

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761066Orig1s000

PRODUCT QUALITY REVIEW(S)



U.S. FOOD & DRUG
ADMINISTRATION

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Biotechnology Products

LABELS AND LABELING REVIEW

Date of review:	April 22, 2019
Reviewer:	Vicky Borders-Hemphill, PharmD Labeling Review Specialist Office of Biotechnology Products (OBP)
Through:	Brian Janelsins, PhD, Product Quality Reviewer OBP/Division of Biotechnology Review and Research I
Application:	BLA 761066
Applicant:	Samsung Bioepis Co., Ltd.
Submission Date:	October 25, 2018
Product:	Eticovo (etanercept-ykro)
Dosage form(s):	Injection
Strength and Container-Closure:	25 mg/0.5 mL and 50 mg/mL in single-dose prefilled syringe
Purpose of review:	The Applicant submitted a biologics license application for Agency review.
Recommendations:	The prescribing information, medication guide, instructions for use, and carton labeling (submitted on April 19, 2019) and container labels (submitted on April 5, 2019) were reviewed and found to be acceptable (see Appendix C) from an OBP labeling perspective.

Materials Considered for this Label and Labeling Review	
Materials Reviewed	Appendix Section
Proposed Labels and Labeling	A
Evaluation Tables	B
Acceptable Labels and Labeling	C

n/a = not applicable for this review

DISCUSSION

We evaluated the proposed labels and labeling for compliance with applicable requirements in the Code of Federal Regulations (see Appendix B).

CONCLUSION

The prescribing information, medication guide, instructions for use, and carton labeling (submitted on April 19, 2019) and container labels (submitted on April 5, 2019) were reviewed and found to be acceptable (see Appendix C) from an OBP labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

Prescribing Information/Medication Guide (submitted on October 25, 2018

<\\cdsesub1\evsprod\bla761066\0038\m1\us\114-labeling\114a-draft-label\draft-labeling-text-redline.pdf>)

Instructions for Use (submitted on October 25, 2018

<\\cdsesub1\evsprod\bla761066\0038\m1\us\114-labeling\114a-draft-label\pfs-instructions-for-use.pdf>)

Appendix B: Evaluation Tables

Evaluation Tables: Label^{1,2} and Labeling³ Standards

Container⁴ Label Evaluation

Proper Name <i>(for container of a product capable of bearing a full label)</i>	Acceptable
21 CFR 610.60, 21 CFR 201.50, 21 CFR 201.10	☐ Yes ☐ No ☒ N/A
<i>Recommended labeling practices (placement of dosage form below the proper name):</i>	☐ Yes ☐ No ☒ N/A
Manufacturer name, address, and license number <i>(for container of a product capable of bearing a full label)</i>	Acceptable
21 CFR 610.60 (a)(2), 21 CFR 201, 21 CFR 201.1(a), 21 CFR 201.1(h)(5), 21 CFR 201.1(h)(6), 21 CFR 201.100(e)	☐ Yes ☐ No ☒ N/A
<i>Recommended labeling practices (using the following qualifying statement "Manufactured by:"):</i>	☐ Yes ☐ No ☒ N/A
Lot number or other lot identification <i>(container capable of bearing a full label shall bear)</i>	Acceptable
21 CFR 610.60, 21 CFR 201.18, 21 CFR 201.100	☐ Yes ☐ No ☒ N/A
Expiration date <i>(container capable of bearing a full label shall bear)</i>	Acceptable
21 CFR 610.60, 21 CFR 201.17	☐ Yes ☐ No ☒ N/A
<i>Recommended labeling practices (the expiration date appears on all aspects of the package):</i>	☐ Yes ☐ No ☒ N/A
Product Strength	Acceptable
21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	☒ Yes ☐ No ☐ N/A

¹ Per 21 CFR 1.3(b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.

² Per 21 CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.

³ Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.

⁴ Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.

<i>Recommended labeling practices (expression of strength for injectable drugs): Reference: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 176 USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A
Multiple dose containers <i>(recommended individual dose)</i>	Acceptable
21 CFR 610.60, 21 CFR 201.55	☐ Yes ☐ No ☒ N/A
Statement: "Rx only"	Acceptable
21 CFR 610.60, 21 CFR 201.100	☒ Yes ☐ No ☐ N/A
Recommended labeling practices: <i>prominence of Rx Only</i>	☒ Yes ☐ No ☐ N/A
Medication Guide	Acceptable
21 CFR 610.60, 21 CFR 208.24	☐ Yes ☐ No ☒ N/A
No Package for container	Acceptable
21 CFR 610.60	☐ Yes ☐ No ☒ N/A
Proper Name <i>(for container bearing a partial label)</i>	Acceptable
21 CFR 610.60, 21 CFR 201.10	☒ Yes ☐ No ☐ N/A
Manufacturer name, address, and license number <i>(for container bearing a partial label)</i>	Acceptable
21 CFR 610.60, 21 CFR 201.10	☒ Yes ☐ No ☐ N/A
Recommended labeling practices: <i>(U.S license number for container bearing a partial label)</i>	☒ Yes ☐ No ☐ N/A
Lot number or other lot identification <i>(for container bearing a partial label)</i>	Acceptable
21 CFR 610.60, 21 CFR 201.10	☒ Yes ☐ No ☐ N/A
Expiration date <i>(for container bearing a partial label)</i>	Acceptable
21 CFR 201.17	☒ Yes ☐ No ☐ N/A
No container label	Acceptable

21 CFR 610.60	☐ Yes ☐ No ☒ N/A
<u>Ferrule and cap overseal (for vials only)</u>	<u>Acceptable</u>
<i>Recommended labeling practices: United States Pharmacopeia (USP), General Chapters: <7> Labeling (Ferrules and Cap Overseals)</i>	☐ Yes ☐ No ☒ N/A
<u>Visual inspection (for vials only)</u>	<u>Acceptable</u>
21 CFR 610.60(e)	☐ Yes ☐ No ☒ N/A
<u>NDC numbers</u>	<u>Acceptable</u>
21 CFR 201.2, 21 CFR 207.35	☒ Yes ☐ No ☐ N/A
<u>Route of administration</u>	<u>Acceptable</u>
21 CFR 201.5, 21 CFR 201.100	☒ Yes ☐ No ☐ N/A
Recommended labeling practices: route of administration statement to appear after the strength statement on the principal display panel	☒ Yes ☐ No ☐ N/A
<u>Preparation instructions</u>	<u>Acceptable</u>
21 CFR 201.5	☐ Yes ☐ No ☒ N/A
Recommended labeling practices: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430)	☐ Yes ☐ No ☒ N/A
<u>Package type term</u>	<u>Acceptable</u>
<i>Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. USP chapter <659> Packaging and Storage Requirements</i>	☐ Yes ☐ No ☒ N/A
<u>Misleading statements</u>	<u>Acceptable</u>
21 CFR 201.6	☒ Yes ☐ No ☐ N/A
<u>Prominence of required label statements</u>	<u>Acceptable</u>
21 CFR 201.15	☒ Yes ☐ No ☐ N/A
<u>Spanish-language (Drugs)</u>	<u>Acceptable</u>

21 CFR 201.16	☐ Yes ☐ No ☒ N/A
<u>FD&C Yellow No. 5 and/or FD&C Yellow No. 6</u>	<u>Acceptable</u>
21 CFR 201.20	☐ Yes ☐ No ☒ N/A
<u>Phenylalanine as a component of aspartame</u>	<u>Acceptable</u>
21 CFR 201.21	☐ Yes ☐ No ☒ N/A
<u>Sulfites; required warning statements</u>	<u>Acceptable</u>
21 CFR 201.22	☐ Yes ☐ No ☒ N/A
<u>Bar code label requirements</u>	<u>Acceptable</u>
21 CFR 201.25, 21 CFR 610.67	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices:</i> <i>Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011</i> <i>Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786)</i>	☒ Yes ☐ No ☐ N/A
<u>Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products)</u>	<u>Acceptable</u>
21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A
<u>Net quantity</u>	<u>Acceptable</u>
21 CFR 201.51	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices:</i> <i>Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463)</i> <i>Guidance: Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products, June 2015 (line 68, 93-99)</i> <i>USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).</i>	☐ Yes ☐ No ☒ N/A
<u>Usual dosage statement</u>	<u>Acceptable</u>
21 CFR 201.55, 21 CFR 201.100	☐ Yes ☐ No ☒ N/A

<u>Inactive ingredients</u>	<u>Acceptable</u>
21 CFR 201.100	☐ Yes ☐ No ☒ N/A
Recommended labeling practices: USP General Chapters <1091> Labeling of Inactive Ingredients	☐ Yes ☐ No ☒ N/A
<u>Storage requirements</u>	<u>Acceptable</u>
<i>Recommended labeling practices:</i> <i>USP General Chapters <7> Labeling</i> <i>USP General Chapters <659> Packaging and Storage Requirements</i>	☐ Yes ☐ No ☒ N/A
<u>Dispensing container</u>	<u>Acceptable</u>
21 CFR 201.100	☐ Yes ☐ No ☒ N/A

Package⁵ Label Evaluation

<u>Proper name</u>	<u>Acceptable</u>
21 CFR 610.61, 21 CFR 201.50, 21 CFR 201.10	☒ Yes ☐ No ☐ N/A
<u>Manufacturer name, address, and license number</u>	<u>Acceptable</u>
21 CFR 610.61, 21 CFR 201.1(a), 21 CFR 201.1(h)(5), 21 CFR 201.1(h)(6), 21 CFR 201.100(e)	☒ Yes ☐ No ☐ N/A
Recommended labeling practices: OPQ-OBP-RP-014	☒ Yes ☐ No ☐ N/A
<u>Lot number or other lot identification</u>	<u>Acceptable</u>
21 CFR 610.61	☒ Yes ☐ No ☐ N/A
<u>Expiration date</u>	<u>Acceptable</u>
21 CFR 610.61, 21 CFR 201.17	☒ Yes ☐ No ☐ N/A
<u>Preservative</u>	<u>Acceptable</u>
21 CFR 610.61	☒ Yes ☐ No

⁵ Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus, this includes the carton, prescribing information, and patient labeling.

	☐ N/A
Number of containers	Acceptable
21 CFR 610.61	☐ Yes ☐ No ☒ N/A
Strength/volume	Acceptable
21 CFR 610.61, 21 CFR 201.10, 21 CFR 201.100	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices:</i> <i>Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 176</i> <i>USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A
Storage temperature/requirements	Acceptable
21 CFR 610.61	☒ Yes ☐ No ☐ N/A
Recommended labeling practices: USP General Chapters: <7> Labeling	☒ Yes ☐ No ☐ N/A
Handling: "Do Not Shake", "Do not Freeze" or equivalent	Acceptable
21 CFR 610.61	☒ Yes ☐ No ☐ N/A
Multiple dose containers (recommended individual dose)	Acceptable
21 CFR 610.61	☐ Yes ☐ No ☒ N/A
Route of administration	Acceptable
21 CFR 610.61, 21 CFR 201.5, 21 CFR 201.100	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (route of administration statement recommended locations):</i>	☒ Yes ☐ No ☐ N/A
Known sensitizing substances	Acceptable
21 CFR 610.61	☐ Yes ☐ No ☒ N/A
Inactive ingredients	Acceptable
21 CFR 610.61, 21 CFR 201.100	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices:</i> <i>USP General Chapters <1091> Labeling of Inactive Ingredients</i>	☒ Yes

<i>USP General Chapters <7> Labeling</i>	☐ No ☐ N/A
<u>Source of the product</u>	<u>Acceptable</u>
21 CFR 610.61	☐ Yes ☐ No ☒ N/A
<u>Minimum potency of product</u>	<u>Acceptable</u>
21 CFR 610.61	☒ Yes ☐ No ☐ N/A
<u>Rx only</u>	<u>Acceptable</u>
21 CFR 610.61, 21 CFR 201.100	☒ Yes ☐ No ☐ N/A
Recommended labeling practices: Rx only prominence	☒ Yes ☐ No ☐ N/A
<u>Divided manufacturing</u>	<u>Acceptable</u>
21 CFR 610.63 (Divided manufacturing responsibility to be shown)	☐ Yes ☐ No ☒ N/A
<u>Distributor</u>	<u>Acceptable</u>
21 CFR 610.64 (Name and address of distributor)	☐ Yes ☐ No ☒ N/A
<u>Bar code</u>	<u>Acceptable</u>
21 CFR 610.67, 21 CFR 201.25	☒ Yes ☐ No ☐ N/A
Recommended labeling practices: <i>Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011</i> <i>Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786)</i>	☒ Yes ☐ No ☐ N/A
<u>Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products)</u>	<u>Acceptable</u>
21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A
<u>NDC numbers</u>	<u>Acceptable</u>
21 CFR 201.2, 21 CFR 207.35	☒ Yes ☐ No ☐ N/A
<u>Preparation instructions</u>	<u>Acceptable</u>

21 CFR 201.5	☒ Yes ☐ No ☐ N/A
Recommended labeling practices: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430) USP General Chapters <7> Labeling	☐ Yes ☐ No ☒ N/A
<u>Package type term</u>	<u>Acceptable</u>
<i>Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. USP chapter <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A
<u>Misleading statements</u>	<u>Acceptable</u>
21 CFR 201.6	☐ Yes ☐ No ☒ N/A
<u>Prominence of required label statements</u>	<u>Acceptable</u>
21 CFR 201.15	☒ Yes ☐ No ☐ N/A
<u>Spanish-language (Drugs)</u>	<u>Acceptable</u>
21 CFR 201.16	☐ Yes ☐ No ☒ N/A
<u>FD&C Yellow No. 5 and/or FD&C Yellow No. 6</u>	<u>Acceptable</u>
21 CFR 201.20	☐ Yes ☐ No ☒ N/A
<u>Phenylalanine as a component of aspartame</u>	<u>Acceptable</u>
21 CFR 201.21	☐ Yes ☐ No ☒ N/A
<u>Sulfites; required warning statements</u>	<u>Acceptable</u>
21 CFR 201.22	☐ Yes ☐ No ☒ N/A
<u>Net quantity</u>	<u>Acceptable</u>
21 CFR 201.51	☒ Yes ☐ No ☐ N/A
Recommended labeling practices: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463)	☐ Yes ☐ No ☒ N/A
<u>Usual dosage statement</u>	<u>Acceptable</u>

21 CFR 201.55, 21 CFR 201.100	☒ Yes ☐ No ☐ N/A
Dispensing container	Acceptable
21 CFR 201.100	☐ Yes ☐ No ☒ N/A
Medication Guide	Acceptable
21 CFR 610.60, 21 CFR 208.24	☒ Yes ☐ No ☐ N/A

Prescribing Information and Patient Labeling Evaluation

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
PRODUCT TITLE	Acceptable
21 CFR 201.57(a)(2)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices: Draft Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry (January 2018)</i>	☒ Yes ☐ No ☐ N/A
DOSAGE AND ADMINISTRATION	Acceptable
<i>Recommended labeling practices: USP nomenclature for diluents and intravenous solutions</i>	☐ Yes ☐ No ☒ N/A
DOSAGE FORMS AND STRENGTHS	Acceptable
21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) USP chapter <659> Packaging and Storage Requirements Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 176 USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A
Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION	Acceptable

21 CFR 201.57(c)(3)(iv)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices:</i> <i>USP nomenclature for diluents and intravenous solutions</i>	☐ Yes ☐ No ☒ N/A
3 DOSAGE FORMS AND STRENGTHS	Acceptable
21 CFR 201.57(c)(4)	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Confirm your product's identifying characteristics. We revised per your 3.2.P.1 submission <i>The Applicant revised as requested</i>	
<i>Recommended labeling practices:</i> <i>Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018)</i> <i>USP General Chapters <659>, USP General Chapters <7></i>	☒ Yes ☐ No ☐ N/A
11 DESCRIPTION	Acceptable
21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices:</i> <i>USP General Chapters <1091>, USP General Chapters <7></i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: We deleted the proprietary name from the first paragraph since this paragraph discusses the drug substance. <i>The Applicant revised as requested</i> We revised the list of inactive ingredients to appear in alphabetical order (see USP General Chapters <1091> <i>The Applicant revised as requested</i>	
16 HOW SUPPLIED/ STORAGE AND HANDLING	Acceptable
21 CFR 201.57(c)(17)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices: to ensure placement of detailed storage conditions for reconstituted and diluted products</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Revise the room temperature storage information to appear as a range. The studies that were conducted to support the in-use storage duration were all done at 25 ± 2°C. Because of this, we recommend that you revise to a range of 23 – 27°C or a limit of NMT 25°C (e.g., "...syringes at room temperature up to 77°F (25°C)". Ensure that	

you submit revised carton labeling reflecting revisions to the alternative room temperature storage duration and temperature range stating the temperature in both F and C.

The Applicant revised as follows: "single-dose prefilled syringes at room temperature between 73°F to 81°F (23°C to 27°C) for a maximum single period of 14 days is permissible, with protection from light and sources of heat. Once a single-dose prefilled syringe has been stored at room temperature, it should not be placed back into the refrigerator. If not used within 14 days at room temperature, the single-dose prefilled syringe should be discarded"
Acceptable

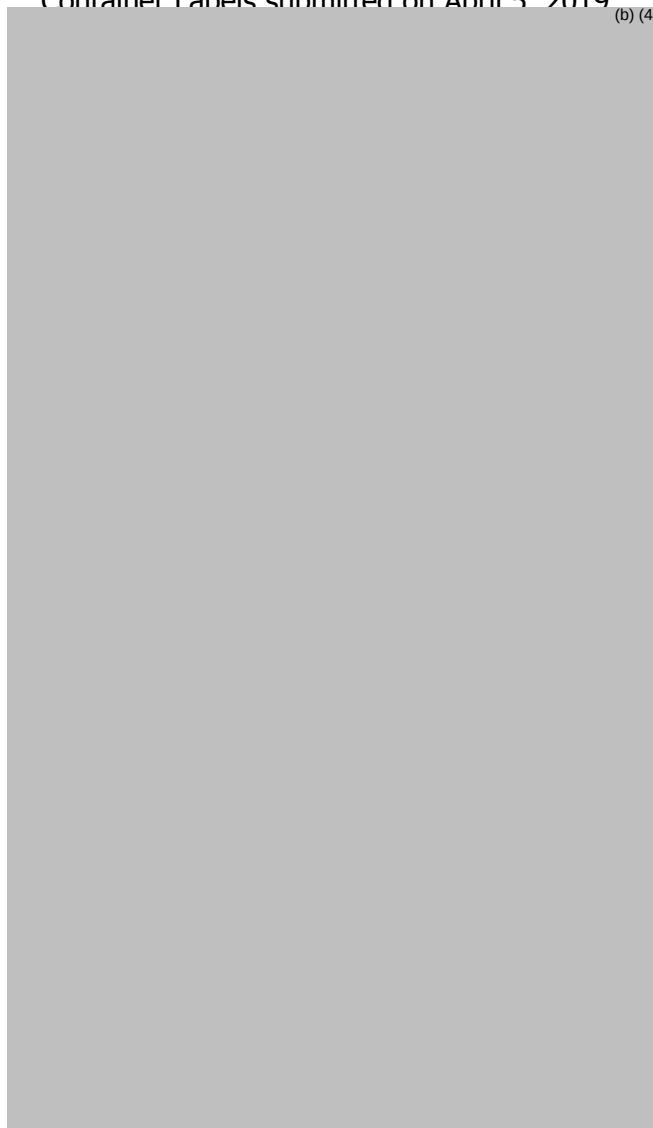
MANUFACTURER INFORMATION	Acceptable
21 CFR 201.100(e), 21 CFR 201.1, 19 CFR 134.11	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices: 21 CFR 610.61 (add the US license number for consistency with the carton labeling), and 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)</i>	☒ Yes ☐ No ☐ N/A
MEDICATION GUIDE, PATIENT INFORMATION LABELING, INSTRUCTIONS FOR USE	
TITLE (NAMES AND DOSAGE FORM)	Acceptable
Regulation for Medication Guide: 21 CFR 208.20(a)(7)	☒ Yes ☐ No ☐ N/A
<i>Recommended Labeling Practice: To ensure consistency with the product title in the Highlights of Prescribing Information (see Draft Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry (January 2018). For the recommended dosage form (see USP General Chapters: <1> Injections, Nomenclature and Definitions, Nomenclature form).</i>	☒ Yes ☐ No ☐ N/A
STORAGE AND HANDLING	Acceptable
<i>Recommended labeling practices: To ensure that applicable storage and handling requirements are consistent with the information provided in the PI (Reference: Section 2 (Dosage and Administration) and Section 16 (How Supplied Storage and Handling) of the PI)</i>	☒ Yes ☐ No ☐ N/A
INGREDIENTS	Acceptable
<i>Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: We revised to ensure that the inactive ingredients are in alphabetical order (see USP General Chapters <1091>: Labeling of inactive ingredients in alphabetical order) <i>The Applicant revised as requested</i>	
MANUFACTURER INFORMATION	Acceptable

21 CFR 201.1, 19 CFR 134.11, 21 CFR 208.20(b)(8)(iii)	☒ Yes ☐ No ☐ N/A
<i>21 CFR 610.61 (add the US license number for consistency with the carton labeling), 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)</i>	☒ Yes ☐ No ☐ N/A

APPENDIX C. Acceptable Labels and Labeling

Prescribing Information/Medication Guide/Instructions for Use (submitted on April 19, 2019
<\\cdsesub1\evsprod\bla761066\0056\m1\us\draft-labeling-text-clean-pdf.pdf>)

Container Labels submitted on April 5, 2019 (b) (4)





Vicky
Borders-Hemphill

Digitally signed by Vicky Borders-Hemphill
Date: 4/22/2019 10:58:46AM
GUID: 50814c7000007a3d59329f660d8ddf02



Brian
Jannelsins

Digitally signed by Brian Jannelsins
Date: 4/23/2019 03:44:29PM
GUID: 54b8280e000855ed28b059d11c54a788

Biosimilar BLA Review

Recommendation: Approval

BLA Number: 761066
Review Number: 2nd Round
Review Date: 04/09/2019

Drug Name/Dosage Form	SB4 Etanercept Biosimilar (Eticovo)
Strength/Potency	25 mg/0.5 mL and 50 mg/mL solution in pre-filled syringes (PFS)
Route of Administration	Subcutaneous
Rx/OTC dispensed	Rx
Indication	Rheumatoid Arthritis, Polyarticular Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Plaque Psoriasis
Applicant	Samsung Bioepis
US agent, if applicable	Biologics Consulting Group Inc.

