to proximity ~200 nm by GST-FcγRIIIa, which binds to Fc region of hIgG1. SB2, with its Fc portion, will compete with the hIgG1 conjugated on the acceptor beads for the binding of GST-FcγRIIIa, which binds to GSH-coated donor beads. Therefore, the signal is inversely proportional to the concentration and binding activity of SB2.
This method is defined as an assay testing for biological potency assay according to ICH Q2 (R1) guideline. Qualification was performed on specificity, linearity, precision, accuracy and range of reference product binding to FcγRIIIa to confirm suitability of this method for the analysis purposes.

Results for FcγRIIIa (158V/V) binding activity in SB2 DS and DP ranged from 88% to 141%. Three of ten batches of SB2 were slightly higher than the quality ranges of US Remicade (75-130%) and EU Remicade (70-128%). The binding activity of EU Remicade (Min: 72%, Max: 114%) was within the quality range of US Remicade except one lot (Lot No. 2RMA68401) that was lower than the US quality range. The sponsor concluded that the slight differences across SB2, US and EU Remicade (1-13%) were not significant because those were still within assay variability (intermediate precision in %RSD from method qualification was 5-10%).

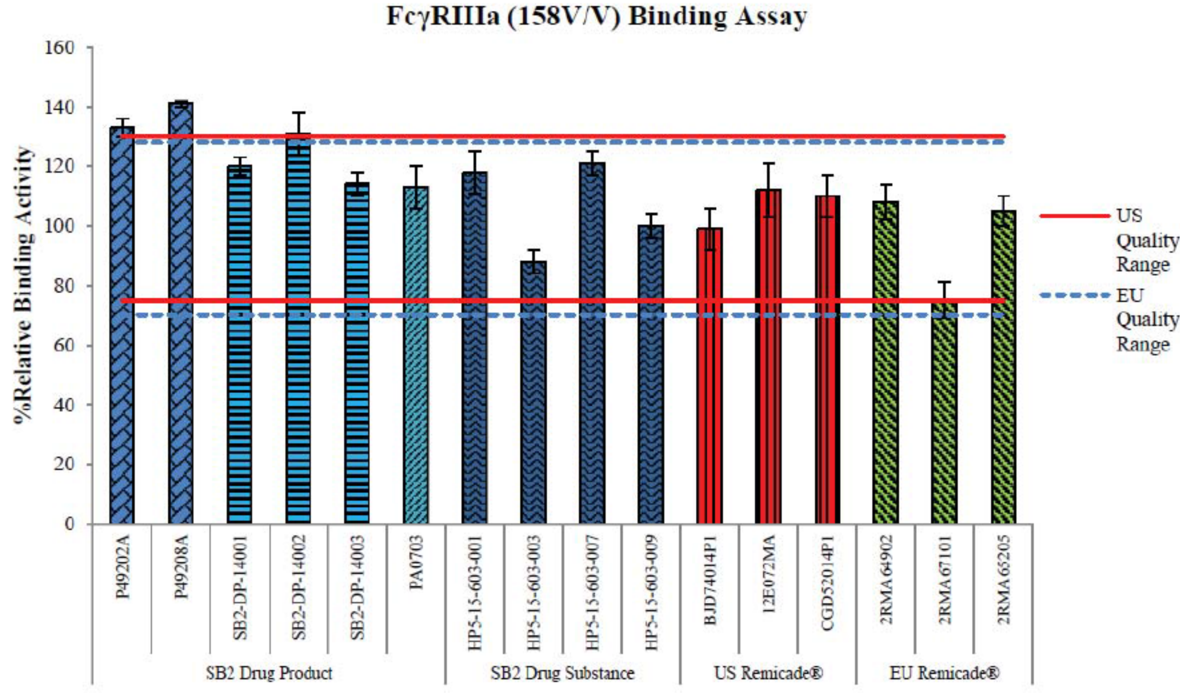


Figure 3.2.R.4–18. Similarity of FcγRIIIa (158V/V) Binding Activity between SB2 and Remicade® (by AlphaScreen®)

Reviewer comments: *Seven of ten SB2 lots fell within the quality range for US-Remicade, failing to meet the Tier 2 criterion of ≥90%. On July 29, 2016, an IR was sent to the sponsor to address the uncertainty in the analytical similarity with respect to FcγRIIIa receptor binding and to support analytical similarity with respect to reverse signaling and other biological functions. This IR specifically requested additional data for following assays related to FcγRIIIa or its associated effector function (data for ADCC activity with NK92-CD16 cells for 10 SB2 lots had previously been requested):*

- FcγRIIIa binding assay (158V/V) by SPR (Tier 3)

- FcγRIIIa binding assay (158F/F) by SPR (Tier 3)

- ADCC assay using healthy donor PBMC (Tier 3, reviewed under 3.2.R.4.2.3.9)

The additional FcγRIIIa binding assays are reviewed below, the ADCC assays are reviewed in the subsequent section.

FcγRIIIa binding assay (158V/V) by SPR (SB2:US:EU = 10:14:13 lots) (Tier 2 attribute)

FcγRIIIa (158V/V) binding affinity

SB2 and Remicade® was also measured by SPR, and similarity of the binding affinity was assessed by quality range approach. In response to the July 29, 2016 FDA information request, additional lots of Remicade compared to the original submission were included in the analysis and the quality ranges were re-established accordingly, as mean ± 3 SD from 14 lots of US Remicade® and 13 lots EU Remicade.

SPR results for FcγRIIIa (158V/V) binding affinity (in units of dissociation equilibrium constant, K_D) in SB2 DS and DP ranged from 1.18E-06 to 1.39E-06, which was within the quality range of US Remicade (8.48E-07 to 1.43E-06). The result for one DP batch (SB2-DP-14003) was 1.39E-06, which was slightly higher than the quality range of EU Remicade (9.67E-07 to 1.36E-06).

Assay qualification: Samsung Bioepis validated the SPR method for testing FcγRIIIa Binding Affinity following ICH guideline Q2 (R1), which include validation parameters, specificity, linearity (125-8000 nM), precision (% RSD of K_D: 5%), quantitation limit, robustness, working range, and accuracy. The parameters examined for this FcγRIIIa binding assay of SB2 indicated that the method performance is suitable for routine testing, including QC and stability testing.

Reviewer comment: *SPR based binding assay is an orthogonal method for measuring FcγRIIIa binding. The slight differences between SB2 and US Remicade in FcγRIIIa(158V/V) binding activity detected by AlphaScreen assay are not detected in the SPR binding assay.*

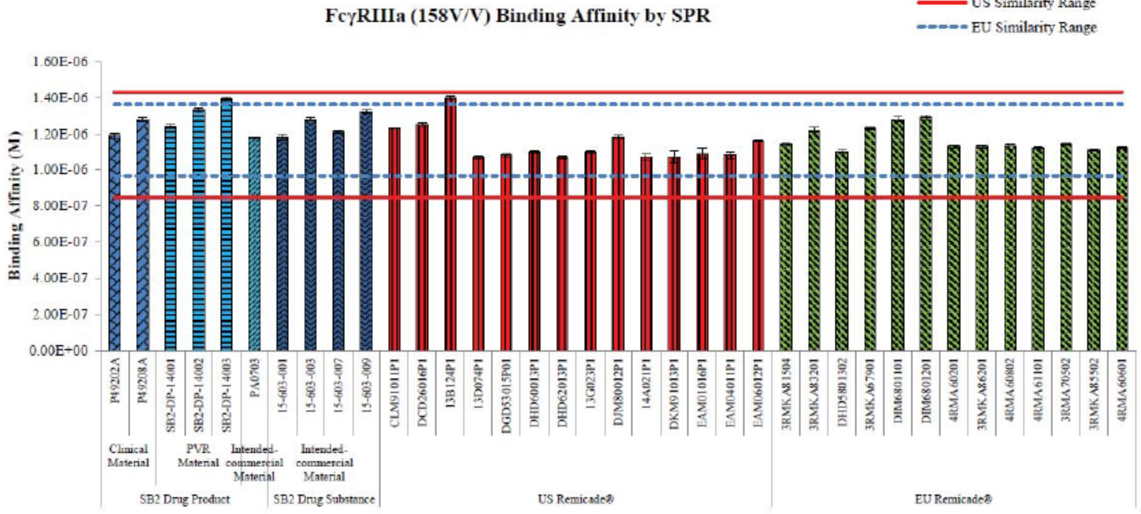


Figure 3.2.R.4–19. Similarity of FcγRIIIa (158V/V) Binding Affinity between SB2 and Remicade® (by SPR)

<u>FcγRIIIa binding assay (158F/F) by SPR (SB2:US:EU = 10:12:4 lots)</u> (Tier 3 attribute)
The FcγRIIIa receptor has a polymorphism at amino acid 158, and the Phe variant (158F/F) is thought to be of lower affinity than the Val (V/V) variant. FcγRIIIa (158F/F) binding affinity of SB2 and Remicade® were measured by SPR, and the sponsor assessed similarity of the binding affinity was assessed by a quality range approach. All 10 lots for SB2, which ranged from 1.21E-06 to 1.93E-06 M, fell within the quality range of 1.00E-06 to 2.01E-06 M for US-Remicade. The result for one DS batch (HP5-15-603-003) was 1.93E-06 M, which was slightly higher than the quality range of EU Remicade® (9.34E-07 to 1.81E-06 M). However, ADCC activity, which has correlation with FcγRIIIa binding, was similar between SB2,US Remicade, and EU-Remicade. This assay was qualified and is suitable for this use, but a detailed summary of the qualification is not included here for this Tier 3 attribute.

Reviewer comment: *SB2 is similar to US-Remicade for FcγRIIIa (158F/F) binding affinity. The slight difference observed in FcγRIIIa (158V/V) affinity for SB2 compared to EU-Remicade is not observed for the 158F/F form of the receptor.*

Reviewer conclusions on similarity with respect to FcγRIIIa binding assay*. The three SB2 lots, P49202A, P49208A, and DP-14002, with out of range results for NK cells based FcγRIIIa binding analysis all passed the SPR based and other orthogonal FcγRIIIa similarity analyses and all fell within the US-Remicade quality range for both ADCC assays (see review details in section R.4.2.3.9).*

The binding activity in NK based FcγRIIIa binding assay correlated noticeably with the NK cell-mediated ADCC activity measured for all the available SB2, US and EU lots. This indicates that the NK cell-based FcγRIIIa binding may be predicative of infliximab ADCC

activity in the assay measuring NK-cell mediated ADCC activity. Given the fact that ADCC is the more biologically relevant activity compared to the FcγRIIIa binding assay, we agree with the sponsor that the relatively high values observed for the three out-of-range SB2 lots for FcγRIIIa binding did not lead to an ADCC activity outside the ranges obtained for the reference product and therefore does not suggest a significant potential difference in clinical activity. A lack of difference in SPR based FcγRIIIa binding affinity provides additional evidence that the effect may be relatively minor and does not suggest a major difference in Fc receptor binding affinity. Additionally, the glycosylation profile, which is linked to binding affinity for Fc receptors and the resulting ADCC and other biological activities, was also similar between SB2 and US-Remicade. Overall, the data support that SB2 is sufficiently similar to US-Remicade with respect to FcγRIIIa binding affinity to assure that the resulting ADCC activity is similar.

Overall, the data support that SB2 is sufficiently similar to US-Remicade with respect to FcγRIIIa binding affinity to assure that the resulting ADCC activity is similar between the product. To mitigate risk of drift in FcγRIIIa binding affinity and to ensure that future SB2 lots have FcγRIIIa binding affinity levels comparable to those shown in the similarity assessment to yield similar ADCC activites to the reference product, we asked the sponsor to include FcγRIIIa binding as a DS release test. On Nov 23, 2016, we sent the following IR:

Fc effector functions such as ADCC activity are likely a clinically significant mechanism of action for this product. To ensure tight control over ADCC and other Fc-mediated activities, add a FcγRIIIa binding affinity test to the SB2 DS release specification. Update Sections 3.2.S.4.1 and 3.2.S.4.5 to reflect the change.

Sponsor's response (Dec. 1, 2016 in amendment eCTD0029):
"The Applicant agreed will add the FcγRIIIa binding affinity test [SPR-based] to the SB2 DS specifications. (b) (4)

.

To establish the action limit of IPT, FcγRIIIa binding affinities of SB2 batches were measured using qualified SPR-based binding assay. Results from a total of 14 batches of SB2 DS and DP were used (five batches of clinical DP, three batches of PVR DP, one batch

of intended commercial DP, and five batches of intended-commercial DS). Due to the limited number of DS batches, results of DP batches were also included. A two-sided tolerance interval with a 95%confidence level covering 99% of the population was calculated from the data. This resulted in a range of 72-121% with mean of 98%. The range was further adjusted to 75-133% for a more symmetrical distribution and to account for possible variability during technical transfer and method validation. In conclusion, the action limit for FcγRIIIa binding was determined as < 75% or > 133%."