The BLA was initially submitted on May 25, 2017. A Complete Response (CR) letter for product quality deficiencies was issued on March 23, 2018 (see OBP Executive Summary for initial BLA 761066 review cycle, dated March 23, 2018). A BPD Type 1 meeting was held on May 10, 2018 to discuss the CR deficiencies. On October 25, 2018, Samsung submitted responses to address the deficiencies identified in the CR letter.

Product Overview

Note: There is no change in this section from the Executive Summary filed on 3/23/2018 in Panorama.

SB4 is a homodimer of a fusion protein consisting of the extracellular ligand binding domain of human TNFR2/p75 and the Fc domain of human IgG1. The mechanism of action (MOA) of SB4 involves binding soluble Tumor Necrosis Factor Alpha (TNF α) and TNF-beta (TNF β) and membrane-bound TNF α to inhibit binding to TNF receptors, blocking downstream TNF signaling. SB4 is a highly glycosylated fusion protein with each single chain consisting of three N-linked glycosylation sites and 13 potential O-linked glycosylation sites. The Fc portion of SB4 can induce low levels of effector function such as antibody dependent cellular cytotoxicity (ADCC); however, this pathway does not contribute to the mechanism of action of SB4. The SB4 drug product is supplied in two presentations of 25 mg/0.5mL and 50 mg/mL in a pre-filled syringe (PFS) and is intended for the treatment of several auto-immune disorders including Rheumatoid Arthritis, Polyarticular Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis and Plaque Psoriasis.

Quality Review Team

Discipline	Reviewer	Branch/Division
Drug Substance	Brian Janelsins	OBP/DBRRI
Drug Product	Brian Janelsins	OBP/DBRRI
Analytical Similarity Assessment	Brian Janelsins	OBP/DBRRI
Immunogenicity	Brian Janelsins	OBP/DBRRI
Labeling	Vicki Borders-Hemphill	OPQ/OPRO
Facility	Michael Shanks/Zhihao Peter Qiu	OPF/DIA/Branch 1
Microbiology	Max Van Tassell (Drug Substance) Jessica Hankins (Drug Product)	OPF/DMA/DMABIV

	Reyes Candau-Chacon (QAL)	
Application Team Lead	Rachel Novak	OBP/DBRRI
OBP Tertiary Reviewer	Marjorie Shapiro	OBP/DBRRI
OBP RBPM	Oumou Barry	OPQ/OPRO

Multidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Brandi Wheeler	CDER/ODEII/DPARP
Cross-disciplinary Team Lead	Rachel Glaser	CDER/ODEII/DPARP

1. Names:

- a) Proprietary Name: Eticovo
- b) Trade Name: Eticovo
- c) Non-Proprietary/USAN: Eticovo (etanercept-ykro)
- d) CAS name: 185243-69-0
- e) Common name: SB4
- f) INN Name: etanercept
- g) Compendial Name: N/A
- h) OBP systematic name: Fus: RPROTFRAG P20333 (TNR1B_HUMAN); MABFRAG HUMAN (IGG1 FC) [SB4]
- i) Other Names: BIIB602E

Communications with applicant (OBP and DMA):

Communication/Document	Date
Information Request (OBP)	02/4/2019
Information Request (DMA)	02/21/2019
Information Request (DMA)	03/05/2019
Information Request (OBP)	03/13/2019
Information Request (OBP)	03/28/2019
Information Request (OBP)	04/04/2019
Information Request (OBP)	04/08/2019

Submissions Reviewed (OBP and DMA):

Submission(s) Reviewed (OBP and DMA)	Document Date
761066/0038 (resubmission)	10/25/2018
761066/0042 (response to IR 02/4/2019)	02/19/2019
761066/0043 (response to IR 02/21/2019)	02/26/2019
761066/0046 (response to IR 03/05/2019)	03/08/2019
761066/0048 (response to IR 03/13/2019)	03/18/2019
761066/0049 (response to IR 03/28/2019)	04/01/2019
761066/0050 (response to IR 04/04/2019)	04/05/2019
761066/0051 (response to IR 04/08/2019)	04/09/2019

Quality Review Data Sheet

1. Legal Basis for Submission: 351(k)

2. Related/Supporting Documents:

- A. DMFs: No additional information has been added in the resubmission.
- B. Other documents: IND, Referenced Listed Drug (RLD), or sister application. No additional information has been added in the resubmission.

3. Consults:

Discipline/Topic	Status	Recommendation	Reviewer
Device (Pre-filled Syringe) One Additional Comment in CR letter to add break loose and gliding force to the drug product specifications.	Complete	Approve	Steven Basile/Alan Stevens

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation: **Approval**

The Office of Pharmaceutical Quality (OPQ), CDER, completed the review of the resubmission of STN 761066 for Eticovo (etanercept-ykro) from Samsung Bioepis. The data submitted in this application are sufficient to support a conclusion that the manufacture of Eticovo (etanercept-ykro) is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life. We recommend that this product be approved for human use under conditions specified in the package insert.

The analytical similarity assessment as presented in the original BLA submission was considered adequate to support the conclusion that the biological product, etanercept-ykro, is highly similar to U.S.-licensed Enbrel. No additional analytical similarity data were provided in the resubmission.

Manufacturing location:

- Drug Substance: (b) (4)
- Drug Product: (b) (4)
- Fill size and dosage form: 25 mg/0.5 mL and 50 mg/mL solution in a pre-filled syringe.
- Dating period:
 - Drug Product: 36 months: 2-8°C
 - Drug Substance: (b) (4)
 - Stability Option:

- The stability protocols in this license application are acceptable for the purpose of extending the expiration dating of your drug substance and drug product under 21 CFR 601.12.
- Exempt from lot release
 - Yes
 - Rationale: specified product in accordance with 21 CFR 601.2a.

D. Benefit/Risk Considerations:

The data provided in the analytical similarity assessment demonstrate that SB4 is highly similar to US-licensed Enbrel, notwithstanding minor differences in clinically inactive components. Differences were noted in the assessment among SB4 and US-licensed Enbrel and EU-approved etanercept; however, these differences are thought to be inherent to the manufacturing process and formulation of SB4. They included differences in the hydrophobic variant profile, amount of high molecular weight species (HMWS), and glycosylation profiles; however, these do not preclude a demonstration of highly similar. For details on the analytical similarity assessment, see review uploaded to Panorama on March 11, 2018.

The deficiencies related to manufacturing and controls described in the Complete Response letter dated March 23, 2018 were addressed in the resubmission (see details below). Overall, the OPQ review of manufacturing and controls in the resubmission and in the initial BLA submission confirmed that the processes and methods used for drug substance and drug product manufacture, release, and stability testing are sufficient to assure a consistent and safe product.

The commercial manufacture of etanercept-ykro drug substance at (b) (4) and of drug product at (b) (4) is recommended for approval by DIA, OPF, as a prelicense inspection of the drug substance manufacturing site was performed during the original submission review cycle (b) (4) and the facility was classified as VAI. The prelicense inspection was waived at the drug product manufacturing sites based on facility profile evaluation. No new facility information was provided in the resubmission.

B. Recommendation on Phase 4 (Post-Marketing) Commitments (DMA):

1. Implement (b) (4) monitoring during sterile filtration of the SB4 drug product at (b) (4)
2. Implement (b) (4) monitoring during sterile filtration of the SB4 drug product at (b) (4)

II. Summary of Quality Assessments:

The original BLA submission had the following deficiencies: 1) inadequately qualified primary and working reference standards; 2) insufficient data to support the limit of in vitro cell age (LIVCA) and assurance of Master Cell Bank (MCB) clonality; 3) inadequate control of critical quality attributes, including protein concentration, potency, HMWS, purity, extractable volume at release and/or end of shelf life (EOSL) for DS and DP and DP identity testing; 4) DP shipping validation; 5) (b) (4) sterilization validation and appropriate process parameters for sterile filtration; and 6) other additional concerns and requests for clarification.

The CR deficiencies are discussed below as they relate to the drug substance and drug product. The additional comments communicated in the CR letter will not be discussed in detail in this review; however, all of the items were adequately addressed (for details see OBP Technical Document Review uploaded to Panorama on 04/10/2019).

A. Drug Substance [etanercept-ykro] Quality Summary

In the original submission, the primary reference standard was not adequately characterized to ensure comparability between the material used in clinical studies, commercial material and the material used in the analytical similarity assessment. In brief, the primary reference standard (PRS) was qualified against the interim reference standard (IRS), which was used to release clinical material; however, the qualification study did not assess potency using an adequate number of replicates to determine the true value of the PRS relative to the IRS. In addition, there appeared to be a sizable difference in potency between the PRS and IRS; however, it was unclear if this trend was real or if it was due to an inadequate number of replicates being performed. The IRS was no longer available to repeat the qualification studies. Since the PRS was not appropriately qualified, the working reference standard (WRS) was also considered to be not suitable.

In addition, there were insufficient data to support the LIVCA, as well as a lack of assurance of the clonality of the MCB. Therefore, the proposed upstream manufacturing control strategy proposed for etanercept-ykro was not sufficient.

In the resubmission, the applicant addressed the following as they relate to the manufacture of the drug substance:

- **Qualification of the Primary Reference Standard (CR items 1a-d):** To address the concerns regarding the qualification of the PRS, data were provided to evaluate the potency of the current PRS against a research reference standard lot (EBS-127; U.S.-licensed Enbrel) used to assess commercial material in the analytical similarity studies. EBS-127 was appropriately qualified against the previous research reference standard (EBS-052) and bridging data were provided in the resubmission to demonstrate similar potency values for the TNF α binding and neutralization assays between the IRS (used to release clinical material) and EBS-052. The qualification of the PRS against EBS-127 was sufficient. As the PRS is now appropriately qualified, the WRS is also suitable for its intended use.
- **Control Strategy for the Upstream Manufacturing Process (CR Items 2a-c):** To address the concerns concerning the LIVCA and the residual uncertainty of the clonality of the MCB, the applicant proposed a LIVCA based on current commercial manufacturing experience and [REDACTED] (b) (4)
[REDACTED]
[REDACTED] Based on the information provided in the resubmission, the SB4 upstream manufacturing process appears to be adequately controlled.

- **Dating period and storage conditions:** The proposed shelf-life for the DS is [REDACTED] (b) (4) months stored at [REDACTED] (b) (4)

B. Drug Product [etanercept-ykro] Quality Summary:

In the original submission, several deficiencies related to the manufacture of the drug product were noted. The most significant deficiencies were identified relating to the drug product filling control strategy to ensure consistent protein concentration and extractable volume to meet the intended label claim. In addition, there were concerns over the sterile filtration process and inadequate data to support that shipping of the product for commercial distribution would not impact product quality.

In the resubmission, the applicant addressed the following as they relate to the manufacture of the drug product:

- **Protein Content (CR Comment 3a):** In the original submission, the 50 mg/ml presentation appeared to show a slight decrease in protein concentration when comparing drug substance lots to the corresponding drug product lots. Because the drug product manufacturing process is (b) (4), the applicant was asked to clarify this discrepancy. In the resubmission, it was noted that protein concentration for drug substance is tested at a different location (b) (4) than for drug product (b) (4). An evaluation was performed to demonstrate consistent protein concentration in multiple lots of commercial drug substance and the corresponding drug product, including drug product manufactured at both (b) (4). An evaluation was also performed to determine if the testing sites, (b) (4) could impact the data. The data provided support that there is no significant difference between protein concentration of drug substance and corresponding drug product material irrespective of the site used for drug product manufacturing or the site used for testing. The trend noted previously is not apparent upon analysis of the commercial material to date.
- **DP Control for Extractable Volume (OBP CR Comment 3b):** Regarding the acceptance criteria for extractable volume for both the 50mg/ml and 25 mg/ml presentations, the applicant revised the lower limits for extractable volume from (b) (4) and the upper limit for extractable volume for the 25 mg/0.5 mL syringe from (b) (4) respectively, to ensure delivery of the appropriate volume of product to meet the label claim.
- **DP Fill Control Strategy (OBP CR Comment 3c):** For both drug product manufacturing facilities (b) (4) the applicant provided adequate detailed information describing how the (b) (4) is controlled in real time during manufacturing and what actions are taken when samples are outside the rejection/action limit.
- **Drug Product Shipping Validation (OBP CR Comment 4):** Additional data from real-time shipping studies were provided to support validation of commercial drug product shipping and provide assurance that SB4 product quality will be maintained during shipping and distribution.
- **Drug Product Identity Testing (OBP CR Comment 5):** The applicant updated the drug product manufacturing process in Section 3.2.P.3.3 to ensure that samples for identity testing for drug product release will be taken after the labeling operations have been completed to comply with 21 CFR 610.14.

- **Microbial Control (DMA CR Comment 6 and 7):** In the current drug product manufacturing process, (b) (4) is monitored during sterile filtration. The applicant provided data correlating (b) (4) during sterile filtration at both drug product manufacturing sites (b) (4) to ensure that (b) (4) during the microbial retention study.
- **Dating period and storage conditions:** The proposed shelf-life for the 50 mg and 25 mg drug product strengths is 36 months when stored at 5±3°C.
- C. Novel Approaches/Precedents:** None
- D. Any Special Product Quality Labeling Recommendations:** For patient convenience, Eticovo (etanercept-ykro) may be stored at 25±2°C for 2 weeks within the expiry period.
- E. Establishment Information:** No new information was provided in the resubmission.
- F. Lifecycle Knowledge Management:**
 - a. Drug Substance:
 - i. Protocols approved:
 - 1. Requalification of WRS
 - 2. Requalification of PRS
 - 3. Post-approval Stability
 - ii. Outstanding review issues/residual risk: None
 - iii. Future inspection points to consider: None
 - b. Drug Product
 - i. Protocols approved:
 - 1. Post-approval stability
 - ii. Outstanding review issues/residual risk: None
 - iii. Future inspection points to consider: None



Rachel
Novak

Digitally signed by Rachel Novak
Date: 4/11/2019 01:04:28PM
GUID: 52e163f70002ba9e745b4e39384c76d7



Marjorie
Shapiro

Digitally signed by Marjorie Shapiro
Date: 4/11/2019 01:39:46PM
GUID: 508da6d700026360986b5a21cc1642e3



Reyes
Candau-Chacon

Digitally signed by Reyes Candau-Chacon
Date: 4/11/2019 02:15:34PM
GUID: 508da7160002977f7ca389c8f849b707

BLA STN 761066 (Resubmission)

Eticovo (etanercept-ykro)

Samsung Bioepis Co., Ltd.

Brian Janelins, Ph.D. (Primary Reviewer)
Rachel Novak, Ph.D. (Secondary Reviewer, ATL)

Division of Biotechnology Review and Research I
Office of Biotechnology Products

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

Etanercept-ykro (SB4) is a homodimer of a fusion protein consisting of the extracellular ligand binding domain of human TNFR2/p75 and the Fc domain of human IgG1. The mechanism of action of SB4 involves binding soluble TNF- α and TNF- β and membrane-bound TNF- α ; thereby, preventing binding of TNF to TNF receptors and downstream TNF signaling. Samsung submitted a BLA under the 351(k) pathway for approval of SB4 as a biosimilar to US-licensed Enbrel (SDN 1, 05/25/2017). Sufficient information and data were provided to demonstrate that SB4 is highly similar to US-licensed Enbrel notwithstanding minor differences in clinically inactive components; however, the BLA was not approved due to insufficient product quality information and data to support a conclusion that the manufacture of SB4 is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life. A Complete Response (CR) letter, including 5 CR comments and 11 additional comments written by OBP, was issued to Samsung on 03/23/2018. Samsung held a Type 1 BPD meeting with the Agency on 05/10/2018 to discuss the deficiencies and a path forward (refer to the meeting minutes, uploaded to DARRTS on 06/07/2018).

This memo contains the OBP product quality review of the information and data provided in the resubmission (SDN 38) and in response to information requests (IRs; SDN 42, 02/19/2018; SDN 48, 03/18/2019; SDN 49, 04/01/2019; SDN 51, 04/05/2019; and SDN 52, 04/09/2019) that were communicated to Samsung during the review cycle. Based on the totality of information and data provided, Samsung has adequately addressed all the OBP-noted deficiencies and additional comments outlined in the CR letter. Therefore, OBP recommends approval of BLA 761066 for SB4 as a biosimilar to US-licensed Enbrel without any post-marketing commitments or requirements. Based on the data provided in the resubmission (Sections 3.2.S.7.3 and 3.2.P.8.3), we recommend an expiration dating period of (b) (4) months at or below (b) (4) and 36 months at 5 $\pm$ 3°C for SB4 drug substance and drug product, respectively, while stored in the intended commercial container closure systems. In addition, we agree that the final packaged SB4 drug product can be stored at room temperature at 25°C (e.g., 23 – 27°C or NMT 25°C) for a maximum single period of 2 weeks.

II. List of Deficiencies to be Communicated

There are no deficiencies.

III. List of Post-Marketing Commitments/Requirements

There are no post-marketing commitments or requirements.

TABLE OF CONTENTS

REVIEW

MODULE 1

1.11.1 Product Quality Information

Hold Comment 1

The data and information provided in your response on January 12, and February 14, 2018, to the Agency's information requests (IRs) dated December 19, 2017 (IR #13) and February 7, 2018 (IR #1) demonstrate that the primary reference standard (PRS) was not appropriately qualified with respect to biological activity (i.e., TNF- α binding activity and TNF- α neutralization activity) and protein concentration, and therefore, is not appropriate for its intended use. Because the PRS was not appropriately qualified, the working reference standard (WRS), which was qualified against the PRS, is also not appropriate for its intended use. Therefore, there is a lack of assurance that the commercial materials are not going to drift from SB4 clinical materials and the materials used to establish the analytical similarity.

Reviewer Comment: While not discussed in Samsung's response to the comment, the Agency agreed during the BPD Type 1 meeting that the assessment of protein concentration performed during the qualification of reference materials is acceptable. Samsung clarified that the reference materials were assigned protein concentration based on multiple independent determinations performed by the validated protein concentration method and the protein concentration of the reference materials were assessed by duplicate measurements during the dilution step of the potency assays.

- a. Generate an appropriately qualified reference material based on the advice provided in the Agency's IRs dated December 19, 2017 and February 7, 2018. Upon the generation of the new qualified reference material, provide data to adequately link this material to the materials used in the clinical studies and analytical similarity assessment. We recommend using a two-tiered system for utilizing reference standard material for routine testing of commercial product.

Response to Hold Comment 1a: To address the Agency's comment, Samsung reassessed the suitability of the PRS in lieu of generating new reference material. The initial qualification of the PRS against the interim reference standard (IRS), which was used to release clinical material, did not include enough replicates to generate a true potency value to determine whether an assignment of (b) (4) potency can be made for the PRS. Because IRS was exhausted, it could not be used to reassess the qualification of the PRS. The 3rd Research Reference Standard (RRS, EBS-127) was chosen to requalify the PRS with respect to potency. The adequacy of Samsung's approach, data, and conclusion is reviewed below.

Reviewer Comment: Samsung has used multiple reference standards throughout development to release SB4 lots and assess analytical similarity of SB4, US-licensed Enbrel, and EU-approved etanercept lots. Refer to the review of the original BLA submission (uploaded to the CDER Informatics Platform on 03/11/2018) for information about each reference standard, how the reference standards were qualified, and the qualification issues identified during the original review cycle.

3 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Reviewer Comment: Sufficient data were provided to support the qualification of the PRS and the link between PRS and reference material used in the analytical similarity assessment and reference material used to release clinical material. Because the WRS was appropriately qualified against the PRS (mean potency of (b) (4) and (b) (4) for TNF- α binding and TNF- α neutralization, respectively, (see original BLA review), an adequate link has been established between the WRS and reference materials that were used to demonstrate analytical similarity and release clinical materials. Overall, the data support the potency assignment of (b) (4) % for the reference materials used throughout development and that an adequate level of assurance can be made that the commercial materials are not going to drift from clinical material and material used to establish the analytical similarity. Samsung has adequately addressed this portion of the comment.

- b. Re-assess and revise SB4 drug substance and drug product lot release and stability specifications, as appropriate.**

Response to Hold Comment 1b: Samsung did not perform a reassessment of the drug substance and drug product specifications for the TNF- α binding ((b) (4) % relative potency) and TNF- α neutralization ((b) (4) % relative potency) assays.

Reviewer Comment: Because there was no change in the PRS or WRS, this is acceptable.

- c. Re-test the currently manufactured SB4 lots for release and stability using the appropriately qualified reference material, as appropriate, if these lots are intended to be release for commercial use in the US.**

Response to Hold Comment 1c: The currently manufactured drug substance and drug product lots were not retested because the current reference material used to release the lots (i.e., WRS) was determined to be acceptable. Samsung clarified that the current WRS will continue to be used to release commercial material.

Reviewer Comment: This is acceptable.

- d. Provide an updated requalification protocol for the reference material (e.g., primary and working reference standards) to include the advice that was given in the Agency's information requests dated December 19, 2017 and February 7, 2018.**

Response to Hold Comment 1d: Samsung performs both stability and requalification testing to support the expiry of the PRS and WRS. Requalification and stability protocols for the current PRS and WRS were provided and Section 3.2.S.2.5 was updated in the resubmission. While PRS information in Section 3.2.S.5 includes sections related to the stability (Section 3.2.S.5.1.3.1) and requalification (Section 3.2.S.5.1.3.2) testing programs, the WRS information in Section 3.2.S.5 includes a section related to the stability testing program (Section 3.2.S.5.2.3), but not the requalification testing program. For these testing programs described in Section 3.2.S.5, Samsung implemented the Agency's recommendation that the PRS used in potency testing be evaluated against the WRS and the WRS used in potency testing be evaluated against the PRS for the remaining time-points. Likewise, the stability and requalification protocols for the

current PRS and the requalification protocol for the current WRS were updated to include the same testing scheme. However, the stability protocol for the WRS was not updated.

Reviewer Comment: *The changes made to Section 3.2.S.5 and the stability and requalification protocols in the resubmission were insufficient to ensure stability during continued use of the PRS and WRS. An IR (03/28/2019) was communicated to Samsung to provide additional updates to Section 3.2.S.5 and the stability and requalification protocols. Based on the Agency's comments, Samsung updated the stability and requalification programs for the PRS and WRS as discussed below (SDN 49, 04/01/2019). From the next testing time-points for the requalification of the PRS (b) (4) and WRS (b) (4), the potency assays will be run three times to determine whether the mean of the replicates is within an acceptance criterion of (b) (4) relative potency. To monitor any significant deviation from the potency values obtained at the time of initial qualification, trend analysis will be performed based on the trending of results obtained during routine testing. Section 3.2.S.5 was also updated to include the current QC acceptance criteria agreed by the Agency for stability and requalification testing of the PRS and WRS. To support the expiry of the PRS and WRS, requirements for stability and requalification testing must be met. Samsung also updated the stability and requalification protocols to align with the information present in Section 3.2.S.5.*

(b) (4)

Overall, sufficient information and data were provided to support the stability and requalification programs for the PRS and WRS. To support qualification of new PRS and WRS materials, Samsung will have to submit a Prior Approval Supplement (PAS) to the BLA with appropriate information and data after the BLA is approved.

Hold Comment 2

The data and information provided in the submission and in your response dated February 13, 2018, to the Agency's information request dated February 2, 2018 (IR #1) was insufficient to support the limit of *in vitro* cell age (LIVCA) of (b) (4) and the proposed control limit of the (b) (4) Characterization and assessment of LIVCA using (b) (4) study is not considered sufficiently representative of cell culture behavior during the commercial cell culture process. In addition, the information provided in the IR response on February 13, 2018 (IR #7) concerning the generation of the SB4 Master Cell Bank (MCB) suggests that the cell bank is not clonal (b) (4). Taken together, the overall control strategy for the upstream cell culture process is inadequate and requires additional levels of control. To ensure product quality and cell culture process consistency, implement the following controls and update all the appropriate sections of the BLA with this information:

- a. Establish LIVCA using an appropriate cell culture model that is sufficiently representative of the commercial cell culture process. For example, (b) (4)
- c. Implement a critical control limit for the number (b) (4) to ensure that the LIVCA (based on comment 2a) is not exceeded by the (b) (4) during routine manufacturing. Provide information and/or data to justify the control for the limit of (b) (4)

Response to Hold Comment 2a and 2c: Samsung acknowledged the Agency's concern and determined LIVCA based on (b) (4)

Sections 3.2.S.2.2, 3.2.S.2.3, and 3.2.S.2.4 were updated with the LIVCA control limits.

Reviewer Comment: The limits to control for LICVA are acceptable and are supported by appropriate data. The limits ensure that LIVCA is not exceeded due to unexpected manufacturing deviations. Samsung has adequately addressed this portion of the comment, and the adequacy of the control strategy for the cell culture process as a whole is discussed below.

b. Establish in-process controls (IPCs) for

(b) (4)

These ranges should be supported by data from development studies using an appropriate cell culture model, PPQ and/or commercial manufacturing runs.

Response to Hold Comment 2b:

(b) (4)

[Redacted]

(b) (4)

[Redacted]

Reviewer Comment:

(b) (4)

[Redacted]

Data were provided to

support that the scale-down model is representative of the full-scale process (Figures 3 – 5, Table 16). Furthermore, the time in culture is also supported by the (b) (4) controls discussed above in “response to comment 2a and 2c.” Sufficient data and information were provided to support the ranges for (b) (4).

Although the (b) (4) steps was not upgraded to an IPC, sufficient control is provided to ensure (b) (4) is acceptable. Considering concerns about the monoclonal derivation of the MCB, the updates made to the cell culture process control strategy allow for a well-controlled process. Samsung has adequately addressed this comment.

Hold Comment 3

The information provided in the submission and in the responses received by the Agency on February 2, 6, and 14, 2018, and during the teleconference held with the Agency on February 8, 2018, is not adequate to support that the currently proposed drug product filling control strategy provides sufficient assurance that each pre-filled syringe (PFS) is filled with sufficient SB4 product to meet the current US label claim of 50 mg/mL and 25 mg/0.5mL for Enbrel.

- a. Although the protein concentration for drug product process validation batches filled at (b) (4) are within the acceptance criterion range of (b) (4) at release, the protein concentration is consistently less than 50 mg/mL while the drug substance lots used to fill these drug product lots did not have this issue. For example, drug substance lot 15-602E-002 had a protein concentration of (b) (4) at release and the resulting drug product lot, 00003, had a protein concentration of (b) (4). Because the drug product is (b) (4), it is unclear why there is such variability between the drug substance protein concentration and the subsequent drug product protein concentration. Explain this discrepancy.

Response to Hold Comment 3a: Samsung evaluated the potential difference in protein concentration between drug substance and drug product lots. Samsung noted that drug substance and drug product lots are manufactured at different sites (b) (4) respectively), and data provided in the original submission show that drug substance and drug product were tested at different sites for protein concentration evaluations at release (b) (4) respectively). Samsung evaluated whether there is (i) a step in the drug product manufacturing process that could impact protein concentration, (ii) a difference in protein concentration from the two drug product manufacturing sites, and (iii) a difference in the testing methods that could lead to different protein concentration results.

Manufacture of drug product

The drug product manufacturing process is (b) (4). Data were provided that demonstrated the protein concentration of commercial material did not significantly change from the initial manufacturing step of drug substance (b) (4) up to filling of the drug product (b) (4) at the (b) (4) site (Table 13). Protein concentration results from in-process testing were also provided for drug product lots manufactured at (b) (4) however, data from these lots are from non-commercial lots, which did not have the observed difference in protein concentration from drug substance to drug product. Furthermore, the protein concentration was not tested at each manufacturing step at (b) (4) to allow for

a meaningful comparison. Additional data were provided in the resubmission that demonstrated the protein concentration of commercial lots manufactured at (b) (4) (b) (4) was similar to that of commercial lots manufactured at (b) (4) (b) (4) Table 14).

Testing methods

Samsung specified minor differences (i.e., (b) (4) (b) (4) before analysis, and acceptable ranges in BSA measurements; Table 15) between the protein concentration testing methods at (b) (4) (b) (4); these differences were classified as non-critical. Initially, Samsung re-analyzed the protein concentration of the commercial drug substance lot 15-602E-002 (b) (4) (b) (4) original submission) and the corresponding drug product lot 00003 (b) (4) (b) (4) original submission) using (b) (4) (b) (4) methods at the Samsung Bioepis laboratory in Korea. The lots were re-analyzed by two analysts three times on three separate days by each method. The data support that the protein concentration of drug substance lot 15-602E-002 is comparable to that of the corresponding drug product lot 00003 when evaluated by the (b) (4) (b) (4) respectively) and (b) (4) (b) (4) respectively) test methods (Table 16). Statistical analysis demonstrates that the test methods did not generate statistically different results for the drug substance (p value of 0.280) and drug product (p value of 0.379) lots (Tables 17 and 18). Additionally, statistical analysis demonstrates that the drug substance and drug product results are not statically different when analyzed by the (b) (4) (b) (4) (p value of 0.517) and (b) (4) (b) (4) (p value of 0.670) test methods (Tables 19 and 20).

A summary of the long-term stability data was provided for the commercial drug substance and drug product lots referenced in the original submission. While the protein concentration did not significantly change from the initial testing time-point to the 24-month testing time-point for drug substance 15-602E-001 and 15-602E-003 drug substance lots, there was a slight change for drug substance lot 15-602E-002. It was also noted the stability testing of the 15-602E-002 drug substance lot, and the corresponding drug product lot 00003, was more variable (i.e., 2.3% RSD) than the other lots.

Table 21: Protein Concentration Results of SB4 Process B PVR DS from Long-term Stability Study

DS Batch No.	Stability Period (months)							%RSD
	0 ^a	3	6	9	12	18	24	
15-602E-001	(b) (4)							1.2%
15-602E-003	(b) (4)							1.3%
15-602E-002	(b) (4)							2.3%

^a The initial point result was obtained at (b) (4) All others were obtained at (b) (4)

Table 22: Protein Concentration Results of SB4 Process B PVR DP from Long-term Stability Study

DP Batch No.	Stability Period (months) ^a								%RSD
	0	3	6	9	12	18	24	30	
00001	(b) (4)								1.2%
00002	(b) (4)								1.3%
00003	(b) (4)								2.3%

^a All results were obtained at (b) (4)

Lastly, protein concentration values reported for all available commercial drug substance lots and corresponding (b) (4) (b) (4) drug product lots were provided (Tables 24 and 25). The data show

that the overall difference in mean values from drug substance to drug product (n=43) was only 0.7 mg/ml with an overall variability of 1.3% RSD for (b) (4) material (n=43). Similarly, the overall difference in mean values from drug substance to drug product was only 0.6 mg/ml with an overall variability of 1.0% for (b) (4) material (n=15). The largest variability observed between the protein concentration of a drug substance lot and a corresponding drug product lot was 4.2% for (b) (4) material and 2.8% for (b) (4) material, which are within the 5% RSD validation limit for intermediate precision and reproducibility.

Reviewer Comment: Sufficient information and data were provided to support that the difference in protein concentration from drug substance lot 15-602E-002 and the corresponding drug product lot 00003 is likely the result of method variability and the reporting of extreme values by chance. Additional data generated from numerous lots were provided to support that there is no significant difference between protein concentration of commercial drug substance and corresponding drug product material irrespective of the site used for drug product manufacturing or the method testing site used. Samsung has adequately addressed this portion of the comment.

- b. While the labeling allows (b) (4) when considering the control strategy, the current criteria would allow the release of PFS filled outside appropriate limits. The 50 mg/mL syringes may be underfilled, because a volume of (b) (4) deliverable volume) is allowed, and the 25 mg/0.5 mL syringes may be filled to an inappropriately high level of (b) (4) deliverable volume). As requested previously on February 7, 2018, revise the lower limits for extractable volume (Section 3.2.P.5.1) and (b) (4) (Section 3.2.P.3.3) for the 50 mg/mL syringe (i.e., increase the extractable volume criterion from (b) (4) and revise the upper limits for extractable volume and (b) (4) for the 25 mg/0.5 mL syringe (i.e., decrease the extractable volume criterion from (b) (4) to ensure the delivery of appropriate volume of product.

Response to Hold Comment 3b: Samsung revised the acceptance criteria for extractable volume of 50 mg and 25 mg drug product material (Table 28). Sections 3.2.P.5.1 and 3.2.P.5.6 were updated to include an increase in the lower limit of the 50 mg presentation (b) (4) and decrease in the upper limit for the 25 mg presentation (b) (4). Because of the change in extractable volume limits, the (b) (4) for the 50 mg drug product manufactured at (b) (4) has been revised from (b) (4). Section 3.2.P.3.4 was updated with this information.

Reviewer Comment: The revised limits for release testing of extractable volume and (b) (4) ensure that the appropriate amount of product is delivered to meet the label claim for each presentation. Samsung has adequately addressed this portion of the comment.

- c. In the IR response received by the Agency on February 6, 2018, (Question 1) and during the teleconference with the Agency on February 8, 2018, insufficient information was provided regarding the filling control strategy including how (b) (4) is monitored and controlled and how (b) (4) excursions are investigated and handled. For both (b) (4) provide a detailed description in Section 3.2.P.3.3 of how the (b) (4) is controlled in real time during manufacturing. Include the monitoring frequency, number of samples taken, and rejection/action and alert limits. (b) (4)
- Clearly define the actions taken when samples are outside the rejection/action limit;

these should include activities such as segregation of the portion of the lot associated with the out of range sample(s), (b) (4)

Response to Hold Comment 3c: Samsung updated the (b) (4) control strategy per the Agency's recommendations in Section 3.2.P.3.3 for 50 mg drug product manufactured at (b) (4) and 50 mg and 25 mg drug product manufactured at (b) (4)

(b) (4)

Reviewer Comment: The updated (b) (4) control strategies at (b) (4) ensure that (b) (4) is monitored appropriately and (b) (4) excursions are handled appropriately. Samsung has adequately addressed this portion of the comment.

Hold Comment 4

The information and data provided to support the commercial drug product shipping do not provide sufficient assurance that the quality of the DP is maintained during commercial shipping and distribution. The air transport simulation study parameters tested are not representative of routine distribution conditions and cannot on their own be used in lieu of performing real-time DP shipping validation studies. In addition, it is unclear how the supply chain cycling study (Section 3.2.P.8.1) can be used to support the validation of shipping of the drug product from either (b) (4) DP manufacturing sites. Provide shipping validation data for the drug product from real-time shipping studies or from studies that are sufficiently representative of the commercial shipping conditions. The data should include an assessment of product quality pre- and post-shipping. Include a detailed description of how the study was performed and if performed using simulated studies, provide a justification for how the simulated studies are sufficiently representative of the commercial shipping conditions.

Response to Hold Comment 4: Samsung conducted a shipping study based on the commercial shipping route for Korea, which ships drug product manufactured at (b) (4) for secondary packaging then to the distribution center in Korea (b) (4). The estimated transport time from (b) (4) to Korea ((b) (4) hours) is slightly longer than the transport times ((b) (4) hours and (b) (4) hours) for the USA commercial shipping routes (b) (4).

(b) (4) Alternatively, drug product manufactured at (b) (4) may undergo secondary packaging at the site and would then be shipped directly to the distribution center. Therefore, the route chosen for the shipping study is considered representative (or could be considered worst-case) to the USA commercial shipping routes.

Seven drug product lots manufactured at (b) (4) including commercial material (n=3), were evaluated in the study (Table 30). Pre-shipment analysis was performed at the QC testing sites and post-shipment analysis was performed at Korea. The non-compendial QC test methods performed at (b) (4) were transferred to the testing site at Korea, and the QC compendial test methods were verified at Korea with the exception of sterility and bacterial endotoxin, which were outsourced to (b) (4). Sufficient information and data were provided to demonstrate that the transferred non-compendial test methods perform adequately at the Korea testing site (Attachments 4-1 and 4-2). The pre-shipment data are generally comparable to the post-shipment data (Tables 31 – 37); however, a consistent minor increase in HMWs was noted post-shipment (i.e., 1.2% to 1.6%, 1.2% to 2.0%, 1.6% to 1.8%, 1.5% to 2.3%, 1.5% to 2.0%, and 1.2% to 2.1%).

Reviewer Comment: *The slight increase in HMWs post-shipment is not expected to impact the potency and safety of the product (refer to Section 3.2.P.8.3 of the review for additional discussion concerning patient exposure to HMWs). Overall, sufficient information and data were provided to support that the product quality of the commercial drug product is maintained during commercial shipment from (b) (4) to USA for distribution. Samsung has adequately addressed this comment from the OBP perspective. We defer to OPF/DMA for review of the sterility and endotoxin method validation reports.*

Hold Comment 5

As requested in an IR, dated February 6, 2018 and via teleconference with the Agency on February 8, 2018, update the drug product manufacturing process in Section 3.2.P.3.3 to ensure that samples for identity testing for drug product release will be taken after the labeling operations have been completed to comply with 21 CFR 610.14.

Response to Hold Comment 5: Samsung updated Section 3.2.P.3.3 for the 50 mg drug product manufactured at (b) (4) and 50 mg and 25 mg drug product manufactured at (b) (4) to specify that drug product samples for identity testing at release will be taken after the labeling operations have been completed per 21 CFR 610.14.

Reviewer Comment: *Samsung has adequately addressed this comment.*

Additional Comment 1

We do not agree that the information provided on February 13, 2018, is adequate in response to the Agency's IR on February 7, 2018 (IR #2) for the classification o (b) (4)

(b) (4) as non-key control parameters. Upgrade these process parameters to key-controlled parameters (KCPs). In addition,

the (b) (4) is not supported by appropriate data. Tighten the upper end of the range to (b) (4) based on data provided in the viral clearance studies. Update Section 3.2.S.2.2 or Section 3.2.S.2.4 as appropriate.

Response to Additional Comment 1:

(b) (4)

(b) (4) The updated changes to the operating ranges for (b) (4) are reflected in Section 3.2.S.2.6.1 (Table 138).

Reviewer Comment: The totality of information and data provided in the original submission, Type 1 BPD meeting package, and resubmission support the NKCP classification of (b) (4)

. In conclusion, Samsung has adequately addressed this comment.

Additional Comment 2

The response received on February 6, 2018, to the Agency's information request on January 29, 2018 (IR #1 and #2) regarding the revision of acceptance criteria for release and stability was not adequate. The following acceptance criteria should be revised (see also comment 1b under "Product Quality") based on information provided in the resubmission and in the IR response on February 6, 2018, and Sections 3.2.S.5.1 and 3.2.P.5.1 updated accordingly:

- a. The upper end of the acceptance criteria for the TNF- α binding assay should be lowered for DS and DP at release and stability.
- b. The upper end of the acceptance criteria for the TNF- α neutralization assay should be lowered for DS and DP at release and stability.
- c. The acceptance criteria for HIC peak 2 and peak 3 should be tightened further for DS and DP at release and stability.
- d. DP stability acceptance criterion for HMWS by SEC method should be tightened further.
- e. DP stability acceptance criteria for purity by reduced CE-SDS method and HIS should be tightened further.