Reviewer comment*: We agree that SPR based FcγRIIIa binding assay is appropriate for release test since cell based binding assay could be more variable with higher intermediate precision for release. The minimum and maximum binding activities of US and EU lots from the SPR method are in a tighter range, which is suitable for control as a release, than those for the Alphascreen assay.*

We also agree to that FcγRIIIa binding can be included as an in-process test (b) (4) *during the interim prior to the completion of method validation* (b) (4) *The sponsor proposed the action limit of,* (b) (4) *% relative to the affinity of the reference standard, which was based on historical data from SB2 batches. We made a side-by-side comparison of those limits to the US quality ranges for the SPR method, and the proposed action limits for the in-process test are very close the US- and EU-Remicade quality ranges (70-139% and 71-129%, respectively), and it is even tighter than the quality range for US-Remicade at the high end. Therefore, we concluded that the action limits of* (b) (4)*% are appropriate to control FcγRIIIa binding from drifting away the determined acceptable quality ranges from the similarity analysis. Implementation of this assay into the DS release specification will be a PMC.*

3.2.R.4.2.3.9 Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC) (SB2:US:EU = 10:46:30 lots)

The ADCC activity is determined through a cell-based assay. The ADCC response is characterized by the interaction of the Fc region of the target-bound antibody with certain Fc receptors (FcγRs) on the effector cell surface. Therefore, binding to both transmembrane TNF-α and Fcγ receptor is required for the activation of ADCC.

Two assays were performed to assess ADCC activity. In the first (Tier 2) ADCC assay, ADCC was assessed using a stable mouse cell line that overexpress human membrane TNF-α on the cell surface (3T3mTNFα cells) as target cells, and a human natural killer cell line expressing CD16 (NK92-CD16 cells) as effector cells. The results for ADCC activity in in this assay for SB2 DS and DP ranged from 72% to 135%, which was well within the quality ranges of US Remicade (59-141%) and EU Remicade (48-156%). The activity of EU Remicade® (Min: 62%, Max: 137%) was also within the quality range of US Remicade.

In the second (Tier 3) ADCC assay, ADCC was assessed using peripheral blood mononuclear cells (PBMCs) from a healthy donor (FcγRIIIa 158V/F) as effector cells to mimic physiologically more relevant condition. The ADCC activity of SB2 was within both quality ranges of US Remicade (67-167%) and EU Remicade (65-172%) in the PBMC assay.

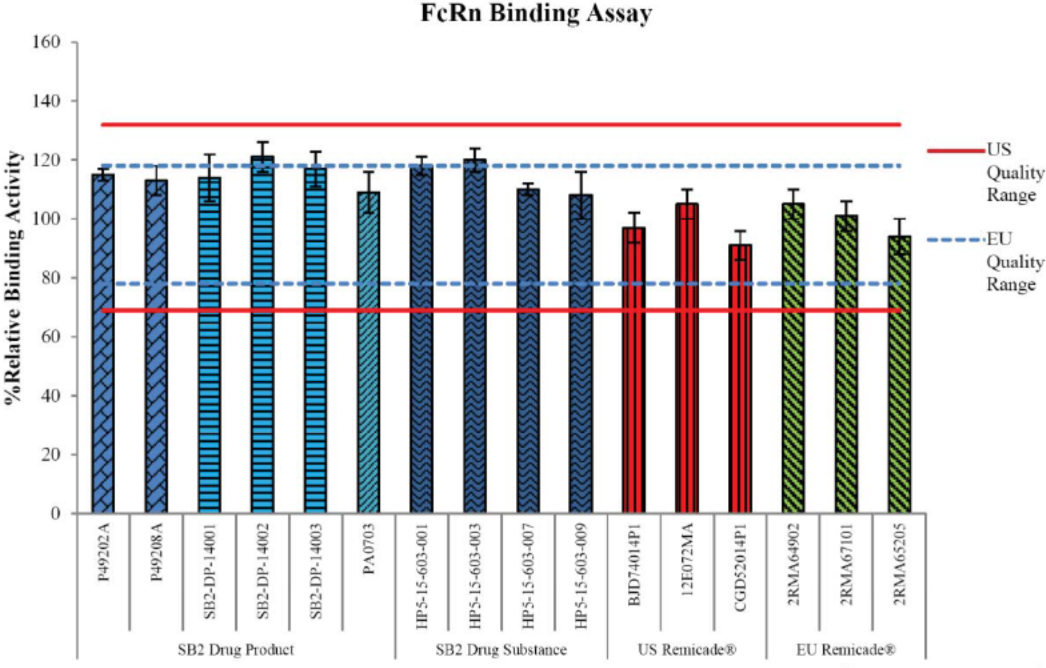
Assay qualification (Doc#:00927): The ADCC assay (NK92-CD16 effector cells) was performed using a stable mouse cell line that overexpress human membrane TNF-α on the cell surface (3T3mTNFα cells) as target cells, and a human natural killer cell line expressing CD16 (NK92-CD16 cells) as effector cells. Samples were incubated with 3T3mTNFα cells and NK92-CD16 cells for 4 hours. Following incubation, the cell plate was incubated with a luminogenic peptide substrate, and the resulting signal was quantified with a luminometer. The method was developed and qualified for determination of relative ADCC activity of SB2 and Remicade. The system suitability acceptance criteria are the relative ADCC activity of control in between 80% and 125%. Assay specificity, precision (Repeatability: ≤ 20% and intermediate precision: ≤ 20%), linearity (50-150%), precision, accuracy, working range (50-150%) were validated. In addition, tier 3 assay, PBMC cell based ADCC activity was also adequately qualified, but qualification is not discussed in detail here.

Reviewer comment: *Data from the ADCC assay with NK92-CD16 cells and PBMC support the conclusion that SB2 ADCC activity is within the quality ranges of US and EU Remicade. Assay qualification is adequately conducted to ensure the validity of the testing results.*

During the PAI at Incheon site, graphical data of ADCC tests was provided that demonstrated that the NK92-CD16 cells were demonstrably more sensitive than PBMCs. A scatter plot was presented that demonstrated that the cell line is sensitive to the levels of afucosylation, total afucosylation, and high mannose glycan variants. This data confirmed the intent of ADCC assay as the functional test (b) (4) .

3.2.R.4.2.3.8 FcRn Binding Assay (SB2:US:EU = 10:40:32 lots)

The FcRn binding activity was determined by AlphaScreen®. The FcRn binding assay was performed using a similar procedure as that of FcγRIIIa binding assay. Results for FcRn binding activity in SB2 DS and DP ranged from 108% to 121%, which was within the quality range of US Remicade® (69-132%). The results for one SB2 DP (SB2-DP- 14002) and one SB2 DS (HP5-15-603-003) were 121% and 120%, respectively, which were slightly higher than the quality range of EU Remicade® (78-118%).



igure 3.2.R.4–20. Similarity of FcRn Binding Activity between SB2 and Remicade® (by AlphaScreen®)

Assay Qualification (Doc#: 00241): The amplified luminescent proximity homogenous assay (AlphaScreen®) technology was used to qualify a competitive binding assay to measure the binding activity of Remicade to FcRn. The binding activity of the sample is compared to the binding activity of the reference standard and the result is reported as percent relative binding activity. The qualification results showed that linearity (50-150%), precision (Repeatability: ≤ 20% and intermediate precision: ≤ 5%), accuracy, range were satisfied with all acceptance criteria.

Reviewer comment: *The FcRn binding activities for all 10 SB2 lots were within the quality range of the US-Remicade reference product. The FcRn binding activities of two SB2 lots are slightly higher than the EU-Remicade quality range. There is 5% intermediate precision for this assay, so the 2-3% difference of the results from EU upper limit could be considered within assay variability.*

FcRn is thought to be involved in the salvage pathway of IgG antibodies, and the most likely impact of FcRn differences between products would be the clearance of serum infliximab. Of note, the results in the pivotal clinical PK study (SB2-G11-NHV) showed that the PK characteristics of SB2, US- and EU-Remicade were similar. Therefore, any subtle difference in FcRn binding affinity between SB2 and EU-Remicade that may be suggested by 2 of 10 SB2 lots falling just outside EU-Remicade quality range is unlikely to suggest any impact to PK.

3.2.R.4.2.3.10 Complement-dependent Cytotoxicity (CDC) (SB2:US:EU = 10:32:26 lots)
CDC is an immune mechanism associated with the complement system. An IgG antibody first binds via its antigen-binding site to its specific target on a cell surface. Then, the Fc portion is recognized by C1q, a component of the complement complex. This interaction initiates the classical complement pathway, mediating formation of the membrane attack complex and consequent cell lysis.

Results for CDC activity in SB2 DS and DP ranged from 93% to 107%, which was well within the quality ranges of US Remicade® (84-110%) and EU Remicade® (85-116%). The activity of EU Remicade® (Min: 87%, Max: 114%) was also within the quality range of US Remicade® except one lot (Lot No. DHD5801302) that was slightly higher than the US quality range. The gap of EU Remicade® and US quality range was slight (4%) and still within assay variability (intermediate precision in %RSD from method qualification was 3-4%). Therefore, it is concluded that SB2 is similar to US Remicade® in terms of CDC activity.

Assay Qualification (RD_03850): The assay was performed in 96-well plates using a cell line overexpressing human membrane TNF-α on the cell surface (Jurkat-mTNF-α cell) using cytotox-Glo detection system. Human serum was used as a complement source. Samples were incubated with Jurkat-mTNF-α cells. Following incubation, the numbers of viable cells were measured by the detection of a luminogenic peptide substrate and the resulting signal was quantified with a luminometer. This CDC assay was assessed in the system suitability (80-125%), specificity, linearity, precision (Repeatability: ≤ 20% and intermediate precision: ≤ 20%), accuracy, and range. All of results were satisfied with their acceptance criteria.
Reviewer comment: *Assay qualification is adequately qualified demonstrating that the analytical procedure is suitable for measurement of relative CDC activity of SB2. Results for CDC activity for all SB2 DS and DP lots are within the quality ranges of US and EU Remicade. The data support similarity with respect to this biological activity.*

3.2.R.4.2.3.11 C1q binding (SB2:US:EU = 10:42:31 lots)
The globular heads of C1q exclusively bind to the CH2 domain of IgG molecules. C1q is the first component which binds to the antigen-antibody immune complexes. C1q binds antigen-antibody immune complexes via the Fc region of IgG and IgM (known as the C1q complex). Therefore C1q is important for CDC (Kohno et al., 2005). The binding ability of SB2 and Remicade® to the complement component C1q was assessed.

Results for C1q binding activity in SB2 DS and DP ranged from 103% to 114%, which was within the quality range of EU Remicade® (76-116%). The results for two of ten batches of SB2 DP (HP5-15-603-001 and HP5-15-603-007) were 113% and 114%, respectively, which are slightly higher than the quality ranges of US Remicade® (81-112%).

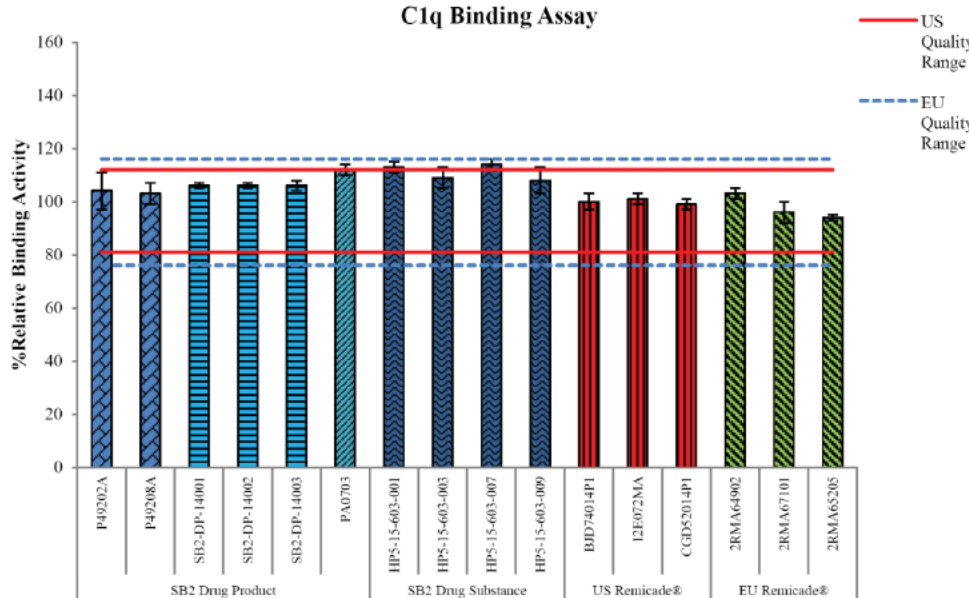


Figure 3.2.R.4–23. Similarity of C1q Binding Activity between SB2 and Remicade®

Assay qualification (Doc #. 07207): The objective of the qualification was to qualify an ELISA-based binding assay to measure the binding of SB2 to C1q. The results showed that specificity, linearity, precision (Repeatability: ≤ 10% and intermediate precision: ≤ 10%), accuracy, and working range are satisfied with all acceptance criteria. Consequently, it is suitable for measuring the binding activity of SB2 (a biosimilar product of Remicade) using ELISA.

Reviewer comment: *Two out of the ten SB2 lots have only slightly higher C1q binding activity 113% and 114% comparing the US-Remicade quality range 81- 112%. However this difference is marginal and likely within the variability of the assay. The Fc-glycoforms, which would be a potential difference between the products that could affect C1q affinity and CDC, are similar between SB2 and US- and EU-Remicade. The functional consequence of C1q binding is CDC activity, and the CDC results for SB2 were similar (all met Tier 2 quality range criteria) between SB2 and US- and EU-Remicade. Thus, the available evidence suggests that any potential difference in C1q affinity does not impact CDC function and does not suggest does a potential clinical impact.*

3.2.R.4.2.3.12 charge variants (SB2:US:EU = 5:43:41 lots)

Cation-exchange chromatography (CEX) and imaged capillary isoelectric focusing (icIEF) as orthogonal methods are applied to compare charge variants between SB2 and Remicade.