Response to Additional Comment 2: The applicant updated the drug substance and drug product acceptance criteria for the potency and purity assays according to the Agency's recommendations (SDN 38, 42, 48, and 49). Sections 3.2.S.4.1 and 3.2.P.5.1 were updated with the final drug substance and drug product release and shelf-life specifications, as shown below. The initially proposed acceptance criteria limits are described in the original submission (SDN 1, 05/25/2017).

Drug Substance (Section 3.2.S.4.1)

Table 1: Drug Substance Specification

Test Item			Release Acceptance Criteria	Shelf-life Acceptance Criteria	Analytical Procedure
General tests	Appearance	Clarity	(b) (4)		Ph.Eur. 2.2.1
		Colour			Ph.Eur. 2.2.2
	pH				Ph.Eur. 2.2.3/USP <791>
	Osmolality				Ph.Eur. 2.2.35/USP <785>
Identity	icIEF of desialylated protein				Module 3.2.S.4.2.2
	Competitive inhibition binding assay to TNF- α by FRET				
Quantity	Protein concentration (A_{280})				Module 3.2.S.4.2.3
Glycan content	Total sialic acid (TSA)				Module 3.2.S.4.2.4
Biological activity	Competitive inhibition binding assay to TNF- α by FRET				Module 3.2.S.4.2.5
	TNF- α neutralisation assay by NF- κ B reporter gene				
Purity and impurity	CE-SDS (reducing)	Total purity			Module 3.2.S.4.2.6
		%Highest single impurity			
	SEC				
	HIC	Peak 2			
		Peak 1			
	Peak 3				
Safety	Microbial enumeration	TYMC			Ph.Eur. 2.6.12/USP <61>
		TAMC			
	Endotoxin		Ph.Eur. 2.6.14/USP <85>		

^a N/P: Not performed.

Drug Product (Section 3.2.P.5.1)

Table 1: SB4 Pre-filled Syringe Release and Shelf-life Specifications

Test Item			SB4 50 mg PFS		SB4 25 mg PFS		Analytical Procedure
			Release Acceptance Criteria	Shelf-life Acceptance Criteria	Release Acceptance Criteria	Shelf-life Acceptance Criteria	
General tests	Appearance	Clarity	(b) (4)				Ph. Eur. 2.2.1
		Colour					Ph. Eur. 2.2.2
		Visible particles					Ph. Eur. 2.9.20
	pH						Ph. Eur. 2.2.3/ USP <791>
	Osmolality						Ph. Eur. 2.2.35/ USP <785>
Identity	icIEF of desialylated protein						Module 3.2.S.4.2.2
	Competitive inhibition binding assay to TNF- α by FRET						Module 3.2.S.4.2.2
Quantity	Protein concentration (A_{280})						Module 3.2.S.4.2.3
	Extractable Volume						Ph. Eur. 2.9.17/ USP <1>
Glycan content	Total sialic acid (TSA)						Module 3.2.S.4.2.4
Biological activity	Competitive inhibition binding assay to TNF- α by FRET						Module 3.2.S.4.2.5
	TNF- α neutralisation assay by NF- κ B						Module 3.2.S.4.2.5

Test Item			SB4 50 mg PFS		SB4 25 mg PFS		Analytical Procedure
			Release Acceptance Criteria	Shelf-life Acceptance Criteria	Release Acceptance Criteria	Shelf-life Acceptance Criteria	
Purity and impurity	reporter gene		(b) (4)				Module 3.2.S.4.2.6
	CE-SDS (reducing)	Main peak					
		Highest single impurity					
	SEC						Module 3.2.S.4.2.6
	HIC	Peak 2					Module 3.2.S.4.2.6
		Peak 1					
Peak 3							
Safety	Container closure integrity						Module 3.2.P.8.3.2
	Particulate matter	Particle $\geq 10\text{ }\mu\text{m}$					Ph. Eur. 2.9.19/ USP <788>
		Particle $\geq 25\text{ }\mu\text{m}$					
	Endotoxin						Ph. Eur. 2.6.14/ USP <85>
	Sterility						Ph. Eur. 2.6.1/ USP <71>
Functionality	Break loose force		Module 3.2.P.5.2.8				
	Glide force						

^a N/P: Not performed.

Reviewer Comment: The updated drug substance and drug product specifications for release and stability testing are acceptable. Data provided in the original submission and resubmission support the revised

acceptance criteria. Additional changes (e.g., implementation of a reference standard for the HIC assay and clear definition of “comparable to reference standard” for purity assays) were made to several of the methods, which are reviewed below under Additional Comments 3 and 4. Samsung has adequately addressed this comment.

Additional Comment 3

The description of the Total Sialic Acid (TSA) method did not include the procedure for qualifying new N-acetylneuraminic acid (NANA) and N-glycolylneuraminic acid (NGNA) standard stock solutions. Provide information in the method description on how new stock solutions of NANA and NGNA will be qualified before use to ensure method consistency.

Response to Additional Comment 3: A qualification summary for the current standard solutions and descriptions of the requalification procedure for existing standard solutions and the qualification procedure for new standard solutions were provided. New standard solutions are verified against the validation characteristics of the previous standard solutions (i.e., linearity, precision, and accuracy), and statistical equivalence (2-sample equivalence test) between the new and previous solutions must be demonstrated. The current stock standard solutions (i.e., lot SLBJ9968V for NANA; 081M1667V for NGNA) show acceptable linearity, precision, and accuracy and are equivalent to the previous stock standard solutions (Table 43). The expiry of the current stock standard solutions is extended through requalification. A 2-sample equivalence test with a statistical power of 0.982 (n=15) is performed to ensure that the NANA and NGNA peak areas are equivalent from the initial qualification (95% confidence interval, mean $\pm$ 2SD margin). Section 3.2.S.4.2.4.4.5.2 was updated with descriptions of the qualification and requalification procedures.

Reviewer Comment: *Sufficient data were provided to support the qualification of the current standard solutions. The qualification and requalification procedures are acceptable and ensure that the TSA assay provides meaningful and consistent data analysis. Samsung has adequately addressed this comment.*

Additional Comment 4

As discussed in your response dated February 13, 2018, to the Agency’s IR on February 7, 2018, (IR #5a and #5b), include the use of an in-house reference standard for the HIC method system suitability in the resubmission. In addition, include a clear definition of what constitutes as test sample data comparable to reference standard (with respect to number of peaks, rank order of peak area, relative retention time, etc.) for all chromatography methods in the resubmission.

Response to Additional Comment 4: The use of an in-house reference standard was included for system suitability testing of the HIC assay. Additional criteria were implemented that ensure (i) replicate reference standard chromatograms are visually comparable to each other and the example chromatogram (Figure 18, Section 3.2.S.4.2.6) and (ii) release sample chromatograms are visually comparable to those of the reference standard with only peaks 1, 2, and 3 present. Similar criteria were implemented for the other purity/impurity test methods (i.e., SEC and reduced CE-SDS).

Reviewer Comment: *The proposed changes to the HIC, SEC, and reduced CE-SDS assays are acceptable and ensure that the assays provide meaningful data analysis. Samsung has adequately addressed this comment.*

Additional Comment 5

The method co-validation reports for the TNF- α binding and TNF- α neutralization assays did not include the data from the intermediate precision assessment performed at (b) (4). Provide this information in the resubmission.

Response to Additional Comment 5: Details of the intermediate precision assessments for the TNF- α binding and TNF- α neutralization assays were provided in Sections 3.2.S.4.3.2 and 3.2.S.4.3.6, respectively, and support the data provided in the original submission. A follow-up IR was sent (02/05/2019) to clarify that the intention of the original comment was to request the repeatability data, not the intermediate precision data, for the TNF- α binding and TNF- α neutralization assays because it was unclear whether the repeatability data reported in Table 3-5 of the validation reports (Section 3.2.S.4.3) are from analyses performed at (b) (4). In response (Section 1.11.1; SDN 42, 02/19/2019), Samsung noted that the repeatability data provided in the original submission was only generated at (b) (4). Additional data (Tables 28 – 31) were provided that support the repeatability of the TNF- α binding and TNF- α neutralization assays performed at (b) (4) (4% RSD and 7% RSD, respectively). The repeatability of the TNF- α binding and TNF- α neutralization assays performed at (b) (4) is similar to the repeatability of the assays performed at (b) (4) (5% RSD and 10% RSD, respectively).

Reviewer Comment: *Sufficient data were provided to support the validated state of the TNF- α binding and TNF- α neutralization assays at (b) (4). Samsung has adequately addressed this comment.*

Additional Comment 6

The leachables evaluation of the intended pre-filled syringe only included data for up to 12 months at long-term storage conditions. Provide updated data for the evaluation of leachable material and commit to providing updated data up to the proposed expiry date of (b) (4) months under long-term storage conditions in annual reports.

Response to Additional Comment 6: Samsung updated Section 3.2.P.2.4.1.2 with leachables study data for up to 36 months at the long-term storage condition (2-8°C), which was the originally planned shelf-life of the drug product during development. Samsung clarified that a second leachables study that will evaluate drug product samples stored at 2-8°C for up to 48 months, which is beyond the proposed drug product shelf-life, is ongoing. Samsung submitted up to 24 months of data from the study (Section 3.2.P.2.4.1.1) and will submit the remaining data and a complete toxicological evaluation when the study is completed.

The 36 month Study

The amount of chemical compounds from the drug product container closure system into the drug product solution was evaluated at multiple time-points up to 36 months under long-term and accelerated ($25 \pm 2^\circ\text{C}$, $60 \pm 5\%$) storage conditions by several methods. Gas Chromatography/Mass Spectrometry (GC/MS) was used to analyze the samples for Volatile Organic Compounds (VOC) and Semi-Volatile Organic Compounds (SVOC). Liquid Chromatography/Mass Spectrometry (LC/MS) was used to analyze the samples for target Non-Volatile Organic Compounds (NVOC). An LC chromatogram utilizing UV detection was obtained to determine the presence of peaks corresponding to non-target NVOC. Inductively Coupled Plasma Optical Emission Spectroscopy (ICP/OES) was used to analyze the samples for metals. Ion chromatography (IC) was used for the analysis of (b) (4). In addition, (b) (4) was analyzed by GC/MS. Although the

methods were designed to target compounds identified in the extractable studies, the methods can identify all potential sources of leachables (i.e., non-target analytes). Metal analysis shows that (b) (4) was present in all samples under long-term and accelerated storage. No VOC or SVOC were observed in any sample under long-term and accelerated storage, except for (b) (4) at 30 months. (b) (4) was observed in samples at 6 months and 12 months under accelerated storage, but not present in samples stored under long-term storage. No NVOC were observed in any sample of long-term storage, except for (b) (4) from 18 months. Non-target NVOCs were observed in long-term samples over 12 months of storage; however, because of the low level of these peaks, these compounds were not identified. (b) (4) was observed in all samples of long-term and accelerated storage conditions, while (b) (4) was observed in two samples of accelerated storage at the 3 month time-point. The identified compounds were lower than permitted daily exposure (PDE) limits and other toxicological limits (e.g., as specified in the ICH guidelines). The non-identified NVOC compounds identified during the extractable study were also low and could not be identified; however, the concentrations of the unknown peaks were below the Product Quality Research Institute (PQRI) qualification threshold limit of (b) (4) to support a low safety concern regarding carcinogenic effects. The analysis was performed by (b) (4).

The 48 month Study

A similar study was performed to evaluate the amount of chemical compounds in drug product samples stored up to 48 months of long-term and 12 months of accelerated storage conditions. The same methods used in the 36 month study will be used in the 48 month study. Data were reported for compounds identified above the analytical evaluation threshold (AET) of (b) (4) (defined by PQRI) or PDE limits, which would identify a toxicological risk. No analytes were detected above the AET and PDE limits. In this study, the amount of (b) (4) are also being evaluated. (b) (4) ranged from (b) (4) µg/day, which is below the AET level. (b) (4) level was not detected above the (b) (4) mg/day evaluation level. The analysis was performed by (b) (4).

Reviewer Comment: *The leachables studies were performed adequately to allow for meaningful data analysis. As discussed in Section 3.2.P.8.3 of the review, Samsung shortened the shelf-life from (b) (4) months to 36 months. Based on the data from the extractables and leachables studies and the toxicological assessment of identified compounds, including unknown species, sufficient information and data were provided to support that any potential leachables present at shelf-life do not adversely affect product quality. Samsung has adequately addressed this comment.*

Additional Comment 7

Provide data to support the limit for light exposure time (b) (4) during labeling, assembly of plunger rod and backstop, and finished product packaging operations at (b) (4) for drug product manufacturing.

Response to Additional Comment 7: Data from two studies were provided in support of the light exposure time limit at (b) (4). Study 1 analyzed drug product under (b) (4) while Study 2 analyzed drug substance under (b) (4). While only HMW species were evaluated in Study 1, HMW species, appearance, pH, protein concentration, oxidation, and subvisible particles were evaluated in Study 2. The level of HMWs in drug product exposed to (b) (4) did not show a significant increase of HMW species in control and light exposed naked (2.44% to 2.82%, Table 47) and (b) (4) stored (2.44% to 2.55%, Table 48) drug product samples. Data generated from study 2 showed an increasing trend of HMWs from an initial value

of 1.21% to 2.20% on day 3, 2.90% on day 7, and 4.20% on day 14. Additional changes were noted for purity by reduced CE-SDS (98.5% to 97.7%), HIC peak 1 (1.4% to 1.9%), HIC peak 2 (93.3% to 90.5%), HIC peak 3 (5.4% to 7.6%), oxidation at Met₂₇₂ (6.1% to 15.2%) from the initial time-point to day 14 (Table 52). Intermediate time-points were not evaluated for these attributes.

Reviewer Comment: The data provided in the resubmission were not sufficient to support the (b) (4) limit for light exposure at (b) (4). Besides HMWs, it appears that additional product quality attributes are sensitive to light exposure (data from Study 2; data from photostability studies, Section 3.2.P.8.3). Therefore, an IR was sent (02/05/2019) to Samsung to provide additional information and data to support their proposed limit. In response (Section 1.11.1; SDN 42, 02/19/2019), Samsung tightened the light exposure limit to (b) (4) and performed a trending assessment of the Study 2 data to predict the levels of product quality attributes when exposed to (b) (4) (Table 26, not shown). Given the extent of the changes and the nature of the changes from day 0 to day 14 when exposed to (b) (4), the revised light exposure limit is acceptable. Although minor changes were noted with purity and product-related impurities, the changes at day 14 were still within the acceptance criteria and are expected to be within allowed levels after drug product shipment and in-use storage of the final drug product. Furthermore, potency was acceptable at day 14, and although there was a significant increase in oxidation of Met₂₇₂ at day 14, the Met₂₇₂ residue is in an area of the molecule (Fc region) that would not impact TNF- α binding. While it's unclear whether the 15.2% oxidation at Met₂₇₂ would impact PK of SB4, the trending data suggest that the revised light exposure limit would prevent a significant increase (6.1% to 6.4%). Overall, the data are sufficient to support the light exposure limit of (b) (4) during final PFS assembly, labeling, and packaging operations.

The light exposure limit is in conjunction with a time out of refrigeration limit of (b) (4) which was supported by accelerated stability data provided in the original submission (Section 3.2.P.8.3). To align with (b) (4) an IR (03/28/2019) was communicated to Samsung to update Section 3.2.P.3.3 or 3.2.P.3.4 of the BLA to include the time out of refrigeration (b) (4) for secondary packaging operations at (b) (4). In the IR response (SDN 49, 04/01/2019), Samsung updated Section 3.2.P.3.4 to specify that the time out of refrigeration and exposure to light limits for (b) (4) also apply at (b) (4). Samsung has adequately addressed this comment.

Additional Comment 8

(b) (4) validation study (TR-MS-006703) was performed to demonstrate that the (b) (4) used during SB4 upstream manufacturing does not affect cell growth rate or viability; however, this study was performed to support Process A. Because of differences in the media composition between Process A and Process B, the data from this study cannot be leveraged to support the (b) (4) of Process B. Provide data from Process B validation studies that show the maximum allowable (b) (4) does not impact cell growth and viability.

Response to Additional Comment 8: A validation study report (TR-MS-014812) was provided in Section 3.2.S.2.5 (Attachment 8.1) to support the use of Process B media (b) (4). The media used in the study were made at (b) (4) (Table 4.0-1 in the study report).

(b) (4)

Reviewer Comment: The data provided support that (b) (4) will not impact cell growth kinetics, viability of the cultures, and product quality of the material produced at the (b) (4) step. Samsung has adequately addressed this comment.

Additional Comment 9

(b) (4) compatibility studies were provided for up to 12 months of storage in the final drug product presentation under long-term storage conditions. Provide all available product quality data to support the compatibility of the SB4 drug product with expected levels of (b) (4) in the intended pre-filled syringe at long-term conditions up to the proposed expiry period of (b) (4) months in the resubmission.

Response to Additional Comment 9: Based on the information and data provided during the BPD Type 1 meeting, the Agency agreed it was not necessary to complete the (b) (4) spiking study at long-term conditions up to the proposed expiry period of (b) (4) months. Samsung clearly stated that the (b) (4) used in the study was derived from (b) (4), which would include potential sources of (b) (4) incompatibility. The stability data provided from the (b) (4) spiking study at long-term storage conditions demonstrate no impact on product quality (e.g., purity, product-related impurities, oxidation, particulate matter, appearance, pH, and potency) for up to 12 months in the presence of expected levels of (b) (4) and much higher levels of (b) (4). Literature references were provided that suggest that any incompatibility from (b) (4). Furthermore, Samsung referenced long-term stability data generated from drug product filled in syringes with expected levels of (b) (4) and stored at long-term storage conditions for up to 36 months. Section 3.2.P.2.4.1.4 was updated. No additional studies are needed. Refer to the BPD Type 1 meeting package (SDN 35, 04/09/2018) for additional information concerning the references noted above.

Reviewer Comment: The totality of information and data provided support (b) (4) compatibility for drug product filled in the intended commercial pre-filled syringes and stored at long-term conditions up to shelf-life. Samsung has adequately addressed this comment.

Additional Comment 10

Specify that the post-approval stability protocol and commitment for the drug product (Section 3.2.P.8.2) will include one batch of the 50 mg and 25 mg from (b) (4) as well as one 50 mg batch from (b) (4) will be placed on annual stability.

Response to Additional Comment 10: Samsung updated Section 3.2.P.8.2 to clearly state that one lot of the 50 mg and 25 mg drug product from (b) (4) and one lot of the 50 mg drug product from (b) (4) will be evaluated per the post-approval stability protocol each year that material is manufactured.

Reviewer Comment: *The response to the comment is acceptable. However, the drug substance and drug product post-approval stability protocols only included annual testing time-points, which do not ensure that changes in product quality, that could be a result of small unintentional changes to the manufacturing process over time, are detected as soon as possible. An IR was sent to Samsung on 04/04/2019, and in the IR response (SDN 51, 04/05/2019), Samsung updated the drug substance and drug product post-approval stability protocols (Sections 3.2.S.7.2 and 3.2.P.8.2, respectively) to include 3, 6, 9 and 18 month testing time-points and QC acceptance criteria agreed by the Agency for stability testing. This is acceptable.*

Additional Comment 11

Clarify if (b) (4) performs stability testing of the drug product and update Section 3.2.P.3.1, if applicable.

Response to Additional Comment 11: Section 3.2.P.3.1 was updated to clarify that (b) (4) will serve as a back-up site for drug product stability testing with the exception of particulate matter, sterility, and container closure integrity testing.

Reviewer Comment: *This is acceptable. Sufficient data were provided in the original submission to demonstrate the suitability of the assays used for drug product stability testing at (b) (4). Samsung has adequately addressed this comment.*

Module 3

3.2.S Drug Substance

3.2.S.2.3 Control of Materials

(b) (4)

3.2.P Drug Product

3.2.P.8.3 Stability

The BLA included 36 and 18 months of long-term ($5 \pm 3^{\circ}\text{C}$) stability data for Process A clinical and PVR and Process B commercial drug product lots, respectively. In response to the 03/28/2019 IR, Samsung provided updated stability data for several drug product lots to support the proposed drug substance shelf-life of (b) (4) months at (b) (4) (SDN 49, 04/01/2019). In the original submission and resubmission, Samsung claimed a drug product shelf-life of (b) (4) months; however, this was changed to 36 months in the IR response. The updated stability data included 48 months of long-term ($5 \pm 3^{\circ}\text{C}$) data from clinical drug product lots SB4-13D19 and SB4-13I09 and 30 months of long-term data from commercial drug product lots 00001, 00002, and 00003. Results from the updated stability data were within the specification limits. No significant changes were noted with the exception of continuing minor trends for HMWs, HIC peak 3, and purity by reduced CE-SDS (reducing).

HMWs

For the commercial lots, HMWs increased from 1.2 to 2.8% (1.6% change), 1.4% to 3.2% (1.8% change), and 1.3% to 3.1% (1.8% change) from 0 to 30 months. For the clinical lots, HMWs increased from 1.4% to 4.1% (2.7% change) and 1.4% to 3.8% (2.4% change) from 0 to 48 months.

HIC peak 3

For the commercial lots, HIC peak 3 increased from 3.4% to 4.7% (1.3% change), 3.8% to 5.3% (1.5% change), and 4.4% to 5.8% (1.4% change) from 0 to 30 months. For the clinical lots, HIC peak 3 increased from 4.6% to 6.9% (2.3% change) and 4.8% to 6.5% (1.7% change) from 0 to 48 months.

Purity by CE-SDS (reducing)

For the commercial lots, purity by CE-SDS (reduced) decreased from 97.8% to 95.7% (2.1% change), 97.8% to 95.5% (2.3% change), and 98.0% to 95.9% (2.1% change) from 0 to 30 months. For the clinical lots, purity by CE-SDS (reduced) decreased from 97.2% to 95.1% (2.1% change) and 96.7% to 95.3% (1.4% change) from 0 to 48 months.

Reviewer Comment: While only 30 months of long-term stability data generated from commercial lots were provided, adequate release, characterization, and stability data generated from comparability

assessments support that drug product derived from the commercial process (Process B) is sufficiently representative of drug product derived from Process A (clinical and PVR, refer to review of the original BLA). Based on the representativeness of the commercial process to Process A, it's acceptable to leverage the 48 months of long-term stability data generated from Process A clinical lots to support the shelf-life. Overall, data provided in the BLA are sufficient to establish a 36 month shelf-life for the drug product when stored at $5 \pm 3^{\circ}\text{C}$.

In-Use Storage

Samsung has proposed an in-use storage period of (b) (4) weeks at 25°C as part of the storage and handling information in the package insert. In the resubmission, it was shown that HMWs can increase up to 1% during drug product shipping (see response to CR comment 4) and 2% during in-use storage (b) (4) weeks at 25°C). Therefore, a drug product sample at the limit for HMWs with (b) (4) HMWs on stability may result in a worst-case scenario of (b) (4) of HMWs present when the material is administered into the patient. It was requested in the 03/28/2019 IR that Samsung provide a justification, which may include relevant clinical experience, to support that HMWs at (b) (4) will not have an impact on product efficacy, safety, or immunogenicity (03/28/2019 IR). In response, Samsung revised the proposed in-use storage period of (b) (4) weeks at 25°C to 2 weeks at 25°C to reduce the potential increase in HMWs from 2.0% to ~1.0% (Section 1.11.1; SDN 49, 04/01/2019). This in-use time-period is the same as used for US-licensed Enbrel. A summary of the HMWs data generated from patient convenience stability studies to support Samsung's claim is shown below (Table 2). Samsung excluded lot SB4-14C28 from their analysis because the lot is not representative of the other Process A PVR lots; the manufacture of SB4-14C28 included an isolated change (change in (b) (4)) in the upstream manufacturing process that was not implemented with the other Process A lots.

Table 2: %HMW Increase Comparison between SB4-14C28 and Other Batches during Stability Studies

Stability Studies		%HMW Increase from Initial Time Point	
		SB4-14C28	Other than SB4-14C28 (12L11, SB4-13D19, SB4-13I09, SB4-14C20, SB4-14C26)
Long-term stability studies	12 months	1.0%	1.3% ^a
	24 months	1.4%	1.6% ^a
	36 months	2.0%	2.2% ^a
Patient convenience stability studies	2 weeks	2.0%	0.8% ^a
	4 weeks	1.9%	1.3% ^a
	8 weeks	2.6%	2.0% ^a

^a Maximum increase among batches other than SB4-14C28

Reviewer Comment: Commercial drug product lots were not used in the patient convenience stability studies; however, sufficient data generated from accelerated (25°C) stability testing of commercial drug product lots show increases in HMWs (0.6% and 0.8% increase at one month) that align with data generated from the lots used in the patient convenience study when lot SB4-14C28 is excluded. Therefore, the revised in-use storage period of 2 weeks at 25°C is likely to result in a ~1% increase in HMWs, resulting in a potential patient exposure of (b) (4) HMWs under the worse-case scenario.

Samsung also considered the clinical impact of a worst-case scenario of a drug product lot with (b) (4) HMWs. The impact of increasing levels of HMWs on potency of SB4 and etanercept was assessed in heat-stress stability studies. Data generated from conditioned samples showed correlation between HMWs levels and potency as assessed by TNF- α binding and TNF- α neutralization assays ($R^2 = 93\%$ and 74% , respectively). Based on linear regression analysis with a 95% CI, HMWs levels are at (b) (4) in SB4 and etanercept samples when potency is at the lower specification limit.

Reviewer Comment: *Based on the data generated from the analytical similarity assessment, US-licensed Enbrel lots contain a slightly higher content of HMWs (2.1 to 3.4%) than detected in SB4 (0.6 to 2.2%), and the degradation pathways and rates are comparable between US-licensed Enbrel and SB4 (refer to the original BLA review). Therefore, the risk of an impact of (b) (4) HMWs on safety and efficacy is low for SB4 as the HMWs content in SB4 will likely not be greater than that in US-licensed Enbrel when administered into patients. Furthermore, considering the totality of data and information provided, including modifications in the control strategy to control for levels of HMWs in drug product samples, the revised in-use storage period of 2 weeks at 25°C is acceptable.*



Brian
Jannelsins

Digitally signed by Brian Jannelsins

Date: 4/10/2019 02:05:47PM

GUID: 54b8280e000855ed28b059d11c54a788



Rachel
Novak

Digitally signed by Rachel Novak

Date: 4/10/2019 02:18:41PM

GUID: 52e163f70002ba9e745b4e39384c76d7

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.

QAL: Reyes Candau-Chacon, Ph.D.

BLA:	761066
Applicant:	Samsung Bioepis Co, Ltd.
US License Number:	2046
Submission Reviewed:	Original 351(k) BLA resubmission after Complete Response (eCTD sequence 0038)
Product:	SB4 (Proposed biosimilar to etanercept)
Indication:	Rheumatoid Arthritis (RA), Polyarticular Juvenile Idiopathic Arthritis, Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Plaque Psoriasis (PsO)
Dosage Form:	Single dose pre-filled syringe for subcutaneous injection (25 mg and 50 mg)
Manufacturing Site:	Drug product: (b) (4) (b) (4)
FDA Receipt Date:	October 25, 2018
Action Date:	April 25, 2019

Conclusion and Approvability Recommendation

The drug product portion of this BLA, as amended, is recommended for approval from a sterility assurance and product quality microbiology perspective. The following postmarketing commitments should be communicated to the applicant:

1. Implement (b) (4) monitoring during sterile filtration of the SB4 drug product at (b) (4)
2. Implement (b) (4) monitoring during sterile filtration of the SB4 drug product at (b) (4)

Product Quality Microbiology Assessment: Drug Product

Drug Product Quality Microbiology Information Reviewed

Sequence number	Date	Description
0038	10/25/18	BLA Resubmission
0043	02/26/19	Response to IR
0046	03/08/19	Response to IR

Reviewer comment: The original BLA was reviewed in the memos uploaded and archived in Panorama on February 12, 2018 and February 22, 2018. It should be noted that two of the additional comments listed in the February 22, 2018 addendum were not communicated to the applicant, as these items were not viewed to be high risk to the product for patient safety (e.g., the acceptance criterion for shipping validation is low risk, as the acceptance criterion for routine testing is 100% integral units). (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

This memo reviews the drug product complete response items and additional comments communicated to the applicant in the Complete Response (CR) letter. Additionally, the applicant provided endotoxin method qualification for the kinetic turbidimetric method at (b) (4) in Attachment 4-3 and sterility method qualification at (b) (4) in Attachment 4-4. The (b) (4) site performed endotoxin and sterility test for the shipping validation study. These reports are not reviewed, as the (b) (4) site is not used for release testing of the DP.

Drug Product

Complete Response Comments

Product Quality Question 6:

The sterilization validation data provided to support the (b) (4) sterilization of items used to manufacture SB4 at (b) (4) was deficient, as there is no minimum (b) (4) validated. Inadequate validation of sterile product-contact equipment may result in a non-sterile product. Provide sterilization validation for the minimum (b) (4) in the BLA resubmission.

Review of Samsung Response:

The applicant included the sterilization validation information for the minimum (b) (4) in section P.3.5.7.1 [(b) (4) 50 mg]. The initial validation for the minimum configuration of the (b) (4) was performed in April 2018 (refer to Table 40 of section P.3.5 – (b) (4) 50 mg). (b) (4)

[REDACTED]

(b) (4)

SATISFACTORY

Product Quality Question 7:

The BLA does not include (b) (4) as a critical process parameter for sterile filtration. Performing sterile filtration outside of the parameters validated by the microbial retention study may result in a non-sterile product. Include the sterile filtration (b) (4) as a critical process parameter and provide the respective acceptance criteria in section 3.2.P.3.4.

Review of Samsung Response:

The applicant performed a study to correlate (b) (4), as parameters validated by the microbial retention study (b) (4) were not monitored in the original BLA submission. The applicant provided the correlation studies in section P.3.5.4.5 [(b) (4) 50 mg] and P.3.5.4.2 [(b) (4) 50 mg] of the resubmission. Additionally, the acceptance criteria for (b) (4) were included in P.3.4 for each manufacturing site. The information provided in the resubmission is reviewed below.

(b) (4)

(b) (4)

An IR was also sent to the applicant requesting the implementation of (b) (4) monitoring for sterile filtration at (b) (4). The applicant plans to implement (b) (4) monitoring by the (b) (4) at (b) (4) (sequence 0043). The applicant provided a justification for the delayed implementation of (b) (4) monitoring at (b) (4) in sequence 0046, which includes the completion of the following activities: (b) (4).

The in-process control for sterile filtration was updated in P.3.4 to (b) (4), which is based on the microbial retention study report (sequence 0043). P.3.3 was updated to include (b) (4) as an in-process control (implemented (b) (4)). The applicant stated that until (b) (4) will be monitored. Taken together, the correlation study and commitment to implement (b) (4) monitoring mitigates the risk to the product during sterile filtration.

POSTMARKETING COMMITMENT: Implement (b) (4) monitoring during sterile filtration of the SB4 drug product at (b) (4).

(b) (4)

(b) (4)

POSTMARKETING COMMITMENT: Implement (b) (4) monitoring during sterile filtration of the SB4 drug product at (b) (4)

Additional Comments

Question 12

The preliminary action limit of total number of rejected units for filling at (b) (4) is not acceptable. Lower the preliminary action limit of the total number of rejected units for filling at (b) (4) and update section 3.2.P.3.4 accordingly.

Review of Samsung Response:

The Agency agreed during the BPD Type 1 meeting that the applicant could address additional comment 12 after sufficient data is collected from (b) (4). The current preliminary action limit for the total number of rejected units for filling at (b) (4) is listed as (b) (4) for the 50 mg and 25 mg DP; however, this limit will be reassessed after 30 commercial batches of the 50 mg and 25 mg DP are manufactured. Refer to the BPD Type 1 meeting (held May 10, 2018) minutes in DARRTS for additional information.

SATISFACTORY

Conclusion

- I. The DP portion of the BLA, as amended, was reviewed from a product quality microbiology and sterility assurance perspective and is recommended for approval. The following postmarketing commitment should be communicated to the applicant:
 - i. Implement (b) (4) monitoring during sterile filtration of the SB4 drug product at (b) (4)
 - ii. Implement (b) (4) monitoring during sterile filtration of the SB4 drug product at (b) (4)
- II. Product quality aspects other than microbiology should be reviewed by OBP and CDRH.
- III. No inspection follow-up items were identified.

DP Microbiology Information Requests Sent:

Date: 02/04/2019

1. Table 35 indicates that the (b) (4) are the items included in the minimum (b) (4). Clarify whether these items were the worst-case items from the maximum (b) (4). If these items were not the worst-case items, justify why the items were selected.
- 1) The response to the Product Quality Complete Response (CR) item #7 did not address the deficiency. The deficiency in the CR letter stated, “include the sterile filtration (b) (4) as a critical process parameter and provide the respective acceptance criteria in section 3.2.P.3.4.” Performing sterile filtration outside of the parameters validated by the microbial retention study may result in a non-sterile product. In the resubmission, neither (b) (4) are monitored at (b) (4) or (b) (4). PDA Technical Report 26 states that process conditions such as (b) (4) may influence bacterial retention and includes (b) (4) among one of the parameters that needs to be monitored or controlled during filtration. Additionally, the 2004 *Guidance for Industry Sterile Drug Products Produced*

by Aseptic Processing – Current Good Manufacturing Practice states that (b) (4) (b) (4) As stated in the CR letter, implement monitoring of (b) (4) during sterile filtration at (b) (4) and (b) (4) and provide a timeline. Update sections 3.2.P.3.3 and 3.2.P.3.4 of the BLA accordingly.

Date: 03/04/2019

1. The response to Question 2 of sequence 0043 indicates that (b) (4) monitoring will not be implemented at (b) (4) until (b) (4). Additionally, the correlation study at (b) (4) (performed with (b) (4) instead of drug product) indicates that the (b) (4) was (b) (4) which is just below the (b) (4) validated by the microbial retention study (b) (4). Provide a justification for the timeline at (b) (4) as (b) (4) monitoring at (b) (4) will be implemented by (b) (4).



Jessica
Hankins

Digitally signed by Jessica Hankins

Date: 3/26/2019 11:24:42AM

GUID: 57640ae700ea29dfdaa5ef6b52b35c55



Reyes
Candau-Chacon

Digitally signed by Reyes Candau-Chacon

Date: 3/26/2019 12:57:52PM

GUID: 508da7160002977f7ca389c8f849b707



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg. 51, 10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: 03/13/2019
To: Administrative File, STN 761066 (Resub 38)
From: Michael Shanks, Biologist, CDER/OPQ/OPF/DIA
Endorsement: Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA
Subject: Biologic License Application for SB4 (etanercept-xxxx) that is a biosimilar* to Enbrel (etanercept)
US License: 2046
Applicant: Samsung Bioepis Co., Ltd
Mfg Facility: Drug Substance:

(b) (4)

Drug Product:

(b) (4)

Proposed Trade Name: To be determined
Nonproprietary Name: To be determined. Referred to as "Enbrel (etanercept)" by the applicant*)
Dosage: SB4 is presented in single-dose pre-filled syringes of 25 mg (b) (4) and 50 mg (b) (4) to be administered via subcutaneous (SC) injection.
Indication: SB4 (etanercept-xxxx) is indicated for the treatment of Rheumatoid Arthritis(RA), Polyarticular Juvenile Idiopathic Arthritis, Psoriatic Arthritis(PsA), Ankylosing Spondylitis(AS), Plaque Psoriasis(PsO)..
Due Date: 4/25/2019

RECOMMENDATION: This application is recommended as APPROVE from a facility review perspective.

SUMMARY

The subject BLA proposes the manufacture of SB4 (etanercept-xxxx), that is a biosimilar to Enbrel (etanercept). Samsung Bioepis Co., Ltd's SB4 Drug Substance (DS) and Drug Product (DP) is a homodimer of a chimeric protein genetically engineered by fusing the extracellular ligand binding domain of human TNFR2/p75 to the Fc domain of human IgG1. SB4 DS is produced by Chinese hamster ovary (CHO) cell expression system as a dimeric, secreted, soluble protein. (b) (4)

A Pre-license inspection for SB4 Drug Substance was conducted on (b) (4) at (b) (4). A 6-item FDA Form 483 was issued, and the initial recommendation is approve for this BLA. A final classification of the (b) (4) pre-license inspection was acceptable. Regarding the current application for SB4 (etanercept-xxxx) drug product manufacturing at (b) (4), (b) (4) both PAI's were waived and concurred by DIA, DMA, and OBP. The Drug Product manufacturing sites, (b) (4) were approve based on their inspection history, profile and a ORA District File recommendation of approve. All other related manufacturing and testing facilities have an acceptable compliance status.

ASSESSMENT

DRUG SUBSTANCE FACILITIES

3.2.S Drug Substance [Substance – Manufacturer]

3.2.S.2. Manufacture

3.2.S.2.1 DS Manufacturers.

The sites proposed for SB4 Drug Substance manufacture and testing is presented below in Table 1.

Table 1. Proposed Sites for SB4 DS Manufacture, Cell Banking and Testing Operations

Site Name	Address	FEI Number	Responsibilities
		(b) (4)	Drug Substance manufacturing, packaging, and testing.
			Manufacturing and storage of the MCB and WCB.
			Storage of the MCB and WCB.
			Storage of the MCB and WCB.
			Storage of the MCB and WCB.
			Drug Substance In-process testing .
			Drug Substance In-process testing .
			Drug Substance release and stability testing.
			Drug Substance stability testing.
			Drug Substance stability testing.
			Drug Substance storage.

Reviewer Comment 1: The facilities for manufacture of SB4 DS are adequately described.

—Satisfactory—

• Prior Inspection History for DS Manufacturing and Testing Sites

		(b) (4)

—*Satisfactory*—

CONCLUSION

Descriptions provided for the (b) (4) Manufacturing ApS (b) (4) SB4 Drug Substance and the (b) (4) and (b) (4) Drug Product facilities proposed for DS and DP manufacture were reviewed. All other related manufacturing and testing facilities have an acceptable compliance status. The current compliance status for the proposed DS and DP manufacturing is **acceptable** and a recommended of **approve** is made from a facilities assessment standpoint.

Michael Shanks
Biologist
OPF Division of Inspectional Assessment
Branch 1

Zhihao Peter Qiu, Ph.D.
Branch Chief
OPF Division of Inspectional Assessment
Branch 1

Biosimilar BLA Review

Recommendation: Complete Response

BLA Number: 761066

Review Number:

Review Date: 03/23/2018

Drug Name/Dosage Form	SB4 Etanercept Biosimilar
Strength/Potency	25 mg/0.5 mL and 50 mg/mL solution for injection in pre-filled syringes
Route of Administration	Subcutaneous
Rx/OTC dispensed	Rx
Indication	Rheumatoid Arthritis, Polyarticular Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Plaque Psoriasis
Applicant/Sponsor	Samsung Bioepis
US agent, if applicable	Biologics Consulting Group Inc.

Product Overview

SB4 is a homodimer of a fusion protein consisting of the extracellular ligand binding domain of human TNFR2/p75 and the Fc domain of human IgG1. The mechanism of action (MOA) of SB4 involves binding soluble Tumor Necrosis Factor Alpha (TNF α) and TNF-beta (TNF β) and membrane-bound TNF α to inhibit binding to TNF receptors, blocking downstream TNF signaling. SB4 is a highly glycosylated fusion protein with each single chain consisting of three N-linked glycosylation sites and 13 potential O-linked glycosylation sites. The Fc portion of SB4 can induce low levels of effector function such as antibody dependent cellular cytotoxicity (ADCC); however, this pathway does not contribute to the mechanism of action of SB4. The SB4 drug product is supplied in two presentations of 25 mg/0.5mL and 50 mg/mL in a pre-filled syringe (PFS) and is intended for the treatment of several auto-immune disorders including Rheumatoid Arthritis, Polyarticular Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis and Plaque Psoriasis.