The relative contents of acidic variants in SB2 (29.9-34.5%) and basic variants in SB2 (4.8-6.9%) measured by CEX-HPLC were reproducibly slightly higher than those in US and EU Remicade. The profiles of EU Remicade were similar to those of US Remicade. Based on 43 and 41 lots of US and EU Remicade analyzed during development, respectively, the quality range of each charge variant was set as mean ± 3SD. As a result, the relative contents of

acidic and basic variants of SB2 were out of the US (16.9-33.4% and 0.7-5.9%, respectively) and EU quality range (15.4-32.8% and 0.5-5.5%, respectively).

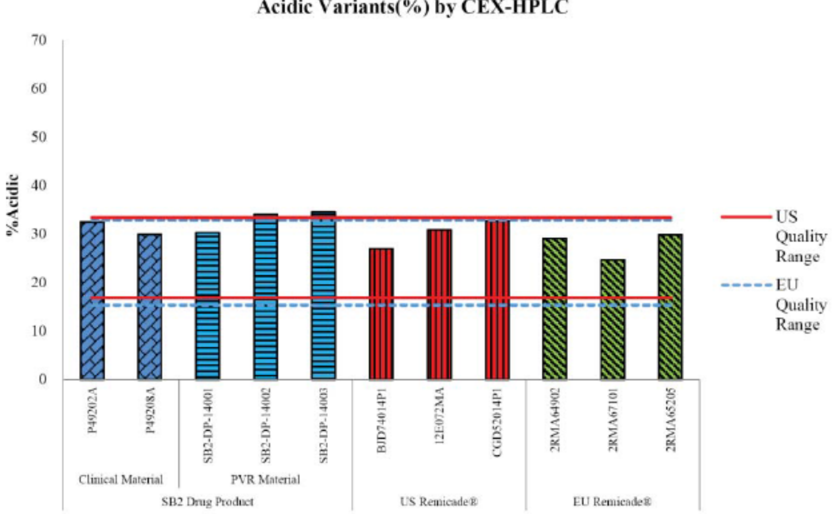


Figure 3.2.R.4–53. Similarity of %Acidic Variants between SB2 and Remicade® by CEX after Carboxypeptidase B Treatment

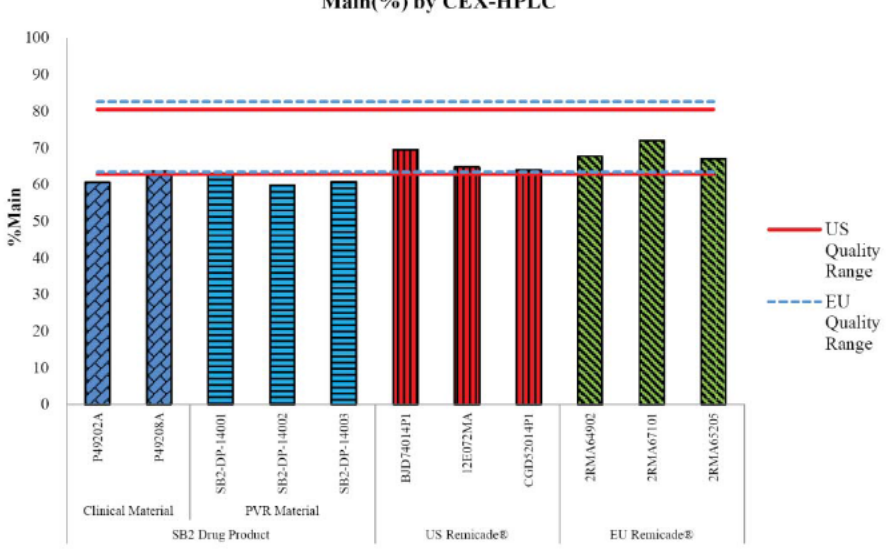


Figure 3.2.R.4–54. Similarity of %Main between SB2 and Remicade® by CEX after Carboxypeptidase B Treatment

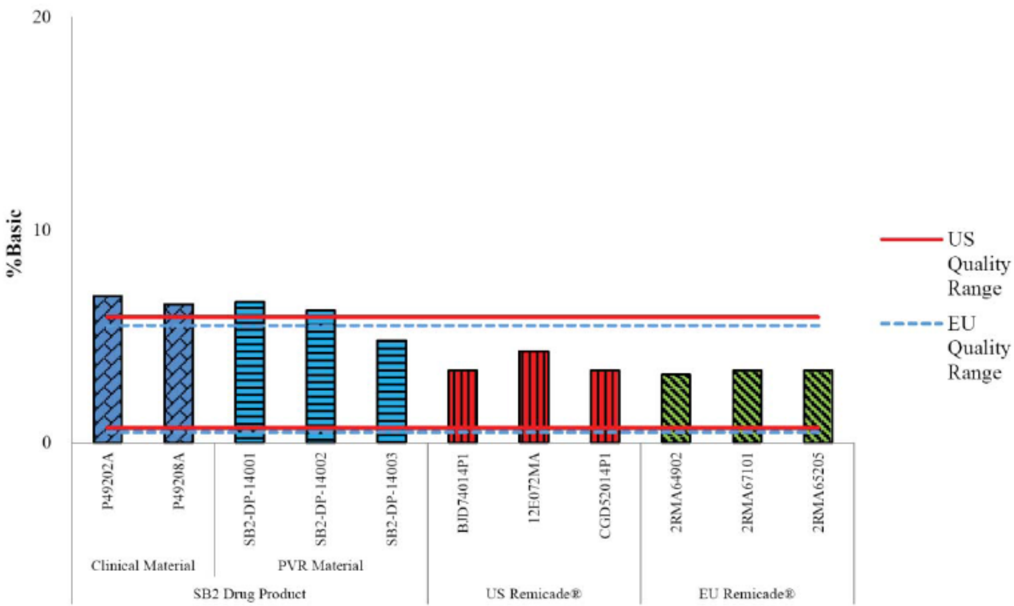


Figure 3.2.R.4–55. Similarity of %Basic Variants between SB2 and Remicade® by CEX after Carboxypeptidase B Treatment

Both CEX and icIEF data suggest that the relative contents of acidic and basic variant in SB2 are slightly higher than those in US and EU Remicade. To identify the possible causes and address the residual uncertainty on the difference in the charged profiles of SB2 and Remicade, the sponsor fractionated samples using CEX and characterized each fraction by intact mass analysis and peptide mapping. The results are showed in the Figure 3.2.R.4-63 below.

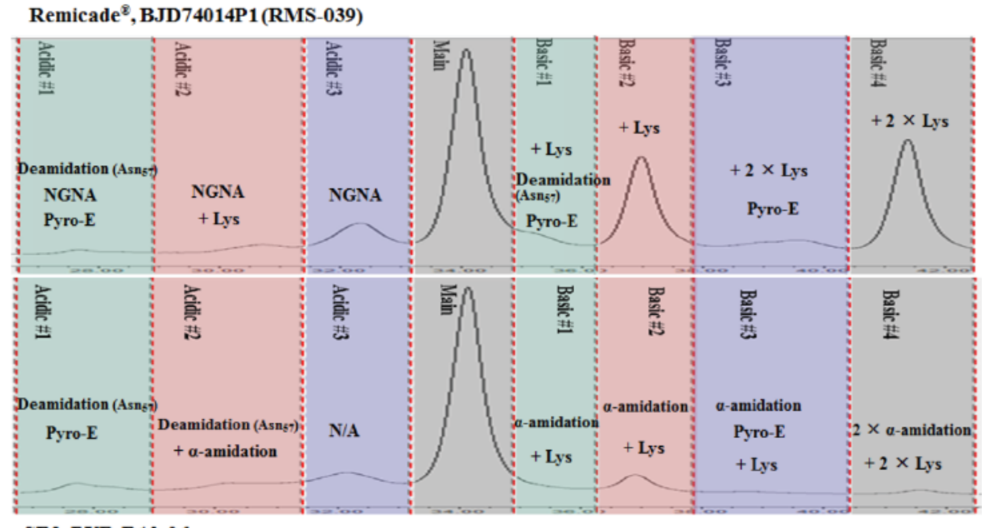


Figure 3.2.R.4–63. Identified PTMs at Each Variants of SB2 and Remicade® without Carboxypeptidase B Treatment

(NGNA; N-glycolylneuraminic acid, +Lys; containing C-terminal one Lys residue, Deamidation (Asn_{57}); deamidation at Asn_{57} in heavy chain, α-amidation.; α-amidation at proline carboxyl residue; pyro-E; pyroglutamic acid in N-terminus of heavy chain.)

Further analysis revealed that the differences between basic variants in SB2 and Remicade were caused by the contents of the C-terminal Lys and α-amidation on C-terminal proline residue. Structural and activity relationship study results showed that there were no significant differences in TNF-α and FcγRIIIa binding activities of the isolated acidic and basic variants between SB2 and Remicade.

***Reviewer comment**: The difference in charge variants observed between SB2 and the reference product was further characterized by analyzing each individual peak in the acidic and basic regions with mass spectrometry, revealing the cause of the difference as incomplete C terminal Lysine cleavage and proline α-amidation. C-terminal Lysine gets enzymatically cleaved when the drug gets in in serum, and consequently the presence or absence of this lysine is not thought to affect in vivo performance. Scientific literature supports that proline α-amidation of the C-terminus of monoclonal antibody does not exert effect on the Fc region mediated effector function. The sponsor further conducted a structure-activity relationship (SAR) study showing that the different levels of basic peaks does not alter the TNF-α and FcγRIIIa binding activity, suggesting that this marginal difference does not alter the SB2 potency and effector function compared to US-Remicade.*

Note that there are 5 lots of SB2 data for CEX-HPLC and icIEF included in the statistical analytical similarity assessment. Although these are analyzed Tier 2 attributes, FDA did not request additional data for the analytical similarity assessment because it was already clear from the 5 lots available that the results for the charge variants were outside the quality ranges of US-Remicade and EU-Remicade.

3.2.R.4.2.4 Similarity Assessment for Tier 3 Attributes (Raw Data/Graphical Comparison)

Tier 3 quality attributes are categorized as six groups including primary structure, carbohydrate structure, physicochemical properties on charge variants, biophysical properties, Fc-related biological activities and additional biological activities.

Raw data or graphical comparisons were used for Tier similarity assessments. When the data from the assay results were quantitative, the sponsor employed a quality range approach (mean ± 3SD) to assess the similarity from a statistical point of view. Thus, with the exception of certain primary and higher order structural characterization tests, most of the Tier 3 attributes include a quality range comparison analogous to those applied for Tier 2 attributes. The US and EU quality ranges were established based on US and EU Remicade data from either side-by-side characterization study or historical analysis data. For quality attributes including charged and galactosylated glycans, FcγRIa, FcγRIIa, and FcγRIIb binding, quality ranges were established by historical data analyzed throughout development. For other quality ranges, the quality ranges were established by data from side-by-side characterization study.

Reviewer comment*: The sponsor also provided the Tier 3 assay qualification reports covering all the biophysical analysis and biological assays. All the method qualifications were determined to be adequate but will not be individually discussed in detail in the subsections below.*

3.2.R.4.2.4.1 Primary Structure

The characterization tests for the primary structure analyses of SB2 and US Remicade included:

- Molecular weight determination by mass spectrometry (LC-ESI-MS)
- Amino acid sequencing using liquid chromatography, coupled to electrospray ionization and tandem mass spectrometry (LC-ESI-MS/MS)
- N- and C-terminal sequencing using LC-ESI-MS/MS
- Peptide mapping by LC-MS
- Identification of disulfide bonds and quantification of free sulfhydryl groups
- Analysis and quantification of PTMs included methionine oxidation (Met oxidation), deamidation, glycation as well as N- and C-terminal modifications

Study results showed that the SB2 primary amino acid sequence is identical to the amino acid sequence of US Remicade. Post-translational modifications and associated “micro-heterogeneities” of SB2 and US Remicade were identified and quantified. The only noticeable difference is that the relative content of C-terminus with Lys for SB2 (1.5-1.9%) was much lower than that of US (23.4-27.6%) and EU Remicade® (25.6-32.3%), whereas C-terminal lysine content was similar between EU- and US-Remicade.

Reviewer comment: *The difference in relative contents of C-terminal Lys was caused mainly by the use of CHO cells as host cells for SB2 production instead of SP2/0 cells, which are used by the originator[1]. The C-term Lys does not possess any physiological effect as it is cleaved by the carboxypeptidase enzyme as it enters the blood. Yet this observed C-terminal lysine difference leads to the different percent of basic variants determined by iCIEF and CEX (see above). The sponsor collected data from pivotal clinical PK study and showed that C-terminal Lys variation does not impact PK profiles. Additionally, the TNF-α binding result showed that C-terminal Lys of the heavy chain did not impact TNF-α binding activity.*

3.2.R.4.2.4.2 Carbohydrate Structure

Glycosylation is included for similarity assessment since it is a critical quality attribute of antibody where the type and degree of glycosylation can have a significant impact on the product efficacy and immunogenicity. The N-linked glycosylation site of SB2 and Remicade was determined using LC-ESI MS/MS. Each sample was denatured with detergent and treated with PNGase F for deglycosylation.

1 Publically available information.

The overall chromatography patterns were similar across SB2, US and EU Remicade. The majority of the identified glycan peaks were also identical across those products.