Quality Review Team

Discipline	Reviewer	Branch/Division
Drug Substance	Brian Janelins	OBP/DBRRI
Drug Product	Brian Janelins	OBP/DBRRI
Analytical Similarity Assessment	Brian Janelins	OBP/DBRRI
Immunogenicity	Brian Janelins	OBP/DBRRI
Labeling	Vicki Borders-Hemphill	OPQ/OPRO
Facility	Michael Shanks/Zhihao Peter Qiu	OPF/DIA Branch 1
Microbiology	Maxwell Van Tassell (Drug Substance) Jessica Hankins (Drug Product) Reyes Candau-Chacon (QAL)	OPF/DMA/DMABIV
Application Team Lead	Rachel Novak	OBP/DBRRI
CMC statistics	Yu-Yi Hsu/Meiyu Shen	OB/DBIV
OBP Tertiary Reviewer	Marjorie Shapiro	OBP/DBRRI
CMC RBPM	Oumou Barry	OPQ/OPRO

Mutidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Brandi Wheeler	CDER/ODEII/DPARP
Cross-disciplinary Team Lead	Nikolay Nikolov	CDER/ODEII/DPARP
Medical Officer	Rachel Glaser	CDER/ODEII/DPARP
Pharm/Tox	Ijeoma Uzoma/Tim Robinson (TL)	CDER/ODEII/DPARP
Clinical Pharmacology	Bavna Saluja/Anshu Marathe (TL)	CDER/ODEII/DPARP
Statistics	Ginto Pottackal/Greg Levin (TL)	CDER/OB/DBII

1. Names:

- a) Proprietary Name: To be determined
- b) Trade Name: To be determined
- c) Non-Proprietary/USAN: To be determined (etanercept-ykro)
- d) CAS name: 185243-69-0
- e) Common name: SB4
- f) INN Name: etanercept
- g) Compendial Name: N/A
- h) OBP systematic name: Fus: RPROTFRAG P20333 (TNR1B_HUMAN); MABFRAG HUMAN (IGG1 FC) [SB4]
- i) Other Names: BIIB602E

Communications with sponsor (OBP):

Communication/ Document	Date
Filing Letter	07/24/2017
Information Request	08/02/2017
Information Request	11/21/2017
Information Request	12/19/2017
Information Request	01/18/2018
Information Request	01/24/2018
Information Request	01/29/2018
Information Request	02/02/2018
Information Request	02/07/2018
T-Con with Samsung (OBP and DMA)	02/08/2018

Communications with sponsor (DMA):

Communication/ Document	Date
Information Request	06/22/2017
Information Request	10/27/2017
Information Request	12/8/2017
Information Request	12/14/2017
Information Request	1/8/2018
Information Request	01/26/2018
Information Request	2/12/2018
Information Request	02/15/2018

Submissions Reviewed:

Submission(s) Reviewed (OBP)	Document Date
761066/0000 (original submission)	05/25/2017
761066/0006 (response to IR 08/02/2017)	08/09/2017
761066/0017 (response to IR 11/21/2017)	12/11/2017
761066/0020 (response to IR 12/19/2017)	01/12/2018
761066/0024 (response to IR 01/18/2018)	01/25/2018
761066/0026 (response to IR 01/29/2018)	02/02/2018
761066/0027 (response to IR 01/24/2018, 01/29/2018)	02/06/2018
761066/0029 (response to IR 02/02/2018)	02/13/2018
761066/0030 (response to IR 02/07/2018)	02/14/2018

Submission(s) Reviewed (DMA)	Document Date
761066/0001 (Original submission)	05/25/2017
761066/0003 (Response to IR 06/22/2017)	06/30/2017
761066/0014 (Response to IR 10/27/2017)	11/13/2017
761066/0015 (Response to IR 10/27/2017)	11/21/2017
761066/0018 (Response to IR 12/8/2017)	12/15/2017
761066/0022 (Response to IR 12/14/2017)	01/17/2018
761066/0023 (Response to IR 1/8/2018)	01/19/2018
761066/0027 (Response to IR 01/26/2018)	02/06/2018
761066/0031 (Response to IR 2/12/2018)	02/15/2018
761066/0032 (Response to IR 02/15/2018)	02/21/2018

Quality Review Data Sheet

1. Legal Basis for Submission: 351(k)

2. Related/Supporting Documents:

A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code1	Status2	Date Review Completed	Comments
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	01/08/2018	N/A

1. Action codes for DMF Table: 1- DMF Reviewed; Other codes indicate why the DMF was not reviewed, as follows:
2- Reviewed previously and no revision since last review; 3- Sufficient information in application; 4- Authority to reference not granted; 5- DMF not available; 6- Other (explain under "comments")

2. Adequate, Adequate with Information Request, Deficient, or N/A (There is not enough data in the application; therefore, the DMF did not need to be reviewed).

B. Other documents: IND, Referenced Listed Drug (RLD), or sister application.

Document	Application Number	Description

3. Consults:

Discipline/ Topic	Date Requested	Status	Recommendation	Reviewer
Device (Pre-filled Syringe)	6/6/2017	Complete	Approve	Steen Basile/John McMichael
CDRH OC/Compliance status evaluation	7/13/2017	Complete	No device inspection is needed	Kenneth Chen

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation: **Complete Response**

The Office of Pharmaceutical Quality (OPQ), CDER, has completed review of STN 761066 for SB4 manufactured by Samsung Bioepis. The data submitted in this application are not sufficient to support a conclusion that the manufacture of SB4 is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life. From a CMC standpoint, OPQ is recommending a Complete Response letter be issued to Samsung Bioepis to outline the deficiencies noted below and the information and data that will be required to support approval. Please refer to the Complete Response letter for the complete and final list of deficiencies and comments.

B. Summary of Complete Response Issues:

OBP CR comments (provided by OBP)

1. The data and information provided in your response on January 12, 2018 and February 14, 2018 to the Agency's information requests (IRs) on December 19, 2017 (IR#13) and February 7, 2018 (IR#1) demonstrate that the primary reference standard (PRS) was not appropriately qualified with respect to biological activity (i.e., TNF- α binding activity and TNF- α neutralization activity) and protein concentration, and therefore, is not appropriate for its intended use. Because the PRS was not appropriately qualified, the working reference standard (WRS), which was qualified against the PRS, is also not appropriate for its intended use. Therefore, there is a lack of assurance that the commercial materials are not going to drift from SB4 clinical materials and the materials used to establish the analytical similarity.
 - a. Generate an appropriately qualified reference material based on the advice provided in the Agency's IRs on December 19, 2017 and February 7, 2018. Upon the generation of the new qualified reference material, data should be provided to adequately link this material to the materials used in the clinical studies and analytical similarity assessment. The Agency recommends using a two-tiered system for utilizing reference standard material for routine testing of commercial product.
 - b. Re-assess and revise SB4 drug substance and drug product lot release and stability specifications, as appropriate.
 - c. Re-test the currently manufactured SB4 lots for release and stability using the appropriately qualified reference material, as appropriate, if these lots are intended to be released for commercial use in the US.
 - d. Provide an updated requalification protocol for the reference material (e.g. primary and working reference standards) to include the advice that was given in the Agency's information requests on December 19, 2017 and February 7, 2018.
2. The data and information provided in the submission and in your response on February 13, 2018 to the Agency's information requests on February 2, 2018 (IR#1) was insufficient to

support the limit of in vitro cell age (LIVCA) (b) (4) and the proposed control limit of (b) (4)

Characterization and assessment of LIVCA using (b) (4)

(b) (4) study is not considered sufficiently representative of cell culture behavior during the commercial cell culture process. In addition, the information provided in the IR response on February 13, 2018 (IR#7) concerning the generation of the SB4 Master Cell Bank (MCB) suggests that the cell bank is not clonal (b) (4)

Taken together, the overall control strategy for the upstream cell culture process is inadequate and requires additional levels of control. To ensure product quality and cell culture process consistency, implement the following controls and update all the appropriate sections of the BLA with this information:

- a. Establish LIVCA using an appropriate cell culture model that is sufficiently representative of the commercial cell culture process. For example, (b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)
 - b. Establish key controlled parameter (KCPs) for (b) (4)
(b) (4)
(b) (4) These ranges should be supported by data from development studies using an appropriate cell culture model, PPQ and/or commercial manufacturing runs.
 - c. Implement a critical control limit for the number of (b) (4)
(b) (4) to ensure that the LIVCA (based on comment 2a) is not exceeded by the (b) (4) during routine manufacturing. Provide information and/or data to justify the control for the limit of (b) (4)
(b) (4)
3. The information provided in the submission and in the responses received by the Agency on February 2, 6, and 14, 2018 and during the teleconference held with the Agency on February 8, 2018 is not adequate to support that the currently proposed drug product filling control strategy provides sufficient assurance that each pre-filled syringe (PFS) is filled with sufficient SB4 product to meet the current US label claim of 50 mg/mL and 25 mg/0.5mL for Enbrel.
- a. Although the protein concentration for drug product process validation batches filled at (b) (4) and (b) (4) are within the acceptance criterion range of (b) (4) at release, the protein concentration is consistently less than 50 mg/mL while the drug substance lots used to fill these drug product lots did not have this issue. For example, drug substance lot 15-602E-002 had a protein concentration of (b) (4) at release and the resulting drug product lot, 00003, had a protein concentration of (b) (4). Because the drug product (b) (4), it is unclear why there is such variability between the drug substance protein concentration and the subsequent drug product protein concentration. Explain this discrepancy.
 - b. While the labeling allows (b) (4) when considering the control strategy, the current criteria would allow the release of PFS filled outside appropriate limits. The 50 mg/mL syringes may be underfilled, because a volume of (b) (4) deliverable volume) is allowed, and the 25 mg/0.5 mL syringes may

be filled to an inappropriately high level of (b) (4) deliverable volume). As requested by the Agency on February 7, 2018, revise the lower limits for extractable volume (Section 3.2.P.5.1) and (b) (4) (Section 3.2.P.3.3) for the 50 mg/mL syringe (i.e., increase the extractable volume criterion from (b) (4) and revise the upper limits for extractable volume and (b) (4) for the 25 mg/0.5 mL syringe (i.e., decrease the extractable volume criterion from (b) (4) to ensure the delivery of appropriate volume of product.

- c. In the IR response received by the Agency on February 6, 2018 (Question 1) and during the teleconference with the Agency on February 8, 2018, insufficient information was provided regarding the filling control strategy including how (b) (4) is monitored and controlled and how (b) (4) excursions are investigated and handled. For both (b) (4) and (b) (4) provide a detailed description in Section 3.2.P.3.3 of how the (b) (4) is controlled in real time during manufacturing. Include the monitoring frequency, number of samples taken, and rejection/action and alert limits. (b) (4)
(b) (4) Clearly define the actions taken when samples are outside the rejection/action limit; these should include activities such as segregation of the portion of the lot associated with the out of range sample(s), (b) (4)
(b) (4)
4. The information and data provided to support the commercial drug product shipping do not provide sufficient assurance that the quality of the DP is maintained during commercial shipping and distribution. The air transport simulation study parameters tested are not representative of routine distribution conditions and cannot on their own be used in lieu of performing real-time DP shipping validation studies. In addition, it is unclear how the supply chain cycling study (Section 3.2.P.8.1) can be used to support the validation of shipping of the drug product from either (b) (4) or (b) (4) DP manufacturing sites. Provide shipping validation data for the drug product from real-time shipping studies or from studies that are sufficiently representative of the commercial shipping conditions. The data should include an assessment of product quality pre- and post-shipping. Include a detailed description of how the study was performed and if performed using simulated studies, provide a justification for how the simulated studies are sufficiently representative of the commercial shipping conditions.
5. As requested in an IR on February 6, 2018 and via teleconference with the Agency on February 8, 2018, update the drug product manufacturing process in Section 3.2.P.3.3 to ensure that samples for identity testing for drug product release will be taken after the labeling operations have been completed to comply with 21 CFR 610.14.

Microbiology CR comment (provided by OPV/DMA)

6. The sterilization validation data provided to support the (b) (4) sterilization of items used to manufacture SB4 at (b) (4) was deficient, as there is no minimum (b) (4) validated. Inadequate validation of sterile product-contact equipment may result in a non-sterile product. Provide sterilization validation for the minimum (b) (4) in the BLA resubmission.

7. The BLA does not include (b) (4) as a critical process parameter for sterile filtration. Performing sterile filtration outside of the parameters validated by the microbial retention study may result in a non-sterile product. Include the sterile filtration (b) (4) as a critical process parameter and provide the respective acceptance criteria in section 3.2.P.3.4 of the BLA.

C. Additional Comments (provided by OBP and DMA)

1. The Agency does not agree that the information provided on February 13, 2018 is adequate in response to the Agency's IR on February 7, 2018 (IR#2) for the classification of (b) (4) as non-key control parameters. Upgrade these process parameters to key-controlled parameters (KCPs). In addition, the (b) (4) is not supported by appropriate data. Tighten the upper end of the range to (b) (4) based on data provided in the viral clearance studies. Update Section 3.2.S.2.2 or Section 3.2.S.2.4 as appropriate.
2. The response received on February 6, 2018 to the Agency's information request on January 29, 2018 (IR#1 and #2) regarding the revision of acceptance criteria for release and stability was not adequate. The following acceptance criteria should be revised (see also comment 1b under "Product Quality") based on information provided in the resubmission and in the IR response on February 6, 2018 and Sections 3.2.S.5.1 and 3.2.P.5.1 updated accordingly:
 - a. The upper end of the acceptance criteria for the TNF-α binding assay should be lowered for DS and DP at release and stability.
 - b. The upper end of the acceptance criteria for the TNF-α neutralization assay should be lowered for DS and DP at release and stability.
 - c. The acceptance criteria for HIC peak 2 and peak 3 should be tightened further for DS and DP at release and stability.
 - d. DP stability acceptance criterion for HMWS by SEC method should be tightened further.
 - e. DP stability acceptance criteria for purity by reduced CE-SDS method and HSI should be tightened further.
3. The description of the Total Sialic Acid method did not include the procedure for qualifying new N-acetylneuraminic acid (NANA) and N-glycolylneuraminic acid (NGNA) standard stock solutions. Provide information in the method description on how new stock solutions of NANA and NGNA will be qualified before use to ensure method consistency.
4. As discussed in your response on February 13, 2018 to the Agency's IR on February 7, 2018 (IR #5a and #5b), include the use of an in-house reference standard for the HIC method system suitability in the resubmission. In addition, include a clear definition of what constitutes a test sample as comparable to reference standard (with respect to number of peaks, rank order of peak area, relative retention time, etc.) for all chromatography methods in the resubmission.
5. The method co-validation reports for the TNF-α binding and TNF-α neutralization assays did not include the data from the intermediate precision assessment performed at (b) (4). Provide this information in the resubmission.

6. The leachables evaluation of the intended pre-filled syringe only included data for up to 12 months at long-term storage conditions. Provide updated data for the evaluation of leachable material and commit to providing updated data up to the proposed expiry date of (b) (4) months under long-term storage conditions in annual reports.
7. Provide data to support the limit for light exposure time (b) (4) during labeling, assembly of plunger rod and backstop, and finished product packaging operations at (b) (4) for drug product manufacturing.
8. (b) (4) validation study (TR-MS-006703) was performed to demonstrate that the (b) (4) used during SB4 upstream manufacturing does not affect cell growth rate or viability; however, this study was performed to support Process A. Because of differences in the media composition between Process A and Process B, the data from this study cannot be leveraged to support the (b) (4) of Process B. Provide data from Process B validation studies that show the maximum allowable (b) (4) does not impact cell growth and viability.
9. (b) (4) compatibility studies were provided for up to 12 months of storage in the final drug product presentation under long-term storage conditions. Provide all available product quality data to support the compatibility of the SB4 drug product with expected levels of (b) (4) in the intended pre-filled syringe at long-term conditions up to the proposed expiry period of (b) (4) months in the resubmission.
10. Specify that the post-approval stability protocol and commitment for the drug product (Section 3.2.P.8.2) will include one batch of the 50 mg and 25 mg from (b) (4) as well as one 50 mg batch from (b) (4) will be placed on annual stability.
11. Clarify if (b) (4) performs stability testing of the drug product and update Section 3.2.P.3.1, if applicable.
12. The preliminary action limit of total number of rejected units for filling at (b) (4) is not acceptable. Lower the preliminary action limit of the total number for rejected units for filling at (b) (4) and update section 3.2.P.3.4 accordingly.

Manufacturing location:

- Drug Substance: (b) (4)
- Drug Product: (b) (4)
- Fill size and dosage form: 25 mg/0.5 mL and 50 mg/mL solution for injection in a pre-filled syringe.
- Dating period:
 - Drug Product: (b) (4) months: 2-8 °C
 - Drug Substance: (b) (4)
 - Stability Option (select one below):
 - We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating of your drug substance and drug product under 21 CFR 601.12. However, this is deferred at this time due to the CR action.

- Exempt from lot release
 - Yes
 - Rationale: specified product in accordance with 21 CFR 601.2a.

D. Benefit/Risk Considerations:

To determine whether SB4 is highly similar to US-licensed Enbrel, and to establish the adequacy of the analytical portion of the scientific bridge between SB4, US-licensed Enbrel, and EU-approved Enbrel, Samsung evaluated and compared analytical data from multiple lots of each of the three products. The analytical comparison of SB4 to US-licensed Enbrel was used to support the demonstration that SB4 is highly similar to US-licensed Enbrel, notwithstanding minor differences in clinically inactive components. Pairwise comparisons of SB4, US-licensed Enbrel, and EU-approved Enbrel were used to support the analytical portion of the scientific bridge between the three products to justify the relevance of the comparative data generated using EU-approved Enbrel from some clinical and nonclinical studies.

For the analytical similarity assessment, attributes were assigned into tiers and were assessed dependent on the stringency of the statistical method, using a sufficient number of lots of each product. Assays, including TNF α binding and TNF α neutralization assays, which address the potential mechanism of action of SB4, were considered as part of the Tier 1 analysis and were analyzed by equivalence testing. Analysis of SB4 for Tier 1 met the criteria for equivalence testing. Tier 2 and 3 comparisons involved assessment of amino acid sequences, secondary and tertiary structures, purity, charge and glycan profiles of SB4, US-etanercept and EU-etanercept support the conclusion that the products are highly similar. For some quality attributes, orthogonal methods were used to investigate potential differences. See the table below for a summary of the product quality attributes assessed for SB4 and their respective tier rankings.

Quality Attribute	Specific Attribute Measured	Criticality/ Risk	Method	Tier
Primary Structure	• Amino acid sequence • Disulfide mapping • Site of glycosylation and chemical modification • Free Thiols	High	• UPLC-ESI-MS • FLR	3
Post-Translational Modifications	• Terminal GlcNAc-variants • Alpha-galactosylation • High Mannose Glycans • Tri-antennary glycan Structures • Non-fucosylated glycan variants • Overall Sialylation • Sialylation of N-glycans • Sialylation of O-glycans • Sialic acids (NGNA)	High Moderate Moderate or low	• HILIC-UPLC • HILIC-UPLC • 2-AB labeling/HILIC UPLC • HILIC-UPLC • HPLC	2/3
Higher Order Structure	• Secondary and Tertiary structure	High/High	• Far- and Near-UV circular dichroism	3

			- Differential Scanning Calorimetry - Fourier transform infrared spectroscopy (FTIR) - Hydrogen Deuterium Exchange - Intrinsic and Extrinsic Fluorescence spectroscopy - DLS	
	Wrongly bridged disulfide bonds	High	UPLC-ESI-MS/MS	3
Size Variants	- Main Peak Purity - Aggregation Products - Degradation Products	High/ Moderate	- SEC - HIC - CE-SDS (reducing) - CE-SDS (non-reducing) - SEC-MALS - SV-AUC	2
Bioactivity	- TNF-alpha neutralization - TNF-beta binding - TNF-alpha binding - FcRn binding - CDC Activity - ADCC - TNFa binding on different species - FcγRIIIa binding - FcγRIIa binding - Other FcγR receptors and C1q	Very high High Moderate	- Reporter Gene assay - FRET - FRET - SPR - Cell based - SPR	1/2/3
Product related Substances and impurities	- Acidic Variants - Oxidation - Deamidation - Basic Variants - N-terminal Variants - C-terminal Lys Variants - Glycation	Moderate Low/Low Low/Very Low	- icIEF - UPLC-ESI-MS/MS	2/3
Drug product attributes	- Protein content - pH - Osmolality - Color - Turbidity - Sub-visible particles	High	Compendial Methods	2/3

The data provided in the analytical similarity assessment demonstrate that SB4 is highly similar to US-licensed Enbrel, notwithstanding minor differences in clinically inactive components. Differences were noted in the assessment among SB4 and US-licensed Enbrel and EU-approved

etanercept; however, these differences are thought to be due to inherent differences in the manufacturing process and formulation of SB4. Differences were noted in the hydrophobic variant profile, amount of high molecular weight species (HMWS), and glycosylation profiles; however, these differences do not preclude a demonstration of highly similar.