As tier 2 attributes using quality range approach, afucosylated and high mannose glycans are assessed in Section 3.2.R.4.2.3.1. Here, neutral galactosylated glycans (%Gal) and charged glycans (%Charged) are discussed as tier 3 attributes. Data for a side-by-side study showed that %Charged glycan in SB2 (1.2-1.5%) was slightly lower than that in US and EU Remicade (5.3-10.2% and 5.6-10.4%, respectively), while the level is comparable between US and EU Remicade. The charged glycans of SB2 were reassessed using a quality range approach. Based on 46 and 43 lots of US and EU Remicade analyzed during development, respectively, the quality range of charged glycans was set as mean ± 3SD. As a result, the %Charged glycan of SB2 was within the US and EU quality range (0.1-11.1% and 0.0-13.3%, respectively).

%Charged (Charged Glycans)

Figure 3.2.R.4–47. Similarity of %Charged Glycans between SB2 and Remicade® by HILIC-UPLC

A structure-activity relationship (SAR) study was performed to rule out the uncertainty of whether the marginal difference on charged glycans may have impacts on the efficacy of infliximab. The results demonstrated that there was no difference in FcγRIIIa, FcRn binding, and ADCC activities between sialylated and non-sialylated infliximab.

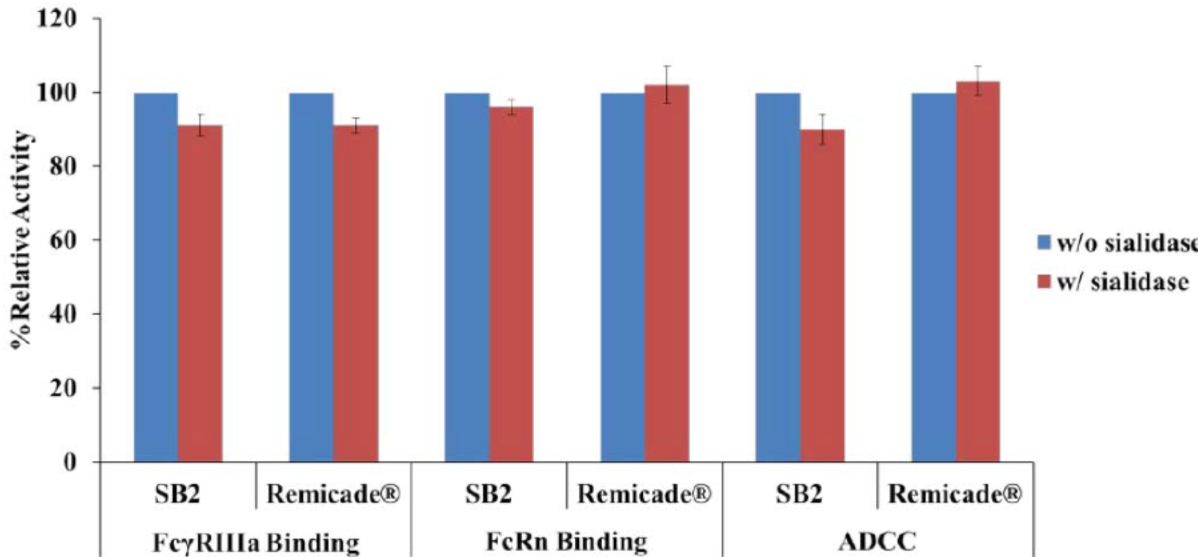


Figure 3.2.R.4–48. SAR Study Results of SB2 and Remicade® for Charged Glycans

***Reviewer comment**: Of note, the levels of charged glycans in SB2 were shown to be consistent (ranging from 1.2 to 1.5%), whereas those in US- and EU-Remicade were shown to have high batch-to-batch variability. Overall, the range of % charge glycan in SB2 is within the quality ranges of charged glycans in data from 46 lots of US Remicade and 43 lots of EU Remicade. The sponsor conducted further analysis showing that the slight difference in charge glycans was caused by higher levels of terminal sialic acid on N-Glycan species of Remicade. Literature studies have reported that terminal sialic acid increases serum half-life of such sialylated serum glycoproteins. Data from the SAR study(Figure 3.2.R.4-48 showing above) indicated that the lower level of %charged glycans on SB2 has no impact on the functional binding activities of the molecule. Additionally, the clinical pharmacology review concluded that there were no significant difference in PK profiles between the products. These results show there is little uncertainty with respect to there being a potential sialylation difference that has any clinical impact.*

3.2.R.4.2.4.3 Biophysical

Biophysical properties were evaluated for SB2 and Remicade orthogonal biophysical techniques. These techniques include far and near-UV circular dichroism (CD), intrinsic and extrinsic fluorescence, fourier transform infrared (FTIR), hydrogen/deuterium exchange mass spectrometry (H/DX-MS), antibody conformation array, differential scanning calorimetry (DSC), size exclusion chromatography coupled to multi angle laser light scattering (SEC/MALLS), sedimentation velocity-analytical ultracentrifugation (SV-AUC), dynamic light scattering (DLS), extinction coefficient, and micro-flow imaging (MFI).

Micro-flow imaging was used for the quantification and visualization of subvisible particles in the µm-size range by flowing a test fluid through the focal plane of a microscope and

obtaining high-speed images. For particles with ≥ 1 µm¸ SB2 contained slight more particles than US Remicade. However, EU Remicade® contained the most particles among SB2, US, and EU Remicade®. For particles with ≥ 2 µm, ≥ 5 µm, and ≥ 10 µm, US and EU Remicade had higher particle counts than SB2. For particles with ≥ 25 µm, SB2 had slightly higher particle counts than US and EU Remicade.

Reviewer comments:

1) *The sponsor conducted a panel of analyses to assess the similarity of biophysical properties between SB2 and reference products. Two lots of SB2 and one lot each for US and EU Remicade were included for each analysis. Data from the biophysical techniques support the conclusion that SB2 is structurally similar to US-Licensed Remicade and EU-Approved Remicade.*

2) *Of note, only one lot each US and EU Remicade was included for subvisible particulate matter analysis, with a result showing slightly different levels of subvisible particles in size ≥ 2 µm, ≥ 5 µm, and ≥ 10 µm, and ≥ 25 µm. SB2 also contains slightly more particles of size ≥ 25 µm than US Remicade. Overall the total levels of particles in different sizes are significantly lower that the USP<787> and <788> recommended limit (≤ 600 particles/container for size > 25µm), so the marginal difference in the particulate matter between SB2 and EU-Remicade lot is considered negligible. Batch analyses from the additional five SB2 DP lots in the section of P.5.4 showed that the levels of SB2 particulate matter (≥ 10µm & ≥ 25µm) are in a similarly tight range (211-506/vial for ≥ 10µm , and 2-15/vial for ≥ 25 µm)with those of the SB2 lots used for similarity assessment, indicating the subvisible particles are well controlled in SB2 DP manufacture process.*

3) *To make apples-to-apples comparisons of protein concentrations measured for SB2 and the reference product, it is necessary to apply a consistent and common excitation coefficient to calculate protein concentrations from UV absorbance measurements. The sponsor utilized an extinction coefficient of 1.4 mL mg^{-1} cm^{-1} for all SB2 and Remicade concentration determinations throughout product development. This coefficient was experimentally derived from characterization of EU-Remicade lots early in development, and later verified using additional EU-Remicade lots. The experimentally derived values for SB2 (1.57 mg^{-1} cm^{-1}), US-Remicade (1.55 mg^{-1} cm^{-1}), and EU-Remicade (1.60 mg^{-1} cm^{-1}) measured side-by-side for the similarity assessment were all similar to each other and consistent with the nominal coefficient of 1.4 mg^{-1} cm^{-1} used for routine concentration determinations. These data support that SB2 has a similar extinction coefficient to the reference product and that the value used in routine measurements of protein concentration is in reasonable agreement with experimentally determined values.*

3.2.R.4.2.4.4 Fc-related Biological Activities

Fc-related biological assays including the FcγRIa binding assay, FcγRIIa binding assay, FcγRIIb binding assay, and FcγRIIIb binding assay were performed to assess the similarity between SB2 and Remicade. See the Tier 2 section of the review above for discussion of FcγRIIIa, FcRn, and C1q receptor binding and for ADCC activity with NK cells and CDC activity.

1. The FcγRIa binding activity of SB2 and Remicade was determined by a fluorescence resonance energy transfer (FRET) assay. This method was developed and qualified for determination of relative binding activity of SB2 and Remicade to FcγRIa. The quality ranges were set as mean ± 3SD based on 43 lots of US Remicade® and 36 lots of EU Remicade® analyzed during development. The FcγRIa binding activity of SB2 was within both quality ranges of US Remicade (79-117%) and EU Remicade (81-118%).
2. The FcγRIIa and FcγRIIb binding activities was determined by AlphaScreen®. The assays were performed using a similar procedure as that of FcγRIIIa binding assay. The methods were developed and qualified for determination of relative binding activity of SB2 and Remicade to FcγRIIa and FcγRIIb. The quality ranges for FcγRIIa were set as mean ± 3SD based on 37 lots of US Remicade and 37 lots of EU Remicade analyzed during development. The FcγRIIa binding activity of SB2 was within both quality ranges of US Remicade (71-128%) and EU Remicade (69-128%). The FcγRIIb binding activity of SB2 was within both quality ranges of US Remicade® (72-127%) and EU Remicade (76-115%). In addition, FcγRIIa and FcγRIIb binding affinities were each assessed using SPR assays with 5 lots of SB2, 6 lots of US Remicade, and 6 lots of EU Remicade, as an orthogonal method to the AlphaScreen® method, and the similarity outcome was subsequently confirmed.
3. FcγRIIIb binding affinity was assessed using an SPR assay. The FcγRIIIb binding affinity of SB2 was within the quality range of US Remicade® (8.80E-06 to 1.20E-05 M) and EU Remicade® (6.39E-06 to 1.33E-05 M) except 1 batch (P49202A) that was slightly higher than the upper limit of the US quality range. Overall, the FcγRIIIb binding activities of SB2 and US Remicade are similar.

3.2.R.4.2.3.13 Transmembrane TNF-α Binding by FACS(SB2:US:EU = 10:12:6 lots)

Transmembrane TNF-α act as a bipolar molecule that transmits signals both as a ligand and a receptor in a cell-to-cell contact manner. The transmembrane TNF-α binding activity was determined by a flow cytometry method in which the relative binding activity to TNF-α on the surface of Jurkat cell expressing transmembrane TNF-α.

For the analysis, 10 batches of SB2 (6 batches of DP and 4 batches of DS) and 18 lots of Remicade (12 lots of US Remicade and 6 lots of EU Remicade) were used. Results showed that the relative transmembrane TNF-α binding activity of SB2 ranged from 91 to 108%, which are within both quality ranges (set as mean ± 3SD) of US Remicade (85-121%) and

EU Remicade (83-121%). Figure below showed that the binding activity of SB2 lots (blue bars) and the quality similarity ranges of US and EU.

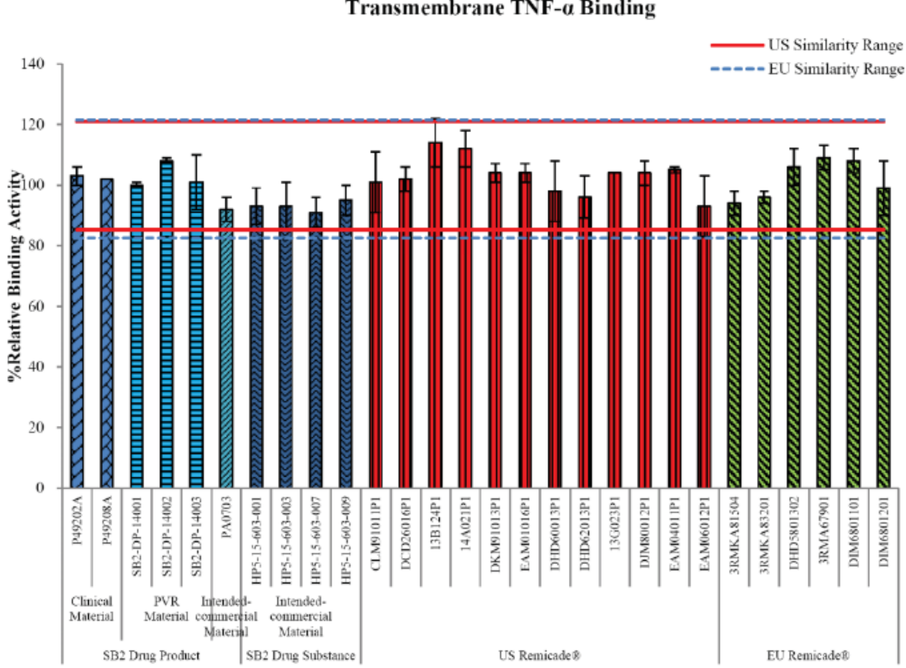


Figure 3.2.R.4–105. Similarity of Transmembrane TNF-α Binding Activity between SB2 and Remicade®

Reviewer comments. The sponsor evaluated this result as a Tier 2 attribute; FDA would accept a Tier 3 analysis for this attribute and therefore the data are presented in the Tier 3 section of the review. Regardless, the data support that SB2 is similar to US-Remicade with respect to affinity to membrane-associated TNF-α. This result is consistent with the apoptosis assay results that showed similarity with respect to "reverse signaling," which is a downstream effect of binding to mTNF-α. The apoptosis data are discussed above in the Tier 2 section.

3.2.R.4.2.4.5 Assessment of regulatory macrophage function

Two sets of experiments were conducted to assess regulatory macrophage function:

1) Evaluation of Regulatory Macrophage Function by Mixed Lymphocyte Reaction (MLR) (SB2:US:EU = 10:12:6 lots)

   Induction of regulatory macrophages is a potential mechanism by which infliximab products may contribute to the resolution of chronic inflammation and the recovery of epithelial cell barrier in inflammatory bowel disease (IBD). Two sets of experiments were performed to assess regulatory macrophage function: Regulatory macrophage induction activity and T-cell anti-proliferation activity of the induced regulatory macrophage.

Macrophage induction activity of SB2 and Remicade was measured by 2-way MLR of human PBMC and subsequent FACS analysis, and similarity of the induction activity were assessed by quality range approach. All 10 SB2 lots (81-113%)were within the quality range (74-120%)for US-Remicade. The result for one batch of SB2 DP batch (SB2-DP-14001) was 81%, which was slightly lower than the EU-Remicade quality range (83-121%). However, the observed difference between SB2 and EU quality range (2%) was unlikely to be significant considering upon the inherent variability of the assay.

***Reviewer comment**: There was observed difference (2%) for one SB2 lot compared to the EU quality range. The assay was set up by using PBMC cells from two different human donors to induce macrophage activity, and thus the assay has high variability. Considering small difference, the small number of lots analyzed, and the inherent variability of the assay, the difference does suggest a clinically meaningful difference from the EU-Remicade comparator.*

2) T-cell anti-proliferation (SB2:US:EU = 10:12:6 lots)

In order to confirm the capability of induced regulatory macrophage function, the T-cell anti-proliferation activity of samples in two-way MLR were evaluated. To measure T-cell proliferation in two-way MLR, the amount of EdU (similar material to BrdU) incorporated into genomic DNA (similar to BrdU) was detected by flow cytometry and T-cell anti-proliferation activity was normalized as %Anti-proliferative activity relative to the human normal IgG control. The %Anti-proliferative activity of SB2 relative to IgG control ranged from 28 to 52%, that of US Remicade ranged from 28 to 46% and that of EU Remicade ranged from 33 to 48%. The quality ranges of US Remicade and EU Remicade were set as mean ± 3SD.

***Reviewer comment**: The regulatory macrophage induction activity and T-cell anti-proliferative activity of SB2 and US Remicade are similar. Given the fact that the regulatory macrophage, a specific subset of macrophage induced by infliximab, contributes to the resolution of chronic inflammation and the recovery of epithelial cell barrier in inflammatory bowel disease (IBD), similarity data from these two sets of experiments are important to support the similarity with respect to potential mechanisms of action related to IBD indications.*

3.2.R.4.2.4.6 Additional Biological Assays

The additional biological assays include: TNF-β binding, transmembrane TNF-α binding, ADCC using peripheral blood mononucleated cells (PBMC), FcγRIIIa (158F/F) binding assay, FcγRIIIa (158V/F) binding using NK cells from PBMC, FcγRIIIb binding using neutrophils, evaluation of regulatory macrophage function, cytokine release activity, and inhibitory activity of apoptosis in vitro IBD model. These biological assays were performed to further characterize SB2 and to assess the binding activity of FcγRIIIa using various conditions to evaluate activity in vitro models of inflammatory bowel diseases (IBD).

Review of each of the biological assays including data from the additional lots is summarized below:

1. TNF-β binding activity was determined by a FRET assay. Infliximab is known to bind to soluble and membrane bound TNF-α, but not to TNF-β.
2. ADCC using healthy donor PBMC assay was performed using peripheral blood mononuclear cells (PBMCs) from a healthy donor (158V/F) as effector cells and 3T3mTNF-α cells as target cells. This is an orthogonal method to the method presented in the Tier 2 section of the review that measures ADCC activity using NK92-CD16 cells as effector cells. *Reviewer note: ADCC with PBMC cells was previously discussed under the ADCC subsection of the Tier 2 attributes section.*
3. FcγRIIIa (158F/F) binding affinity was assessed using SPR assay. The FcγRIIIa (158V/F) binding activity was carried out with NK cells from PBMC, and the relative binding activity was detected using flow cytometry analysis. FcγRIIIb binding assay using neutrophils was determined by flow cytometry method. Results showed that the relative FcγRIIIb binding activity of SB2 ranged from 97 to 99%, US Remicade was 95% and EU Remicade was 96%. These data are consistent with the results of FcγRIIIb binding activity using the SPR method.

   Reviewer note: These results were previously discussed under the FcγRIIIa binding activity in the section of Tier 2 attributes.
4. Evaluation of regulatory macrophage function: it has been reported that regulatory macrophage (a specific subset of macrophage), which is induced by infliximab, contributes to the resolution of chronic inflammation and the recovery of epithelial cell barrier in inflammatory bowel disease (IBD). In addition, in order to confirm the capability of induced regulatory macrophage function, the T-cell anti-proliferation activity of samples in two-way MLR were evaluated. Overall, the regulatory macrophage induction activity and T-cell anti-proliferative activity of SB2 and US Remicade® was considered similar.
5. Inhibition of cytokine release in in vitro IBD model assessed the suppression of proinflammatory cytokine IL-8 released by TNF-α stimulated epithelial cells. Quality range approaches were taken for the similarity assessment, and cytokine release inhibition activity of SB2 and US Remicade was considered similar.
6. Inhibition of apoptosis in IBD model was assessed by suppression of caspase-3/7 activation mediated by TNF-α. Quality range approaches were taken for the similarity assessment, and apoptosis inhibition activity of SB2 and US Remicade was considered similar.

Reviewer comment: *The sponsor conducted these additional biological assays with 5-10 lots of SB2, and a total of 12 lots of reference product, Remicade. Quality range approach was applied for all the quantitative assays, and the results showed that SB2 and US Remicade were considered similar.*

Of note, 1) tier 3 transmembrane TNF-α binding and tier 2 apoptosis assay are the measurements for SB2-mediated reverse signaling. Because this is a potential mechanism of action, measurement of infliximab reverse signaling associated with mTNF-α is considered a Tier 2 attribute by the agency. The data showed similar activity between SB2 and Reference products; 2) support biological activities related to IBD indications, the sponsor specifically conducted similarity assessment between SB2 and reference products on evaluation of regulatory macrophage function, inhibition of cytokine release in vitro, and inhibition of apoptosis. Results support the similarity conclusion.

3.2.R.4.3.1 Comparative Stability Studies with SB2 and Remicade

Stability studies were carried out to demonstrate similarity in terms of the degradation profiles of SB2 and US Remicade. The comparative stability study was performed in accordance with guidelines ICH Q5C and ICH Q1A (R2).

3.2.R.4.3.1.1 Comparability stability of SB2 PVR DP and clinical DP with Remicade under stress condition

The sponsor conducted comparative degradation studies between SB2 PVR, clinical, and pilot lots with Remicade by measuring the following quality attributes:

- General properties (appearance, color, clarity, moisture, pH)
- Quantity
- Subvisible particulate matter
- Purity and impurities by SEC and nrCE-SDS
- Biological activity by TNF-α binding and neutralization
- Additional tests including Oxidation by LC-MS on Met18, Met34, and charge variants by iCIEF

In each comparative stability study under a stress condition, the degradation profiles of the following was compared and monitored during 6 months under stress (40 ± 2ºC, 75 ± 5% RH) storage conditions:

1) SB2 PVR DP as well as US and EU Remicade under stressed condition (Table 3.2.R.4-80)

Table 3.2.R.4–80. Sample Information for Comparative Stability of SB2 PVR DP and Remicade® under Stress Condition

Type	PVR Stability				
Material	SB2 PVR Batches			Remicade®	
	DP			US	EU
Batch Number	SB2-DP-14001	SB2-DP-14002	SB2-DP-14003	EBM12016P1	2RMA69101
Dose	100 mg/vial	100 mg/vial	100 mg/vial	100 mg/vial	100 mg/vial
Manufacture Date	Jul 2014	Jul 2014	Jul 2014	N/A	N/A
Expiry Date	TBD	TBD	TBD	Feb 2017	Oct 2015

The tests not showing significant changes during 6 month storage under stress conditions include appearance, pH, protein content, purity data by nrCE-SDS and charge variants by icIEF. Slight differences were observed in the initial %HMW by SEC (see SEC section of the similarity assessment above).

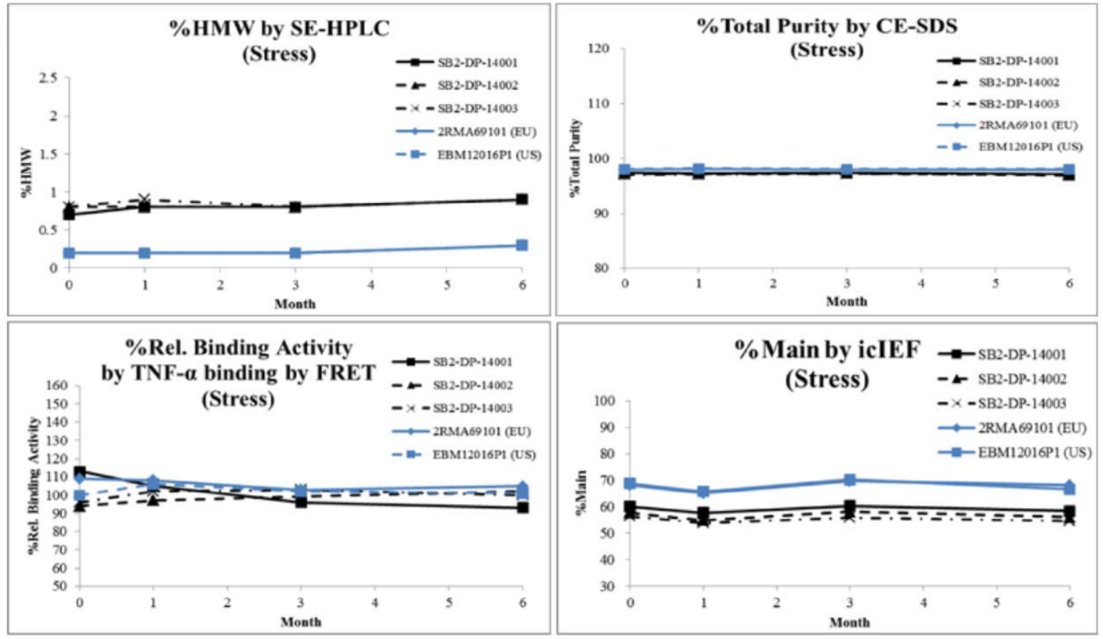


Figure 3.2.R.4–114. Comparative Stability Study Results of SB2 PVR DP and Remicade® under Stress Condition

2) SB2 Clinical DP and EU Remicade under stress condition (Table 3.2.R.4-87)

The degradation rates of SB2 clinical DP were similar to those of EU Remicade. The only differences observed include:

Total purity data tested by CE-SDS was slightly decreased during 6 months both for SB2 clinical DP (97.4-96.6%) and EU Remicade® (98.0-97.5%). Charge variants tested by icIEF showed decrease during 6 months under stress condition for both SB2 clinical DP and EU Remicade®. The relative content of main peak (%Main) of SB2 clinical DP decreased from 60.8% to 54.3% and that of EU Remicade® decreased from 72.0% to 66.7%, while the acidic and basic variants increased.

Table 3.2.R.4–87. Sample Information for Comparative Stability of SB2 Clinica DP and Remicade® under Stress Condition

Type	Clinical Stability	
Material	SB2 Clinical DP	EU Remicade®
Batch Number	P49202A	2RMA67101
Dose	100 mg/vial	100 mg/vial
Manufacture Date	Feb 2013	N/A[a]
Expiry Date	TBD[b]	Aug 2015

[a] Not applicable
[b] To be determined

3) SB2 pilot DP and EU Remicade under accelerated (25°C) and stressed condition(40°C) (Table 3.2.R.4-90)

No difference was observed for appearance, pH, osmolality, moisture, reconstitution time, and purity by SEC. The degradation rate of SB2 pilot DP were shown to be similar to that of EU Remicade. Charge variants tested by icIEF showed a decrease during 6 months under accelerated conditions in both SB2 pilot DP and EU Remicade. Relative content of main peak (%main) of SB2 pilot DP decreased from 58.4% to 57.4% and that of EU Remicade decreased from 71.9% to 70.8%, while the content of the acidic and basic variants increased accordingly.

Table 3.2.R.4–90. Sample Information for Comparative Stability of SB2 Pilot DP and Remicade® under Accelerated and Stress Conditions

Type	Developmental Stability	
Material	SB2 Pilot DP	EU Remicade®
Batch Number	PUR-R12-06-DP	0RMA67903 (for accelerated condition) 2RMKA81701 (for stress condition)
Dose	100 mg/vial	100 mg/vial
Manufacture Date	Aug 2012	N/A
Expiry Date	TBD	Sep 2013 May 2015

Overall, all the results at different time points conform to the pre-determined commercial stability acceptance criteria. The degradation rates of SB2 DP determined by CE-SDS, SEC and iCIEF are similar to that of EU Remicade.