Analysis of peak profiles for hydrophobic variants by hydrophobic interaction chromatography (HIC) demonstrated that SB4 has higher levels of Peak 1 and Peak 2 and lower levels of Peak 3. Peak 1 contains product variants that include low molecular weight species (LWMS) and Peak 3 contains product variants such as HMWS and proteins with mismatched disulfide bonds. Peak 2 contains the main biological component of the protein. Analysis of fractions of Peak 1 and Peak 3 demonstrated decreased potency when compared to Peak 2. The SB4 manufacturing process utilizes (b) (4)

and may explain the lower levels of Peak 3 and subsequent higher levels of Peak 2 in SB4. No differences in potency by either TNF α binding or TNF α neutralization were observed among the three products despite the differences in the HIC peak profile. Disulfide bond analysis of the Peak 3 fractions by Samsung showed that SB4 and US-licensed Enbrel contain the same mismatched variants. In addition, published literature supports that incorrect disulfide bridging in US-licensed Enbrel and EU-approved etanercept (in HIC peak 3) is reversible under serum-like redox conditions, restoring potency to normal levels (Lamanna WC et. al, 2017). The differences in the HIC peak profile do not preclude a demonstration of highly similar.

Analysis of the size profile of SB4 by Size Exclusion Chromatography (SEC) shows that SB4 (0.6-2.2%) has significantly less HMWS than US-licensed Enbrel (2.0-3.4%) and EU-approved etanercept (2.6-4.4%). The formation of HMWS can be influenced by several factors including the manufacturing process, formulation and age of the protein products and are likely to contribute to the differences observed among SB4 and US-licensed Enbrel and EU-approved etanercept; however, they are not expected to have a clinical impact and do not preclude a determination of highly similar.

The analysis of the 50 mg/mL protein concentration showed that SB4 (46.4 – 49.7 mg/mL) was slightly lower than that in US-licensed Enbrel (48.5 – 52.6 mg/mL) and EU-approved etanercept (48.7 – 51.6 mg/mL). Analysis of SB4 drug substance and drug product lots suggest that some drug product lots were consistently on the lower side of the protein concentration acceptance criteria (less than 50 mg/mL); however, the drug substance lots that were used to fill these lots did not have this issue. Because the drug product manufacturing only consists of (b) (4) the reason for this difference is unclear and is addressed in the CR letter.

Analysis of glycan profiles showed that SB4 has slightly higher levels of afucosylated species and lower levels of high mannose species when compared to US-licensed Enbrel and EU-approved etanercept. Differences in levels of high mannose have the ability to impact PK and levels of afucosylation can impact effector function. SB4 had a slightly higher Antibody Dependent Cell-mediated Cytotoxicity (ADCC) activity (2-5%) than US-licensed Enbrel (0-2%) and EU-approved etanercept (0-2%); however, the levels are not expected to have clinical relevance and the slight observed differences do not preclude a demonstration of highly similar.

Although differences among SB4 US-licensed Enbrel and EU-approved etanercept have been observed, these differences do not preclude the determination that SB4 is highly similar to US-licensed Enbrel or the establishment of the scientific bridge among SB4, US-licensed Enbrel and EU-approved etanercept.

D. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable:

Not applicable

II. Summary of Quality Assessments:

The table below summarizes the critical quality attributes and the corresponding control strategy for drug substance and drug product.

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

CQA (type)	Risk	Origin	Control Strategy	Other
TNF-alpha Neutralization (potency)	Efficacy	Intrinsic to molecule	(b) (4)	Included in analytical similarity assessment
TNF-beta Neutralization (potency)	Efficacy	Intrinsic to molecule		Included in analytical similarity assessment
TNF-alpha binding (potency)	Efficacy	Intrinsic to molecule		Included in analytical similarity assessment
Total Sialic Acid (NANA and NGNA)	PK/PD	(b) (4)		Included in analytical similarity assessment
HMWS/Aggregates	Impact on potency, PK/PD and immunogenicity	Manufacturing process		Included in analytical similarity assessment
Hydrophobic variants	Potency/Efficacy	Intrinsic to molecule Manufacturing process		Included in analytical similarity assessment
FcRn binding	PK/PD	Intrinsic to molecule		PTMs that can effect FcRn binding are consistently low
ADCC and CDC Binding to other Fc Receptors	Possible impact on biological activity, not part of MOA			Although CDC and ADCC can be demonstrated in vitro, the activity is very low relative to mAbs. All activities included in characterization and analytical similarity.
Acidic Variants	Impact on PK/PD	(b) (4)		

		(b) (4)	(b) (4)	
Oxidation Deamidation	Impact on PK/PD, immunogenicity			Oxidized and deamidated variants did not appear to effect TNFα binding.

B. Drug Substance [etanercept-xxxx] Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

From the product quality perspective, the manufacturing process for SB4 is not sufficiently controlled to ensure consistent manufacture of product that is comparable to material used in clinical studies or to the material used in the analytical similarity assessment. The reference standard material was not appropriately qualified and, therefore there is a lack of assurance that the product will not drift in potency over time. In addition, there is insufficient data to support the limit of in vitro cell age, as well as, a lack of assurance of the clonality of the MCB. Therefore, the proposed upstream manufacturing control strategy proposed for SB4 is not sufficient and will need to be adjusted.

Table 2: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management. (see example in Attachment 2)

CQA (type)	Risk	Origin	Control Strategy	Other
Protein Concentration	Efficacy	DS Manufacturing	(b) (4)	
Host Cell DNA	Safety and immunogenicity	Cell Culture		DS purification process demonstrates robust clearance
Host Cell Protein	Safety and immunogenicity	Cell Culture		DS purification process demonstrates robust clearance
(b) (4)	Safety and immunogenicity	(b) (4)		Reduced during downstream purification steps to below LOQ
	Safety	Cell Culture		
	Safety	Cell Culture		
	Impact on safety and immunogenicity	Cell Culture	(b) (4)	

			(b) (4)	step to below LOQ.
Bioburden (contaminant)	Safety, Purity, Efficacy (degradation or modification of the product by contaminating microorganisms)	Raw materials and manufacturing process		
Bacterial Endotoxins (contaminant)	Safety, Purity, Immunogenicity	Raw materials and manufacturing process		
Mycoplasma	Safety	Cell Culture		
Viral Contamination	Safety	Cell Culture		Virus clearance validated with small scale spiking studies

- Description:**
 SB4 is a homodimer of a fusion protein consisting of the extracellular ligand binding domain of human TNFR2/p75 and the Fc domain of human IgG1, lacking the CH1 region. SB4 consists of 934 amino acids (467 amino acids for the single chain) and has a molecular weight of approximately 130 kDa (~65 kDa for the single chain). Each single chain contains 22 cysteine (Cys) residues in the Cys-rich TNFR2 domain, 3 Cys residues in the hinge region, and 4 Cys residues in the Fc domain. The Cys residues are linked by intra-chain or inter-chain disulfide bonds.
- Mechanism of Action (MoA):**
 Etanercept binds soluble TNF-alpha and TNF-beta with high affinity. It also binds membrane bound TNF-alpha. Etanercept-bound TNF is blocked from binding the TNFR on cells, inhibiting the downstream effects of TNF signaling. In addition to blocking TNF signaling, there is a potential for SB4 to induce effector function through the Fc portion of the molecule. While etanercept can be shown to have complement dependent cytotoxicity and antibody dependent cellular cytotoxicity activities, both activities are low relative to anti-TNF monoclonal antibodies. Antibody effector function does not contribute to the overall mechanism of SB4.
- Potency Assay:**
 The potency of SB4 is measured using two assays, one for binding to TNFα by Fluorescence Resonance Energy transfer (FRET) and using a cell based TNFα neutralization assay.

For the FRET method, a fluorescent signal is generated when Europium-labeled TNFR2-Fc binds to Cy5-labeled TNF- α . Serial dilutions of SB4 are added to a plate containing Europium-labeled TNFR2-Fc and Cy5-labeled TNF α where SB4 competes with Europium-labeled TNFR2-Fc and Cy5-labeled TNF α resulting in a reduction of fluorescent signal. Binding is measured relative to the reference standard.

TNF-alpha neutralization assessment of SB4 utilizes a NF- κ B reporter gene assay. HEK293 cells expressing the TNF receptor were transfected with a luciferase reporter gene construct under transcriptional control of the NF- κ B dependent promoter. When the cells are incubated with TNF-alpha, NF- κ B signaling is activated, resulting in luciferase expression which can be detected on a luminescence reader in the presence of a luciferase substrate. This activity is inhibited in the presence of SB4. To assess SB4 neutralization of TNF-alpha, serial dilutions of SB4 and a fixed concentration of TNF-alpha are added to the cells and luciferase activity is measured. Potency is reported relative to the SB4 reference standard. This method is used for both SB4 DS and DP release and stability testing.

- Reference Materials:

A two-tiered reference standard system was generated from SB4 material for release and stability testing of SB4 DS and DP. Working reference standard (WRS) lot WRS-SB4-01 was used for testing of commercial material and was qualified against the primary reference standard (PRS) (lot RS053-001). The Interim Reference Standard (IRS) (lot RS-R12-001) was used to qualify the PRS and was used for testing of the clinical material. The IRS is no longer available. Three research reference standards (RRS) (lots EBS-034, EBS-052 and EBS-127) were made from US-licensed Enbrel lots and were used as the reference material in the analytical similarity assessment.

The qualification of the PRS, and subsequently the WRS, was not adequate; therefore, there is a lack of assurance that the commercial product will not drift in potency from the clinical material and the material used to establish that SB4 is highly similar to US-licensed Enbrel. This is the primary reason that the product quality team is recommending a CR action (see CR comments above).

- Critical starting materials or intermediates:

Master Cell Bank (MCB) lot 110370949 was established from the (b) (4) One Working Cell Bank (WCB), lot 110170962 was produced from the MCB.

There is uncertainty about the clonality of the MCB (see CR comments above).

- Manufacturing process summary:

(b) (4)



- Dating period and storage conditions:
The proposed shelf-life for the DS is (b) (4) months at or below (b) (4)

C. Drug Product [etanercept-xxxx] Quality Summary:

From the product quality perspective, issues have been identified with the drug product filling control strategy and the release specifications for extractable volume. The drug product filling strategy will need to be adjusted to ensure consistent filling of the 50 mg/mL presentation.

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes.

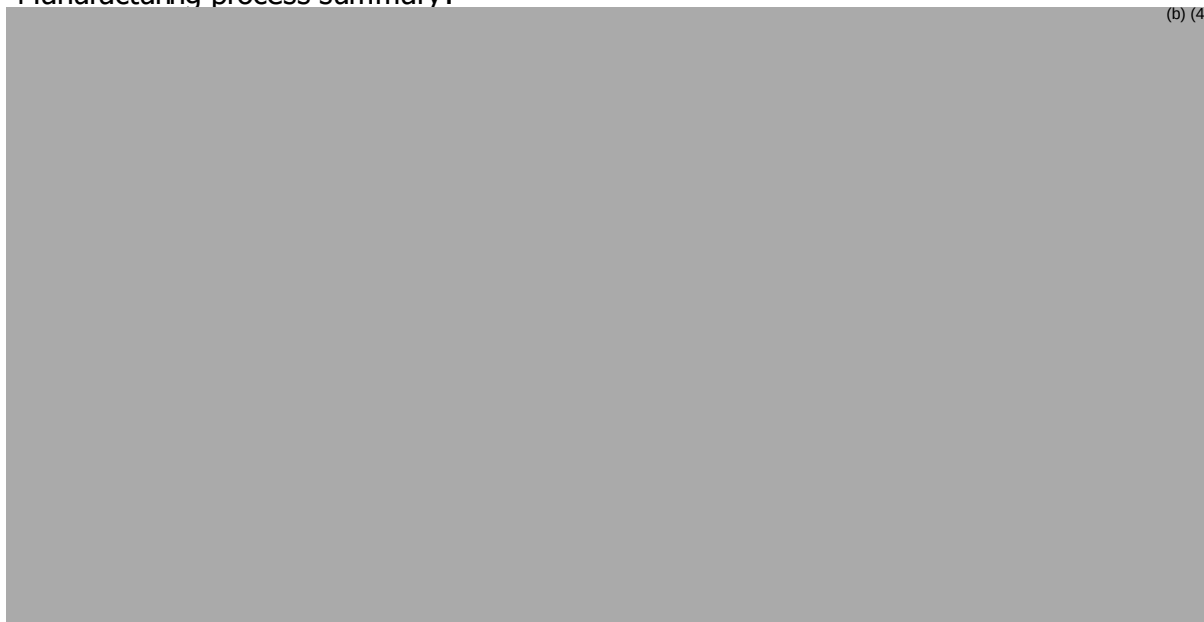
Table 3: Drug Product CQA Identification, Risk, and Lifecycle Management

CQA (type)	Risk	Origin	Control Strategy	Other
Extractable Volume	Efficacy	DP Manufacturing	(b) (4)	Insufficient data and information were provided on the DP filling control strategy and a CR comment will be conveyed. The Applicant has not updated the

			(b) (4) label to match with the US-licensed Enbrel.
Particulate Matter	Impact on immunogenicity and safety	DS/DP manufacturing	(b) (4)
Sub-visible particles	Impact on immunogenicity and safety	DS/DP manufacturing	
Endotoxin (Contaminant)	Impact on safety, purity, and immunogenicity	Contamination may be introduced throughout DP manufacturing process.	
Sterility (Contaminant)	Impact on safety and efficacy (due to degradation or modification of the product)	Contamination may be introduced throughout DP manufacturing.	Sterilization validation data for (b) (4) sterilization is deficient. Also, the (b) (4) for sterile filtration is not listed as a critical process parameter for sterile filtration.
Container Closure Integrity (Contaminant)	Impact on safety (breach in the container closure system may impact product sterility)	May be impacted by storage conditions.	
pH	Impacts product stability and potentially impacts PK/PD	DS/DP manufacturing	(b) (4)
Osmolality	Stability	DS/DP manufacturing	

(b) (4)	Product Safety, Immunogenicity	DP manufacturing and PFS	(b) (4)
Protein concentration	Efficacy	DS/DP manufacturing	Process B lots were consistently less than 50 mg/mL but were still within the acceptance criteria for release. A CR comment will be conveyed to address this discrepancy.

- **Potency and Strength:**
SB4 is supplied as 25 mg/0.5mL and 50mg/mL solution for injection in a pre-filled syringe (PFS). The potency assays are the same as described for the DS.
- **Summary of Product Design:**
The SB4 DP is a clear to opalescent, colorless to pale yellow, sterile, and preservative-free solution for injection that is intended for subcutaneous administration. SB4 is formulated in (b) (4) sodium phosphate, (b) (4) sodium chloride and (b) (4) sucrose at pH 6.2.
- **List of Excipients:**
The list of excipients includes sodium phosphate, sodium chloride, sucrose.
- **Reference Materials:**
The reference materials for the DP are the same materials as used for the DS.
- **Manufacturing process summary:**



(b) (4)

Two deficiencies will be conveyed in the CR letter concerning microbial control. To provide sterilization validation data to support the (b) (4) sterilization of items used to manufacture SB4 at (b) (4) since no minimum (b) (4) were validated. Also, to include (b) (4) as a critical process parameter for sterile filtration since performing sterile filtration outside of the parameters validated by the microbial retention study may result in a non-sterile product.

- Container closure:
Both DP strengths (50 mg and 25 mg) are presented in an identical (b) (4) PFS. The primary packaging of the PFS includes a clear glass barrel ((b) (4) glass), staked needle that is protected by a rubber needle shield that consists of a rigid shell, and plunger stopper. The PFS is then assembled with secondary packaging, i.e., a plunger rod and backstop.
- Dating period and storage conditions:
The proposed shelf-life for the 50 mg and 25 mg DP strengths is (b) (4) months when stored at 5±3°C with an additional (b) (4) weeks storage at 25±2°C within the expiry period.

D. Novel Approaches/Precedents: None

E. Any Special Product Quality Labeling Recommendations:

The sponsor has not updated the specifications for extractable volume to match with the current U.S.-licensed Enbrel label for the 50 mg/mL and 25 mg/mL strengths. In the current state, there is a possibility that the strength could be underestimated for the 50 mg/mL presentation and overestimated for the 25 mg/ 05.mL presentation based on rounding.

F. Establishment Information:

Overall Recommendation: Approval					
DRUG SUBSTANCE					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Drug Substance manufacturing, packaging, and testing.		(b) (4)	Requires PLI	A six-item FDA Form 483 was issued on (b) (4) Firm's response adequate.	Approve
Manufacturing and storage of the MCB and WCB.			Acceptable	N/A	Approve
Storage of the MCB and WCB.			Acceptable	N/A	Approve
Storage of the MCB and WCB.			Acceptable	N/A	Approve

Storage of the MCB and WCB.	(b) (4)		Acceptable	N/A	Approve
Drug Substance In-process testing and Analytical Similarity Data	Samsung Bioepis Co., Ltd.	3010031951	Requires PLI (Analytical Similarity Data)	No Form 483 was issued on November 6, 2017.	Approve
Drug Substance In-process testing	(b) (4)		Acceptable	N/A	Approve
Drug Substance release and stability testing	(b) (4)		Acceptable	N/A	Approve
Drug Substance stability testing	(b) (4)		Acceptable	N/A	Approve
Drug Substance stability testing	(b) (4)		Acceptable	N/A	Approve
Drug Substance storage	(b) (4)		Acceptable	N/A	Approve
DRUG PRODUCT					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Manufacture of pre-filled syringe, QC release testing (sterility test), In-process test (IPT) testing (all tests)	(b) (4)		Waive PLI	N/A	Approve
Manufacture of pre-filled syringe, QC release testing (sterility test), In-process test (IPT) testing (all tests)	(b) (4)		Waive PLI	N/A	Approve
Secondary Packaging	(b) (4)		Acceptable	N/A	Approve

G. Facilities: Descriptions provided for the (b) (4) SB4 Drug Substance and the (b) (4) (b) (4) Drug Product facilities proposed for DS and DP manufacture were reviewed. All other related manufacturing and testing facilities have an acceptable compliance status. The current compliance status for the proposed DS and DP manufacturing is acceptable and a recommended of approve is made from a facilities assessment standpoint.

H. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved: None

- ii. Outstanding review issues/residual risk: See CR comments.
- iii. Future inspection points to consider: See CR comments.

b. Drug Product

- i. Protocols approved: None
- ii. Outstanding review issues/residual risk: See CR comments.
- iii. Future inspection points to consider: See CR comments.

Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

#	Checklist	Yes	No	N/A
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 source		x	
9.	Transgenic Plant source		x	
10.	New Molecular Entity		x	
11.	PEPFAR drug		x	
12.	PET drug		x	
13.	Sterile Drug Product	x		
14.	Other: [fill in information]			
Regulatory Considerations				
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application [fill in number]		x	
16.	Comparability Protocol(s)		x	
17.	End of Phase II/Pre-NDA Agreements tem		x	
18.	SPOTS (special products on-line tracking system)		x	
19.	USAN assigned name		x	
20.	Other [fill in]			
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	
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 {fill-in}			



Reyes
Candau-Chacon

Digitally signed by Reyes Candau-Chacon
Date: 3/23/2018 11:51:51AM
GUID: 508da7160002977f7ca389c8f849b707



Zhihao Peter
Qiu

Digitally signed by Zhihao Peter Qiu
Date: 3/23/2018 11:54:14AM
GUID: 508da7480002bfb5825e149b2b4eb91d



Marjorie
Shapiro

Digitally signed by Marjorie Shapiro
Date: 3/23/2018 12:00:38PM
GUID: 508da6d700026360986b5a21cc1642e3



Rachel
Novak

Digitally signed by Rachel Novak
Date: 3/23/2018 11:50:56AM
GUID: 52e163f70002ba9e745b4e39384c76d7

BLA STN 761066

Non-proprietary Name: etanercept-ykro

Samsung Bioepis Co., Ltd.