Reviewer comment: *The sponsor paired one SB2 PVR, one SB2 clinical DP lot, and one SB2 pilot lot with EU Remicade for degradation and stability studies under stressed conditions. Results from each paired comparison study showed that similar degradation rates, indicating similar degradation mechanisms. All the testing results under stressed conditions up to the six month time point are all within the sponsor's predetermined criteria for the stability studies. There are only very slight decrease in the stability indicating attributes, including relative main peak by iCIEF and total purity by nrCE-SDS, over the six month study time under stress and accelerated conditions. The testing results of the quality attributes are highly similar between SB2 lots and EU Remicade lot.*

3.2.R.4.3.2 Forced Degradation Stability Study

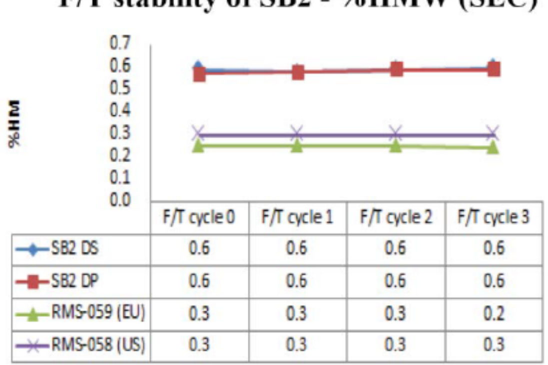
A forced degradation stability study was carried out to assess the similarity in degradation profiles between SB2 and Remicade®, in accordance with guideline ICH Q5C. The study was performed for SB2 pilot DS, DP and US and EU Remicade® under:

1) oxidation inducing conditions: the forced oxidation of Met residues to the sulfoxide form by hydrogen peroxide was assessed. SB2 and Remicade were treated with 0.1% of hydrogen peroxide for 3 to 6 hours, the Met oxidation rate was evaluated at each Met

residue (Met_{18} and Met_{34}, Met_{85}, and Met_{431}). The degree of oxidation of Met residues and the corresponding oxidation rate were similar between SB2 and US Remicade.

2) freeze-thaw cyclings: samples were stored at −70ºC for over 24 hours and thawed at 5°C for 3 hours. This freeze-thaw cycle was repeated three times to simulate the freeze-thaw cycle for analysis of sample and storage.

F/T stability of SB2 - %HMW (SEC)



	F/T cycle 0	F/T cycle 1	F/T cycle 2	F/T cycle 3
SB2 DS	0.6	0.6	0.6	0.6
SB2 DP	0.6	0.6	0.6	0.6
RMS-059 (EU)	0.3	0.3	0.3	0.2
RMS-058 (US)	0.3	0.3	0.3	0.3

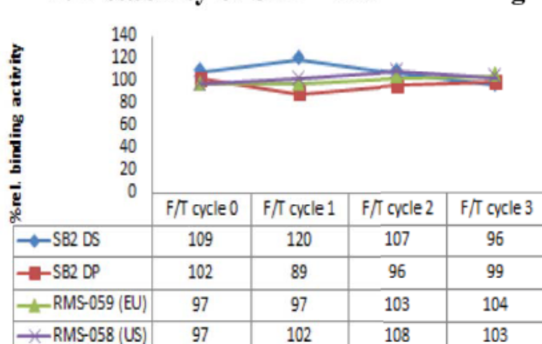
F/T stability of SB2 - %IgG (CE-SDS)

	F/T cycle 0	F/T cycle 1	F/T cycle 2	F/T cycle 3
SB2 DS	96.6	96.5	96.2	96.4
SB2 DP	96.3	96.1	96.5	96.0
RMS-059 (EU)	96.8	96.7	96.8	96.9
RMS-058 (US)	96.3	96.3	96.1	96.1

F/T stability of SB2 - %Main (icIEF)

	F/T cycle 0	F/T cycle 1	F/T cycle 2	F/T cycle 3
SB2 DS	58.2	58.1	59.9	60.8
SB2 DP	60.2	59	60.3	60.3
RMS-059 (EU)	73.7	73.4	74.1	73.9
RMS-058 (US)	71.4	72.4	71	72.5

F/T stability of SB2 - TNF-α binding



	F/T cycle 0	F/T cycle 1	F/T cycle 2	F/T cycle 3
SB2 DS	109	120	107	96
SB2 DP	102	89	96	99
RMS-059 (EU)	97	97	103	104
RMS-058 (US)	97	102	108	103

Figure 3.2.R.4–118. Freeze-thaw Cycling Results of SB2 and Remicade®

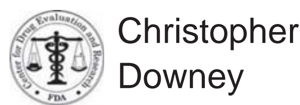
The results of SB2 and the US Remicade demonstrated that there were no changes on the purity/impurities and biological activity profiles in the freeze-thaw cycling study, which suggests similarity between SB2 and US Remicade.

3.2.R.4.3.3 Photostability of SB2 PVR DP and Remicade in immediate and Commercial Product Packaging

This study showed that SB2 PVR DP and US Remicade are not sensitive to the ICH Q1B option 2 light exposure in primary packaging (i.e. glass vials). No critical changes in oxidation rate and potency were observed.

Reviewer comment: *The sponsor provided up to six month comparability stability study data with SB2 pilot and clinical DP lots under stress and accelerated conditions. No product quality differences were observed in the comparability stability studies. Additionally, forced degradation studies under oxidation and freeze-thaw conditions revealed similar product*

quality profiles between SB2 and US Remicade. Together, results support the conclusion that SB2 and US Remicade shared similar stability profiles and degradation pathway.



Digitally signed by Christopher Downey
Date: 12/15/2016 03:44:02PM
GUID: 508da6d9000264ed71c49d80cfe4e31a

Digitally signed by Xianghong Jing
Date: 12/15/2016 02:47:06PM
GUID: 54983cd700435181eca33ebeed0ccdd1

BLA STN 761054

Product name: SB2

Samsung Bioepis Co., Ltd

Review of Drug Product CMC - Product Quality

Timothy Wadkins, PhD, Primary Reviewer
Christopher Downey, PhD, Team Leader

Office of Biotechnology Products
Division of Biotechnology Review and Research II

OBP CMC Review Data Sheet

1. **BLA#:** STN 761054

2. **REVIEW DATE:** December 15, 2016

3. **PRIMARY REVIEW TEAM:**

CDTL:	Nikolay Nikolov
Medical Officer:	Tara Altepeter
Product Quality Team:	Xianghong Jing (DS quality) Timothy Wadkins (DP quality) Christopher Downey (Application Technical Lead)
Immunogenicity:	William Hallett
Microbiology Drug Substance:	Bo Chi
Microbiology Drug Product:	Jessica Hankins
Facilities:	Wayne Seifert
CMC Statistics:	Yu-Ting Weng
Clinical Pharmacology:	Lei He
OBP Labeling:	Jibril Abdus-Samad
RPM:	Christine Ford (DPARP), Keith Olin (OPRO)

4. **MAJOR GRMP DEADLINES**

Filing 74 Day letter:	June 3, 2016
Mid-Cycle Meeting:	August 30, 2016
Wrap-Up Meeting:	December 12, 2016
Primary Review Due:	December 15, 2016
Secondary Review Due:	December 22, 2016
CDTL Review Due:	December 29, 2016
BSUFA Action Date:	January 21, 2017

5. **COMMUNICATIONS WITH SPONSOR AND OND:**

Communication/Document[1]	Date
Information Request	October 27, 2016
Information Request	November 23, 2016
Information Request	December 9, 2016

[1]Communications related to CMC-Product Quality information for Drug Product

6. **SUBMISSION(S) REVIEWED:**

Submission	Date Received	Review Completed (Yes/No)
Response to Information Request	November 7, 2016	Yes
Response to Information Request	December 1, 2016	Yes
Response to Information Request	December 14, 2016	Yes

7. DRUG PRODUCT NAME/CODE/TYPE:

a. Proprietary Name: SB2
b. Trade Name: Renflexis
c. Non-Proprietary/USAN: infliximab-xxxx (pending)
d. CAS name: 170277-31-3
e. INN Name:
f. Compendial Name: not applicable
g. OBP systematic name: MAB CHIMERIC (IGG1) ANTI P01375 (TNFA_HUMAN) [SB2]

8. PHARMACOLOGICAL CATEGORY:

Therapeutic recombinant human monoclonal antibody

9. DOSAGE FORM:

Injection

10. STRENGTH/POTENCY:

100 mg of lyophilized infliximab in a 20 mL vial for intravenous infusion

11. ROUTE OF ADMINISTRATION:

Subcutaneous injection

12. REFERENCED MASTER FILES:

DMF #	HOLDER	ITEM REFERENCED	LETTER OF CROSS-REFERENCE	COMMENTS (STATUS)
		(b) (4)	Yes	DMF is current and will comply with all statements made in it.
			Yes	DMF is current and will comply with all statements made in it.
			Yes	DMF is current and will comply with all statements made in it.

13. INSPECTIONAL ACTIVITIES

OBP did not participate in Drug Product inspectional activities.

14. CONSULTS REQUESTED BY OBP

None.

15. QUALITY BY DESIGN ELEMENTS

The following was submitted in the identification of QbD elements (check all that apply):

	Design Space
x	Design of Experiments
	Formal Risk Assessment / Risk Management
	Multivariate Statistical Process Control
	Process Analytical Technology
	Expanded Change Protocol

16. PRECEDENTS

None.

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

I recommend approval of this 351(k) Biologics License Application.

I recommend an expiration dating period of 30 months for SB2 Drug Product when stored at 2 − 8°C.

I recommend approval of the proposed release and shelf-life specifications for SB2 Drug Product.

II. List Of Deficiencies To Be Communicated

There are no CMC-Product Quality deficiencies precluding approval of this BLA

III. List Of Post-Marketing Commitments/Requirements

There are two Product Quality-related Post-Marketing Commitments, which will include due dates negotiated with the sponsor:

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

IV. Review Of Common Technical Document-Quality Module 1

A. Environmental Assessment Or Claim Of Categorical Exclusion:

The Claim of Categorical Exclusion was reviewed separately by Xianghong Jing as part of the Drug Substance product quality review.

V. Primary Container Labeling Review

The primary container labeling was reviewed separately by Jibril Abdus-Samad with concurrence by Xianghong Jing and Christopher Downey

VI. Review Of Common Technical Document-Quality Module 3.2

CTD Modules in 3.2.P are reviewed in this document. Modules 3.2.S, 3.2.R, and 3.2.A were reviewed separately by Xianghong Jing and Christopher Downey.

VII. Review Of Immunogenicity Assays – Module 5.3.1.4

The immunogenicity assays were reviewed separately by William Hallett and Christopher Downey.

TABLE OF CONTENTS

P DRUG PRODUCT 7
3.2.P.1 Description and Composition of the Drug Product 7
3.2.P.2 Pharmaceutical Development 7
- 3.2.P.2.1 Components of the Drug Product 7
- 3.2.P.2.2 Drug Product 8
- 3.2.P.2.3 Manufacturing Process Development 11
- 3.2.P.2.4 Container Closure System 23
- 3.2.P.2.5 Microbiological Attributes 33
- 3.2.P.2.6 Compatibility 33

3.2.P.3 Manufacture 33
- 3.2.P.3.1 Manufacturer(s) 33
- 3.2.P.3.2 Batch Formula 34
- 3.2.P.3.3 Description of Manufacturing Process and Process Controls 34
- 3.2.P.3.4 Controls of Critical Steps and Intermediates 36
- 3.2.P.3.5 Process Validation and/or Evaluation 38

3.2.P.4 Control of Excipients 46
- 3.2.P.4.1 and 3.2.P.4.4 Specifications and Justification 46
- 3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures 46
- 3.2.P.4.5 Excipients of Human or Animal Origin 46
- 3.2.P.4.6 Novel Excipients 47

3.2.P.5 Control of Drug Product 47
- 3.2.P.5.1, 2 and 6 Specification(s), Analytical Procedures, and Justification of Specification(s) 47
- 3.2.P.5.3 Validation of Analytical Procedures 50
- 3.2.P.5.4 Batch Analyses 53
- 3.2.P.5.5 Characterization of Impurities 54

3.2.P.6 Reference Standards or Materials 55
3.2.P.7 Container Closure System 55
- 3.2.P.7.1 Primary Packaging Materials 55
- 3.2.P.7.2 Secondary Packaging Materials 55

3.2.P.8 Stability 56
- 3.2.P.8.1 Stability Summary and Conclusion & 3.2.P.8.3 Stability Data 56
- 3.2.P.8.2 Post-Approval Stability Commitment 62

3.2.A Appendices Table of Contents 64
- 3.2.A.1 Facilities and Equipment 64
- 3.2.A.2 Adventitious Agents Safety Evaluation 64
- 3.2.A.3 Novel Excipients 64

3.2.R Regional Information (U.S.A.) 64
- 3.2.R.1 Executed Batch Records 64
- 3.2.R.2 Method Validation Package 65
- 3.2.R.3 Comparability Protocols 65

P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product

SB2 drug product (DP) is a sterile, white, lyophilized concentrate for intravenous injection. Lyophilized SB2 DP is reconstituted with 10 mL of sterile water for injection (WFI) to yield a single dose formulation of 10 mg/mL infliximab at pH 6.2, and is further diluted in 0.9% sodium chloride solution for infusion. One single-use vial contains infliximab as the active substance, and the excipients shown in the following table:

Table 3.2.P.1–1. Composition of SB2 DP

Component	Nominal Quantity/Vial	Function	Quality Standard
Infliximab	100 mg	Active substance	In-house[a]
Monobasic sodium phosphate monohydrate	5.55 mg	(b) (4)	USP-NF
Dibasic sodium phosphate heptahydrate	2.60 mg		USP-NF
Sucrose	500 mg		Ph. Eur./USP-NF
Polysorbate 80	0.5 mg		Ph. Eur./USP-NF
Water for Injection[b]	*q.s.*		Ph. Eur./USP-NF

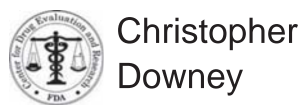
[a] Specification of SB2 DS (infliximab) is provided in Section 3.2.S.4.1 Specification.
[b] WFI evaporates during SB2 DP manufacturing process.

SB2 DP does not contain preservatives. (b) (4) DP manufacture consists of (b) (4) (see Section 3.2.P.3 below).

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

58 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page



Christopher Downey

Digitally signed by Christopher Downey
Date: 12/15/2016 04 07:32PM
GUID: 508da6d9000264ed71c49d80cfe4e31a

Timothy Wadkins

Digitally signed by Timothy Wadkins
Date: 12/15/2016 04 00:18PM
GUID: 55919d6600e16c43f14b0f7f7c1732bc

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Division of Biotechnology Research and Review II
Silver Spring, MD 20903

Memorandum of Review

STN:	BLA 761054
Subject:	Immunogenicity Review
Date:	7/22/2016
Review/Revision Date:	10/04/2016
Primary Reviewer:	William Hallett, PhD
Secondary Reviewer:	Christopher Downey, PhD, Team Leader
RPM:	Keith Olin
Applicant:	Samsung Biologics
Product:	SB2 – a proposed biosimilar to Infliximab
Indication:	Same as for infliximab
Received:	**7**/22/2016

EXECUTIVE SUMMARY

The assays submitted to support the immunogenicity portion of the SB2 biosimilar were adequately validated. The sponsor used one screening assay for anti-drug antibodies (ADA) for the two studies, SB2-G11-NHV and SB2-G31-RA. The sponsor then used a cell-based assay for neutralizing antibodies (Nabs) in SB2-G11-NHV and a ligand binding assay for SB2-G31-RA. The validation reports for all three assays were reviewed and found to be acceptable. The screening assay had adequate sensitivity and drug tolerance, two often problematic areas for these assays. The NAb assays are adequate to make determinations of neutralizing activity.

I. REVIEW – Immunogenicity

5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

The analysis of anti-drug antibody (ADA) using a single bridging ligand binding assay (with SB2 as the ligand) was used for the determination of ADAs in the clinical "Phase I" study in normal healthy subjects (SB2-G11-NHV) and "Phase III" study of rheumatoid arthritis (SB2-G31-RA). This assay was part of a typical 3-tiered approach of a screening assay, a confirmatory assay, and a NAb assay. The sponsor then used two different neutralizing assays, one cell-based assay for the SB2-G11-NHV study and a ligand binding assay for the SB2-G31-RA study.

Screening Assay

Reviewer Note: *Information for the screening assay came from 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods and from validation reports located in 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies*

The sponsor used a single bridging ligand-binding ECL assay was used for determination of ADAs in the SB2-G11-NHV and SB2-G31-RA. Clinical samples were pre-treated by acid-dissociation to reduce drug interference. The positive controls were either an affinity purified monkey anti-SB2 polyclonal or human anti-Remicade monoclonal antibodies. The assay was validated with both SB2 and Remicade. The results below show the two assays perform comparably with either anti-SB2 or anti-Remicade antibodies, in either normal healthy serum (NHS) or rheumatoid arthritis (RA) serum.

Table 2.7.1.1-8. Comparison of Relative Sensitivity between SB2 and Remicade® Assay in the Method Validation for the Clinical Phase III Study

Parameter	ADA Assay		NAb Assay	
	SB2 Assay	Remicade® Assay	SB2 Assay	Remicade® Assay
Relative sensitivity	82.7 ng/mL in NHS (anti-SB2 antibodies)	32.4 ng/mL in NHS (anti-SB2 antibodies)	2777 ng/mL in NHS (anti-SB2 antibodies)	3280 ng/mL in NHS (anti-SB2 antibodies)
	14.8 ng/mL in NHS (anti-Remicade® antibodies)	11.2 ng/mL in NHS (anti-Remicade® antibodies)	424 ng/mL in NHS (anti-Remicade® antibodies)	509 ng/mL in NHS (anti-Remicade® antibodies)
	386 ng/mL in RA (anti-SB2 antibodies)	172 ng/mL in RA (anti-SB2 antibodies)	2678 ng/mL in RA (anti-SB2 antibodies)	6824 ng/mL in RA (anti-SB2 antibodies)
	77.3 ng/mL in RA (anti-Remicade® antibodies)	46.1 ng/mL in RA (anti-Remicade® antibodies)	555 ng/mL in RA (anti-Remicade® antibodies)	942 ng/mL in RA (anti-Remicade® antibodies)

Source: Report No. IYZ5 Table 10 (ADA assay); Report No. RCDA2 Table 14 (NAb assay)

Reviewer Comment*: I agree with the sponsor's assessment that the assay performs comparably with either SB2 or Remicade when using either NHS or RA serum. The sensitivities are approximately 2 fold different with the SB2 or Remicade assay within the NHS or within the RA serum assays. There is no clear explanation for these differences, but a possible explanation is the difference in the preparation of the infliximab (SB2) and the EU-Remicade that was used in the assay validation. The differences between the anti-SB2 vs the anti-Remicade antibodies are likely to differing affinities of the polyclonal anti-SB2 and the monoclonal anti-Remicade. These small differences between the SB2 and Remicade-specific assays are not consequential as both are well below the current recommended limit of 500 ng/mL and both could easily detect clinically meaningful antibody responses. Therefore, the sensitivity of both the screening and the Nab assays is acceptable.*

The results for the assay validation of the screening assay performed by PPD are provided in the table below.

Reviewer Comment: The two validation reports for the screening assay (titled 'iyz2' and 'iyz5' in Section 5.3.1.4 of the eCTD), were reviewed in detail by the primary reviewer.

Iyz2 was the initial validation that only used anti-SB2 antibodies as positive controls for validation. Iyz5 used both anti-SB2 and anti-Remicade positive control antibodies in the validation and was performed a year later. A summary of the validation report from izy5 is provided below.

Anti-Infliximab Antibodies in Human Serum

<table>
<tr><th>Validation Parameter</th><th colspan="4">Validation Result</th></tr>
<tr><td>MRD</td><td colspan="4">None</td></tr>
<tr><td>Assay Sample Volume</td><td colspan="4">20.0 µL</td></tr>
<tr><td rowspan="2">PC Levels (anti-Infliximab, lot N12033-2)</td><td>PC2
(HPC)</td><td>PC3
(LPC)</td><td colspan="2">PC4
(LPC corrected)</td></tr>
<tr><td>10000 ng/mL</td><td>77.0 ng/mL</td><td colspan="2">128 ng/mL</td></tr>
<tr><td>Matrix</td><td colspan="4">Human Serum</td></tr>
<tr><td>Sample Storage Temperature</td><td colspan="4">-80 ºC ± 10 ºC</td></tr>
<tr><td>Precision</td><td>NC</td><td>PC2</td><td>PC3</td><td>PC4</td></tr>
<tr><td>Intra-assay</td><td>5.78%</td><td>10.2%</td><td>10.6%</td><td>6.44%</td></tr>
<tr><td>Inter-assay</td><td>26.0%</td><td>22.5%</td><td>17.0%</td><td>14.7%</td></tr>
<tr><td>Normalization Factor for Commercial Normal Human Serum (for screening cut point)</td><td colspan="4">2.064 (additive, square root transformed NC mean)</td></tr>
<tr><td>Normalization Factor for Pre-Dose Human Serum (for screening cut point)</td><td colspan="4">42.15 (additive)</td></tr>
<tr><td>Concentration of SB2 (confirmatory testing)</td><td colspan="4">1.00 µg/mL</td></tr>
<tr><td>Specificity/Confirmatory Cut Point for Commercial Normal Human Serum</td><td colspan="4">52.800%</td></tr>
<tr><td>Specificity/Confirmatory Cut Point for Pre-Dose Human Serum</td><td colspan="4">52.742%</td></tr>
<tr><td>Mean Assay Sensitivity (screening assay)</td><td colspan="4">64.1 ng/mL</td></tr>
<tr><td>Prozone Effect</td><td colspan="4">No apparent hook effect observed at concentrations up to 80.0 µg/mL</td></tr>
<tr><td>Drug Tolerance</td><td colspan="4">100 µg/mL SB2 at 77.0 and 10000 ng/mL anti-infliximab</td></tr>
<tr><td>Recovery/Selectivity</td><td colspan="4">Recovery acceptable with ten out of ten unspiked blank individual lots below the PSCP.
Recovery acceptable for LPC with eight of ten individual lots within 75-125% of plate acceptance.
Seven out of ten individual lots within 75-125% of plate acceptance for HPC.</td></tr>
<tr><td>Drug Comparison</td><td colspan="4">SB2, EU Remicade®, and US Remicade® comparison acceptable.</td></tr>
<tr><td>Hemolysis</td><td colspan="4">No effect from hemolysis on the detection of anti-infliximab antibodies at 10000 and 128 ng/mL.[1]</td></tr>
<tr><td>Lipemia</td><td colspan="4">No effect from lipemia on the detection of anti-infliximab antibodies at 10000 and 128 ng/mL.[1]</td></tr>
<tr><td>Freeze/Thaw Stability</td><td colspan="4">Five cycles thawed at room temperature</td></tr>
<tr><td>Thawed Matrix Stability</td><td colspan="4">24 hours at room temperature</td></tr>
<tr><td>Frozen Matrix Stability</td><td colspan="4">10 days at -25 °C ± 5 °C and 34 days at -80 °C ± 10 °C</td></tr>
</table>

[1] Replicates of HEMPC 3 and LPPC 3 (77.0 ng/mL) were < PSCP although this LPC level was not the final, correct LPC level.

***Reviewer Comments*:**

1. *Regarding the minimum required dilution (MRD), the sponsor did not use an MRD. The impact of lipids and hemolysis to affect LPC was assessed during validation and no impact of lipids or hemolysis was observed for LPC levels down to 77.0 ng/mL. This relative lack of impact from matrix components is adequate,*

as there is no effect attributable to matrix interference; therefore, the lack of an MRD is acceptable.

2. *The sensitivity/drug tolerance of the assay was down to an ADA sensitivity of 77ng/mL in the presence of up to 100 μg/mL SB2. This is better than the recommended sensitivity of 250-500 ng/mL found in the FDA 2009 Draft Guidance for Industry "Assay Development for Immunogenicity Testing of Therapeutic Proteins" and it is acceptable.*
3. *The selectivity, robustness, and stability of the assay were all successfully validated. Additionally, no matrix effects were observed.*

Screening and Confirmatory Cut Points

50 individual lots of NHS (25 male, 25 female) were analyzed in the presence or absence of 1.00 μg/mL SB2. For the screening cut point, a parametric approach was used to calculate the floating cut point. The samples were divided into five panels for analysis, and because the means of each panel were not the same, the sponsor opted to use a normalization correction factor (i.e. 'floating cut point'). The sponsor used a 5% false positive rate to determine the assay normalization factor. The normalization factor is added to the mean of the square root transformed negative control replicates on each plate, and subsequently back transforming the data to the Relative Light Unit (RLU) scale.

Reviewer Comment*: The sponsor's approach to using NHS for the SB2-G11-NHV study is acceptable. The use of a floating cut point is appropriate given the details of the sponsor's cut point analysis and acceptable. There are no review issues with the screening cut point.*

For the confirmatory cut point, the inhibited (with excess product) and uninhibited samples were used to determine the % Signal Inhibition, where %SI = 100 x (1-ratio [Inhibited/Uninhibited]. The sponsor used a parametric approach to determine the confirmatory cut point with a 99.9% confidence interval. Each sample was considered positive if the percent inhibition was ≥ 52.8%.

Reviewer Comment*: We generally recommend sponsor's use a 99.0% confidence interval on the confirmatory assay. However, there is no formal rule or guidance on this. A potential issue with the confidence interval used for the confirmatory assay in SB2-G11-NHV was identified by OSIS during inspection of the testing facility. The sponsor was notified that FDA recommends a 99.0% CI during inspection, performed the analysis both with a 99.9% or 99.0% CI, and found additional 9 patients in their study samples that would be considered positive if a 99.0% CI had been used. These 9 patients were relatively equally divided among the 3 arms of the study, and the difference in the numbers of subjects identified as ADA-positive would not make a decision difference in regards to the biosimilarity of SB2.*

The primary reviewer's opinion, and agreed to by the Quality, Clinical, and Clinical Pharmacology review teams, is that there would be no difference in the approvability of

SB2 based on the updated analysis using a 99.0% CI because the additional samples identified as ADA-positive are mostly equally distributed. Therefore, the data obtained with the 99.9% CI is acceptable for the purposes of biosimilarity.

Neutralizing Antibody (NAb) assay(s)

The sponsor used two different Nab assays. A cell-based assay (validation report: JYZ2) was used for the SB2-G11-NHV (the "Phase I" study) and a ligand binding assay (validation report: RCDA2) was used for SB2-G31-RA (the "Phase III" study).

Reviewer Comments:

1. *The use of a ligand binding assay is not typical, but historically has been acceptable for anti-TNF products whose MOA is to bind to free TNFα and is mimicked well by the ligand binding assay.*

2. *The ligand binding assay, with its lack of complications caused by having a cell mediator, is a 'better' assay in that it's generally more reproducible, and in this case, has improved drug tolerance when compared to the cell-based assay. The sensitivity of the two assays was comparable. The use of two assays, each with an adequate validation, is acceptable.*

Cell-Based Nab Assay used for SB2-G11-NHV

The sponsor's neutralization assay used for SB2-G11-NHV was a cell-based assay. A549 cells expressing the TNF-α receptor, upon engagement by TNFα, lead to downstream signaling events including phosphorylation of NF-κB. The sponsor generated cell lysates from A549 cells and used a Meso Scale Discovery (MSD) platform that was specific for detecting phosphorylated NK-κB. Cells stimulated with TNF-α would produce positive results, and neutralizing antibodies, if present, would result in diminished signals. This assay was capable of detecting 250 ng/mL of NAbs in human serum, and in the presence of 100 ng/mL residual drug product in serum, the assay was capable of detecting 4,000 ng/mL of NAbs.

Summary of Assay Parameters

<table>
<tr><td>Species/Matrix:</td><td colspan="5">Healthy Human Serum</td></tr>
<tr><td>Analysis Method:</td><td colspan="5">Electrochemiluminescent measurement using Meso-Scale Discovery NF-κB kit</td></tr>
<tr><td>Data Capture of RLU (ECL)</td><td colspan="5">MSD Sector Imager 6000</td></tr>
<tr><td>Additional Data Analysis and Calculations:</td><td colspan="5">MSD 3.0.18, Microsoft® Excel 2003 and 2010, Assist LIMS</td></tr>
<tr><td>Screening Assay Cut Point</td><td colspan="5">≥ 1.04 (upper bound 95.0% limit of prediction interval)</td></tr>
<tr><td>Specificity Assay Cut Point</td><td colspan="5">< 1.83 (upper bound 99.0% limit of prediction interval).</td></tr>
<tr><td>Minimum Required Dilution</td><td colspan="5">4:5 (80% serum, starting concentration)</td></tr>
<tr><td>Cell Passage Limit</td><td colspan="5">Passages 11 to 33 determined during validation</td></tr>
<tr><td rowspan="4">Precision across PCs</td><td></td><td colspan="3">LPC/DC</td><td>HPC/DC</td></tr>
<tr><td>Concentration (ng/mL)</td><td>250</td><td>500</td><td>1000</td><td>4000</td></tr>
<tr><td>Inter-assay (%CV)</td><td>5.93</td><td>7.16</td><td>13.3</td><td>11.5</td></tr>
<tr><td>Intra-assay (%CV)</td><td>N/A</td><td>3.18</td><td>N/A</td><td>11.4</td></tr>
<tr><td>Relative Assay Sensitivity</td><td colspan="5">250 ng/mL, although 500 ng/mL was reliably detected.</td></tr>
<tr><td>Selectivity</td><td colspan="5">80% of the unspiked healthy human serum individuals had an overall result of "negative."
90% of the samples spiked at the LPC had an overall result of "positive."
90% of the samples spiked at the HPC level had an overall result of "positive."</td></tr>
<tr><td>Drug Tolerance</td><td colspan="5"></td></tr>
<tr><td>4000 ng/mL PC</td><td colspan="5">Neutralizing antibodies can be detected in samples in the presence of up to 100 ng/mL of excess SB2.</td></tr>
<tr><td>500 ng/mL PC</td><td colspan="5">Neutralizing antibodies can be detected in samples in the presence of up to 25.0 ng/mL of excess SB2.</td></tr>
<tr><td>250 ng/mL PC</td><td colspan="5">Neutralizing antibodies cannot be detected in samples in the presence of up to 25.0 ng/mL of excess SB2. The actual excess SB2 concentration in which this PC level is still neutralizing was not determined during validation.</td></tr>
<tr><td>Drug Comparison</td><td colspan="5">500 ng/mL anti-infliximab can be detected across SB2 (biosimilar), US Remicade® (originator), and EU Remicade® (originator)</td></tr>
<tr><td>Thawed Matrix Stability</td><td colspan="5">24 hours at room temperature and 2-8 °C</td></tr>
<tr><td>Freeze/Thaw Stability</td><td colspan="5">Five cycles</td></tr>
<tr><td>Frozen Matrix Stability</td><td colspan="5">32 days (LPC) and 39 days (HPC) at -80 °C ± 10 °C</td></tr>
<tr><td>Hemolysis Interference</td><td colspan="5">Hemolyzed serum samples with greater than 1% hemolysis demonstrated interference in this assay.</td></tr>
<tr><td>Lipemia Interference</td><td colspan="5">No effect from lipemia on the detection of neutralizing antibodies to Infliximab (SB2)</td></tr>
</table>

The assay used a cut-point system similar to what is seen in screening cut points. The assay has a 'screening' cut point that is used to determine if a sample is putative positive (based on a 95% FDR) and a 'specificity assay cut point' that involves confirming if neutralizing effects are specific to the drug and not caused by signal/noise (S/N) ratio that occurs in samples in the absence of drug. This determination of the specificity assay cut point is based on the upper bound of the 99.0% confidence interval. Assay results greater than the screening assay cut point are considered 'putative positive' and tested against the 'specificity assay cut point' where the results are then classified as 'positive' or 'negative.' The combined results of the two analyses determine if a sample is positive for neutralizing antibodies.

Reviewer Comments:

1. *The assay sensitivity of 250 ng/mL, neat, or 4,000 ng/mL in 100 ng/mL of excess SB2, is typical for sensitivity of cell-based Nab assays, and should be capable of adequately detecting Nabs; therefore, this sensitivity is acceptable.*
2. *The validated precision is very good at <13.3% CV.*
3. *The sponsor's approach to the cut point(s) is not typical, but there is nothing fundamentally wrong with the sponsor's approach as it ostensibly uses a 99.0% confidence approach to determining NAbs which is the FDA's recommended approach. This assay is capable of accurately making a call on the neutralizing activity of an ADA sample and is therefore acceptable.*

Ligand Binding Nab Assay used for SB2-G31-RA

The Nab assay used for SB2-G31-RA is an electrochemiluminescence (ECL) method. Samples are acid treated to remove Ab:drug conjugates and neutralized. Streptavidin coated plates are coated with biotinylated SB2 (BT-SB2). Samples are detected with Sulfo-TAG-labeled rhTNFα (TNFα-Ru) to form a BT-SB2-TNFα-Ru complex in the absence of neutralizing antibodies. Samples with NAbs will bind to biotinylated SB2 and prevent the TNFα-Ru from binding, resulting in a diminished signal.

The summary of the validation for this assay is presented on the following page.

Cut Point

The cut point for the assay was determined by a robust statistical approach. Sera from 50 healthy subjects were assessed by two analysts on separate days. The sponsor performed Outlier determination using the non-transformed data, normality distribution using non-transformed data, investigated the homogeneity of the means and variances, and determined the cut point using a 99.9% prediction interval.

Reviewer Comment*: We generally prefer the 99.0% interval for Nab assays, but the approach used for this analysis is sufficiently robust. The assessment of NAbs for anti-infliximab antibodies generally produces data that indicate that all or nearly all ADAs for both SB2 and Remicade are neutralizing. This finding is based on the fact that ADA's tend to be specific for the murine variable region of the chimeric antibody, and ADA's specific to this portion of the antibody will prohibit binding to TNF-α. The analysis performed by this Sponsor provided a similar conclusion with a high NAb rate among the ADA-positive patients. Therefore, while the assessment of NAbs is not ideal, the results are in agreement with published data and with what we know from other biosimilar applicants and are acceptable.*

Sensitivity

Assay sensitivity was investigated with anti-Remicade and anti-SB2 positive control antibodies in both NHS and RA serum; the ligand remains biotin-SB2 in all assays. The assay's sensitivity determined using anti-SB2 antibodies was 2777 ng/mL in NHS and

2678 ng/mL for RA serum, and the sensitivity determined using anti-Remicade antibodies was 424 ng/mL and 555 ng/mL in NHS and RA serum, respectively.

***Reviewer Comment**: The sensitivity of this assays is typical for this type of assays, and the difference between the two PCs is not surprising because they were generated independently and because the anti-Remicade was a mAb while the anti-SB2 is a pAb. The overall assessment of sensitivity is acceptable.*

Bioanalytical Method Validation Summary
Neutralizing Anti-SB2 and Anti-Remicade® Antibodies in Human Serum

(b) (4) **Project Code**	RCDA2	
Method ID	ICDIM 178	
Analyte	Neutralizing Anti-SB2 and Anti-Remicade® Antibodies	
MRD	None	
Matrix	Human Serum (healthy human and RA serum)	
Method Description	Electrochemiluminescent	
Sample Volume (µL)	35-µL	
Sample Storage Temperature	-80 °C ± 10 °C	
Assay Cut Point for Commercial Normal Human Serum (SNR)	0.713	
Assay Cut point for Pre-Dose Human Serum (SNR)	0.751	
Mean Assay Sensitivity using: Anti-SB2 antibody in NHS Anti-SB2 antibody in RA serum Anti-Remicade® antibody in NHS Anti-Remicade® antibody in RA serum	 2777 ng/mL 2678 ng/mL 424 ng/mL 555 ng/mL	
PC Levels in NHS (anti-Remicade® antibody, lot 0813)	HPC (PC13) 10000 ng/mL	LPC (PC12) 739 ng/mL
PC Levels in RA Serum (anti-Remicade® antibody, lot 0813)	HPC (PC14) 10000 ng/mL	LPC (PC10) 739 ng/mL
PC Levels in NHS (anti-SB2 antibody, lot N13049-2)	HPC (PC16) 25000 ng/mL	LPC (PC19) 4713 ng/mL
PC Levels in RA Serum (anti-SB2 antibody, lot N13049-2)	HPC (PC18) 25000 ng/mL	LPC (PC20) 4713 ng/mL
Drug Tolerance	Up to 10.0 µg/mL of SB2 and 10.0 µg/mL of Remicade® at 4713 ng/mL of anti-SB2 antibody spiked into RA serum, up to 40.0 µg/mL of SB2 and 40.0 µg/mL of Remicade® at 25000 ng/mL of anti-SB2 antibody spiked into RA serum, up to 5.00 µg/mL of SB2 and 5.00 µg/mL of Remicade® at 739 ng/mL of anti-Remicade® antibody spiked into RA serum, up to 40.0 µg/mL of SB2 and 40.0 µg/mL of Remicade® at 10000 ng/mL of anti-Remicade® antibody spiked into RA serum.	

Precision (%) (ECL value)	NC	PC12	PC13	PC16	PC19
Intra-assay in NHS	N/A	3.98	2.09	7.02	6.30
Inter-assay in NHS	19.9	9.40	11.8	N/A	N/A
Precision (%) (SNR)	NC	PC12	PC13	PC16	PC19
Intra-assay in NHS	N/A	3.98	2.10	7.02	6.30
Inter-assay in NHS	N/A	6.58	5.82	N/A	N/A
Precision (%) (ECL value)	NC	PC10	PC14	PC18	PC20
Intra-assay in RA serum	N/A	3.98	4.89	10.2	5.39
Precision (%) (SNR)	NC	PC10	PC14	PC18	PC20
Intra-assay in RA serum	N/A	3.98	4.89	10.2	5.39

Selectivity	Blank selectivity acceptable with ten out of ten unspiked blank individual lots of RA serum above the cut point (classified as negative). Spiked selectivity acceptable for LPC and HPC prepared with anti- Remicade® antibody with ten of ten individual lots of RA serum tested positive (below the RA cut point). Spiked selectivity acceptable for HPC prepared with anti-SB2 antibody with ten of ten individual lots of RA serum tested positive (below the RA cut point). Spiked selectivity acceptable for LPC prepared with anti-SB2 antibody with eight of ten individual lots of RA serum tested positive (below the RA cut point).
TNFα Interference	No interference of TNFα at 0.100 or 0.500 ng/mL in LPC or HPC spiked with anti-SB2 or anti-Remicade® antibody in NHS or RA serum.
Hemolysis	No apparent effect from hemolysis on the detection of anti-SB2 and anti-Remicade® antibodies in NHS.
Lipemia	No apparent effect from lipemia on the detection of anti-SB2 and anti-Remicade® antibodies in NHS.
Analyte Stability in Thawed Matrix in NHS (hrs)	24 hours at room temperature
Freeze-thaw Stability in NHS (cycles)	Five cycles thawed at room temperature

***Reviewer Comments**:*

1. *The details of the validation (found in RCDA2) were examined in greater detail that what needs to be in this review. A few highlights of the validation are presented below.*
2. *The assay was validated with PC antibodies against both SB2 and Remicade. Not surprisingly, the two PCs which were generated separately have different affinities, and PC to PC comparisons are not important. The SB2 PC antibody shows significantly less sensitivity than the anti-Remicade, but both are adequate considering that neutralizing antibodies will be much higher titer than non-neutralizing antibodies, typically. Also, using the anti-Remicade PC, this assay is demonstrated to have very good sensitivity, and can adequately detect patient samples that may have NAbs. Therefore, the sensitivity of this assay using the anti-Remicade PC is acceptable.*
3. *The assay showed minimal matrix effects including matrix effects caused by elevated levels of TNFα in the serum of RA patients.*
4. *Other typical validation parameters, including robustness (via freeze-thaw LPC and HPC), precision, and selectivity were all adequately performed.*
5. *The sponsor provided an adequate validation of the neutralizing assay that was used for the RA study. This validation of the neutralizing assay is acceptable.*

Digitally signed by Christopher Downey
Date: 12/15/2016 02 59:59PM
GUID: 508da6d9000264ed71c49d80cfe4e31a

Digitally signed by William Hallett
Date: 12/15/2016 01:12:49PM
GUID: 5317e2c20000ce395db4bc0c4cf39411