Brian Janelins, Ph.D. (Primary Reviewer)
Rachel Novak, Ph.D. (Secondary Reviewer, ATL)
Marjorie Shapiro, Ph.D. (Tertiary Reviewer)

Division of Biotechnology Review and Research I
Office of Biotechnology Products

OBP CMC Review Data Sheet

1. **BLA#:** STN 761066

2. **REVIEW DATE:** March 10, 2018

3. **PRIMARY REVIEW TEAM:**

Medical Officer: Rachel Glaser and Nikolay Nikolov (TL/CDTL)

Pharm/Tox: Ijeoma Uzoma and Tim Robison (TL)

Product Quality: Brian Janelins and Rachel Novak (TL/ATL)

Microbiology: Maxwell Van Tassell, Jessica Hankins, and Maria Candauchacon (TL)

Facilities: Michael Shanks and Peter Qui (TL)

Clinical Pharmacology: Bavna Saluja and Anshu Marathe (TL)

Statistics: Ginto Pottackal and Greg Levin (TL)

OBP Labeling: Vicky Borders-Hemphill

OPRO RBPM: Oumou Barry

RPM: Brandi Wheeler

4. **MAJOR 21st CENTURY REVIEW DEADLINES**

Filing Meeting: July 11, 2017

Mid-Cycle Meeting: October 18, 2017

Primary Review Due: February 13, 2018

Secondary Review Due: February 20, 2018

Wrap-Up Meeting: February 20, 2018

CDTL Memo Due: February 26, 2018

BSUFA Action Date: March 25, 2018

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

Communication/Document	Date
Filing Letter	07/24/2017
Information Request	08/02/2017
Information Request	11/21/2017
Information Request	12/19/2017
Information Request	01/18/2018
Information Request	01/24/2018
Information Request	01/29/2018
Information Request	02/02/2018
Information Request	02/07/2018
T-Con with Samsung	02/08/2018

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

Submission	Date Received	Review Completed?
761066/0000 (original submission)	05/25/2017	Yes
761066/0006 (response to IR 08/02/2017)	08/09/2017	Yes
761066/0017 (response to IR 11/21/2017)	12/11/2017	Yes
761066/0020 (response to IR 12/19/2017)	01/12/2018	Yes
761066/0024 (response to IR 01/18/2018)	01/25/2018	Yes
761066/0026 (response to IR 01/29/2018)	02/02/2018	Yes
761066/0027 (response to IR 01/24/2018, 01/29/2018)	02/06/2018	Yes
761066/0029 (response to IR 02/02/2018)	02/13/2018	Yes
761066/0030 (response to IR 02/07/2018)	02/14/2018	Yes

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

- a. Proprietary Name: To be determined
- b. Trade Name: To be determined
- c. Non-Proprietary/USAN: etanercept-ykro
- d. CAS name: 185243-69-0
- e. Common name: SB4
- f. INN Name: etanercept
- g. Compndial Name: N/A
- h. OBP systematic name: Fus: RPROTFRAG P20333 (TNR1B_HUMAN);
MABFRAG HUMAN (IGG1 FC) [SB4]
- i. Other Names: BIIB602E

8. **PHARMACOLOGICAL CATEGORY:** TNF inhibitor9. **DOSAGE FORM:** for injection10. **STRENGTH/POTENCY:** 25 mg and 50 mg per pre-filled syringe11. **ROUTE OF ADMINISTRATION:** subcutaneous12. **REFERENCED MASTER FILES:**

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)
(b) (4)			Yes	Adequate information provided in the BLA for its intended use
			Yes	Adequate information provided in the BLA for its intended use
			Yes	Adequate information provided in the BLA for its intended use
			Yes	Adequate information provided in the BLA for its intended use
			Yes	Adequate information provided in the BLA for its intended use

(b) (4)	Yes	Adequate information provided in the BLA for its intended use
	Yes	Adequate information provided in the BLA for its intended use

13. INSPECTIONAL ACTIVITIES

A pre-licensure inspection (PLI) of the drug substance manufacturing facility was conducted at (b) (4) from (b) (4) by Michael Shanks (DIA, lead inspector), Brian Janelsins (OBP), and Ralph Bernstein (OPPQ). A six-item FDA 483 form was issued to (b) (4) at the end of the inspection. The 483 observations included the following: (b) (4)

In addition, several recommendations were conveyed to the firm at the end of the inspection. Responses were received from the sponsor on November 21, 2017. The outcome of the inspection was VAI (02/16/2018). A site visit of the Samsung Bioepis Co., LTD facility (FEI: 3010031951) was conducted by Thuy Thanh Nguyen (DIA, lead inspector) and Jennifer Swisher (OBP) from November 2 to November 6, 2017 to review the analytical similarity data and associated test methods and in-process test methods.

14. CONSULTS REQUESTED BY OBP

OPQ requested a consult for ODE/CDRH to review the pre-filled syringe with needle safety device for SB4. Steen Basile and John McMichael performed the primary and secondary reviews, respectively, and recommend approval from the ODE/CDRH perspective. It was determined that a consult for OC/CDRH was not needed because the device constituent of SB4 is only a pre-filled syringe, and unlike US-licensed Enbrel, does not include an autoinjector.

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
X	Formal Risk Assessment / Risk Management
	Multivariate Statistical Process Control
	Process Analytical Technology
	Expanded Change Protocol

16. PRECEDENTS

None

17. ADMINISTRATIVE

Signature Block

Name and Title	Signature and Date
Brian Janelsins, Ph.D. Staff Fellow (Primary Review) Office of Biotechnology Products Division of Biotechnology Products Review and Research I	See Panorama
Rachel Novak, Ph.D. Biologist (Secondary Review, ATL) Office of Biotechnology Products Division of Biotechnology Products Review and Research I	See Panorama
Marjorie Shapiro, Ph.D. Supervisory Biologist (Tertiary Review) Office of Biotechnology Products Division of Biotechnology Products Review and Research I	See Panorama

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

Sufficient analytical data are provided to support that SB4 is highly similar to US-licensed Enbrel and the establishment of analytical bridges among SB4, US-licensed Enbrel, and EU-approved etanercept. However, OBP recommends that this 351 (k) BLA application not be approved at this time due to deficiencies in the qualification of the established reference standards, leading to a lack of assurance that the commercial material is not going to drift (in potency) from the clinical material and the material used in the analytical similarity assessment.

II. List Of Deficiencies To Be Communicated (draft language, final language can be found in the CR letter)

1. The primary and working reference standards were not appropriately qualified with respect to biological activity (i.e., TNF- α binding activity and TNF- α neutralization activity) and protein concentration. Therefore, there is a lack of assurance that the commercial material is not going to drift in potency when tested against the working reference standard.
2. The requalification procedure for evaluating reference standards on stability was not adequate.
3. Insufficient data was provided to support the clonality of the master cell bank (MCB) and the limit of in vitro cell age (LIVCA). More conservative adjustments may need to be made to the overall control strategy for the upstream manufacturing process as well as the cell bank qualification protocol because of this lack of assurance of clonality for the MCB.
4. Insufficient information was provided regarding the filling control strategy including how (b) (4) is monitored and controlled and how (b) (4) excursions are investigated and handled. In addition, the protein concentration of the 50 mg DP commercial batches are consisting on the lower side of 50 mg/mL, and therefore, the fill process should be adjusted.
5. The classification of (b) (4) (b) (4) in the control strategy for the drug substance is not appropriate. In addition, (b) (4) range of (b) (4) is not supported by appropriate data.
6. The setting of acceptance criteria for many quality attributes on release and stability are too wide in comparison to the clinical and manufacturing experience and should be tightened appropriately.
7. A specific identity test is not performed for a significant number of raw materials upon receipt at the (b) (4) facility. An appropriate identity test

- should be performed on all incoming raw materials at the manufacturing facility [21 CFR 211.84(d)(1)].
8. The description of the Total Sialic Acid method did not include the procedure for qualifying new N-acetylneuraminic acid (NANA) and N-glycolylneuraminic acid (NGNA) standard stock solutions.
 9. The HIC method does not use an in-house reference standard when evaluating test samples. For all chromatography methods, a clear definition of what constitutes as test sample data comparable to reference standard data with respect to number of peaks, rank order of peak area, relative retention time, etc. should be provided.
 10. The method co-validation reports for the TNF- α binding and TNF- α neutralization assays did not include the data from the repeatability assessment performed at (b) (4).
 11. The leachables evaluation of the intended pre-filled syringe only included data for up to 12 months at long-term storage conditions; however, data should be provided up to the proposed expiry date.
 12. Per 21 CFR 610.14, identity testing for the drug product should be performed on samples taken after the labeling operations have been completed. Because samples taken for identity testing for the drug product are taken prior to the completion of labeling operations (Section 3.2.P.3.3), Samsung is not compliant with 21 CFR 610.14.
 13. Insufficient information was provided to support the limit for light exposure time (b) (4) during labeling, assembly of plunger rod and backstop, and finished product packaging operations at (b) (4) for drug product manufacturing.
 14. Insufficient data were provided to support the shipping and handling of drug product manufactured at (b) (4) and (b) (4).
 15. The extractable volume specification limits and (b) (4) for the 50 mg and 25 mg drug product strengths are inappropriate and are not consistent to meet the current label claim for US-licensed Enbrel of 50 mg and 25 mg drug product strengths filled at 1.0 ml and 0.50 ml, respectively.
 16. No data were provided from Process B validation studies that show the maximum allowable (b) (4) does not impact the cell growth of the commercial process.
 17. Insufficient information was provided to demonstrate that expected levels of (b) (4) in the intended pre-filled syringe do not impact product quality and stability of the drug product stored at long-term conditions up to the proposed expiry date.

18. The post-approval stability protocol for the drug product should include one batch of each drug product presentation as well as one 50 mg batch from both (b) (4) and (b) (4)

19. It is unclear if (b) (4) performs QC stability testing of the drug product.

III. List Of Post-Marketing Commitments/Requirement

N/A

IV. Review Of Common Technical Document – Quality Module 1

Environmental Assessment Or Claim Of Categorical Exclusion

Samsung requested categorical exclusion from the environmental assessment requirement under 21 CFR 25.31(g) based on the establishment of bioequivalence requirements for a human drug or a comparability determination for a biologic product subject to licensing. The claim of categorical exclusion is acceptable.

V. Primary Container Labeling Review

The OBP review of the drug product labeling was performed by Vicky Borders-Hemphill (see review in Panorama).

VI. Review of Common Technical Document – Quality Module 3.2

The review of Module 3.2 is provided below.

VII. Immunogenicity Assay Review – Module 5.3.1.4

The review of the immunogenicity assay is included following the review of the analytical similarity assessment.

TABLE OF CONTENTS

3.2.S. DRUG SUBSTANCE.....	11
3.2.S.1 General Information.....	11
3.2.S.1.1 Nomenclature	11
3.2.S.1.2 Structure	11
3.2.S.1.3 General Properties	12
3.2.S.2 Manufacture	12
3.2.S.2.1 Manufacturer(s)	12
3.2.S.2.2 Description of Manufacturing Process and Process Controls and 3.2.S.2.4 Controls of Critical Steps and Intermediates	12
3.2.S.2.3 Control of Materials	29
3.2.S.2.5 Process Validation and/or Evaluation	37
3.2.S.2.6 Manufacturing Process Development.....	50
3.2.S.2.6.1 Manufacturing Process Development	51
3.2.S.2.6.2 Manufacturing Process Development (Comparability).....	64
3.2.S.3 Characterization	66
3.2.S.3.1 Elucidation of Structure and Other Characteristics	66
3.2.S.3.2 Impurities.....	66
3.2.S.4 Control of Drug Substance	69
3.2.S.4.1 Specification and 3.2.S.4.5 Justification of Specifications.....	69
3.2.S.4.2 Analytical Procedures and 3.2.S.4.3 Validation of Analytical Procedures	76
3.2.S.4.4 Batch Analysis.....	95
3.2.S.5 Reference Standard or Materials.....	95
3.2.S.6 Container Closure System	99
3.2.S.7 Stability	101
3.2.S.7.1 Stability Summary and Conclusions and 3.2.S.7.3 Stability Data.....	101
3.2.S.7.2 Post-Approved Stability Protocol and Stability Commitment	102
3.2.P DRUG PRODUCT	103
3.2.P.1 Description and Composition of the Drug Product.....	103
3.2.P.2 Pharmaceutical Development	104
3.2.P.2.1 Component of the Drug Product.....	104
3.2.P.2.2 Drug Product Development.....	105
3.2.P.2.3 Manufacturing Process Development.....	106
3.2.P.2.4 Container Closure System	115
3.2.P.3 Manufacture	118
3.2.P.3.1 Manufacturer(s)	118
3.2.P.3.2 Batch Formula	118
3.2.P.3.3 Description of Manufacturing Process and Process Controls and 3.2.P.3.4 Control of Critical Steps and Intermediates	119
3.2.P.3.5 Process Validation and/or Evaluation	127
3.2.P.4 Control of Excipients.....	137
3.2.P.5 Control of Drug Product	137
3.2.P.5.1 Specifications and 3.2.P.5.6 Justification of Specifications	137
3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures	141
3.2.P.5.4 Batch Analyses	141
3.2.P.5.5 Characterization of Impurities.....	142
3.2.P.6 Reference Standards or Materials	142
3.2.P.7 Container Closure System	142
3.2.P.8 Stability	142
3.2.P.8.1 Stability Summary and Conclusions and 3.2.P.8.3 Stability Data.....	142

3.2.P.8.2 Post-Approval Stability Protocol and Commitment.....	150
3.2.A Appendices.....	151
3.2.A.2 Adventitious Agents Safety Evaluation.....	151
3.2.R Regional Information	156
3.2.R.1 Executed Batch Records	156
3.2.R.4 Analytical Similarity Assessment	156
3.2.R.4.1 Introduction	156
3.2.R.4.2. Similarity Studies with SB4 and EU-Approved Etanercept	157
3.2.R.4.3 Comparative Stability Studies with SB4, US-licensed Enbrel, and EU-approved Etanercept	202
5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies	208

DESCRIPTION OF DRUG SUBSTANCE AND DRUG PRODUCT

SB4 is a proposed biosimilar to US-licensed Enbrel, which is a fusion protein that binds to and neutralizes the activity of TNF- α .

Note: Reviewer comments are italicized, and tables and figures are copied directly from the application, unless otherwise noted.

3.2.S. DRUG SUBSTANCE

3.2.S.1 General Information

3.2.S.1.1 Nomenclature

- International Nonproprietary name (INN): etanercept-ykro
- United States Adopted Name (USAN): etanercept-ykro
- Chemical Abstracts Service (CAS) registry Number: 185243-69-0
- Chemical name: 1-235-tumor necrosis factor receptor (human) fusion protein with 236-467-immunoglobulin G1 (human γ 1-chain Fc fragment), dimer
- Company or Laboratory Code: SB4
- Other Names: BIIB602E (current CMO code); BIIB602, BIIB602A-D (previous CMO code)

3.2.S.1.2 Structure

SB4 is a homodimer of a fusion protein consisting of the extracellular ligand binding domain of human TNFR2/p75 and the Fc domain of human IgG1. The Fc domain of human IgG1 is void of the CH1 region. SB4 consists of 934 amino acids (467 amino acids for the single chain) and has a molecular weight of approximately 130 kDa (~65 kDa for the single chain). Each single chain contains 22 Cys residues (italicized in Figure 1, see below) in the Cys-rich TNFR2 domain, 3 Cys residues in the hinge region, and 4 Cys residues in the Fc domain. The Cys residues are linked by intra-chain or inter-chain disulfide bonds.

1	LPAQVAFTPY	APEPGSTCRL	REYYDQTAQM	CCSKCSPGQH	AKVFCTKTS
51	TVCDSCEDST	YTQLWNWVPE	CLSCGSRCSS	DQVETQACTR	EQNRICTCRP
101	GWYCALSKQE	GCRLCAPLRK	CRPGFGVARP	GTETSDVVCK	PCAPGTFST
151	TSSTDICRPH	QICNVVAIPG	NASMDAVCTS	TSPTSRMAPG	AVHLPQPVST
201	RSQHTQPTPE	PSTAPSTSFL	LPMGPSPPAE	GSTGDEPKSC	DKTHTCPPCP
251	APELLGGPSV	FLFPPKPKDT	LMISRTPEVT	CVVVDVSHED	PEVKFNWYVD
301	GVEVHNAKTK	PREEQYNSTY	RVVSVLTVLH	QDWLNGKEYK	CKVSNKALPA
351	PIEKTISKAK	GQPREPQVYT	LPPSREEMTK	NQVSLTCLVK	GFYPSDIAVE
401	WESNGQPENN	YKTTTPVLD	DGSFFLYSKL	TVDKSRWQQG	NVFSCSVMHE
451	ALHNHYTQKS	LSLSPGK			

Extracellular ligand-binding domain of the human TNFR: Normal letters
Fc domain of human IgG1: Bold letters
N-linked glycosylation site: Boxed letters
Potential O-linked glycosylation site: Normal letters underlined
Cysteine residues: *Italics*

Figure 1: Amino Acid Sequence of SB4 Single Chain

SB4 is a highly glycosylated fusion protein. Each single chain consists of three N-linked glycosylation sites and 13 potential O-linked glycosylation sites (Figure 2). The N-linked glycans in the TNFR domain (Asn₁₄₉ and Asn₃₁₇) consist of mainly fucosylated, biantennary glycans with or without sialic acid (i.e., N-acetylneuraminic acid). The N-linked glycans located

in the Fc domain (Asn₃₁₇) of the molecule are fucosylated, neutral biantennary glycans. Of the 13 potential O-linked glycosylation sites, an average of 8 to 10 sites are occupied with GalNAc β (1-3) Gal core glycan structures that are either mono- or di-sialylated.

3.2.S.1.3 General Properties

The drug substance (DS)

(b) (4)

has an isoelectric point (pI) of 7.4 (main isoform).

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

(b) (4)

3.2.R.4 Analytical Similarity Assessment

3.2.R.4.1 Introduction

EU-approved etanercept was used as a comparator to SB4 in the confirmatory clinical study (SB4-G31-RA), and to support the relevance of the data derived from EU-approved etanercept in demonstrating biosimilarity between SB4 and US-licensed Enbrel, clinical (SB4-G11-NHV

study) and analytical data were provided to establish three-way PK and analytical bridges, respectively, among SB4, US-licensed Enbrel, and EU-approved etanercept. To support a demonstration of analytical similarity, data were provided from similarity studies (Section 3.2.R.4.2) analyzing the structural/physiochemical properties (e.g., primary and higher-order structure, post-translational modifications, purity, product-related impurities, and quantity) and biological activities (e.g., TNF- and Fc-related activities) of SB4, US-licensed Enbrel, and EU-approved etanercept. In addition, data were provided from comparative stability studies comparing the degradation profiles of SB4, US-licensed Enbrel, and EU-approved etanercept under heat stress, oxidative stress, photostress, accelerated, and freeze-thaw cycling conditions (Section 3.2.R.4.3).

Reviewer Comment: The overall evaluation of the analytical similarity assessment is provided at the end of Section 3.2.R.4.3.

3.2.R.4.2. Similarity Studies with SB4 and EU-Approved Etanercept

Evaluation of Quality Attributes by Statistical Approaches

Samsung determined quality attributes that characterize US-licensed Enbrel with respect to structural/physiochemical and biological activities. The quality attributes were then ranked according to their risk of potential clinical impact (i.e., efficacy, immunogenicity, PK/PD, and safety). The risk ranking considered the potential impact of an attribute on clinical performance and the degree of uncertainty around that quality attribute (refer to Section 3.2.S.2.6.1 for additional information concerning the risk ranking tool). Based on the risk ranking, in addition to other factors, such as information and data from product knowledge and in-house characterization studies, the quality attributes were evaluated according to one of three tiers of statistical approaches. Equivalence testing (Tier 1) was used to evaluate quality attributes with the highest risk ranking (RPN above 59) and included assays that evaluate the clinically relevant mechanisms of action (MoA) of US-licensed Enbrel for each indication for which approval is sought. Quality ranges (Tier 2) were used to evaluate quality attributes with a lower risk ranking (RPN between 25 and 59), and visual comparisons (Tier 3) were used to evaluate quality attributes with the lowest risk ranking (RPN score below 25). The quality attributes evaluated in the analytical similarity assessment are shown below in Table 2.

Table 2: Tests and Analytical Methods Used in the Characterization Studies of Similarity Assessment

Tier	Category	Test and Analytical Method	Suitability	Testing Site
Tier 1	TNFR-related biological assay	TNF- α binding assay by FRET	Method qualified	SB
		TNF- α neutralization assay by NF- κ B reporter gene	Method qualified	SB
Tier 2	Purity and impurities	%HMW analysis by SEC	Method qualified	SB
		%Peak 1, 2, and 3 analysis by HIC	Method qualified	SB
		%Main analysis by CE-SDS (Reducing)	Method qualified	SB
		%Main analysis by CE-SDS (Non-reducing)	Method qualified	SB
	Glycan profile	TSA analysis by HPLC	Method qualified	SB
	Quantity	Protein concentration determination by UV/VIS at A ₂₈₀	Method qualified	SB

Tier	Category	Test and Analytical Method	Suitability	Testing Site
	TNFR-related biological assay	LTα3 binding assay by FRET	Method qualified	SB
Tier 3	Primary structure	Molecular weight determination by UPLC-ESI-MS	Calibration ^a	SB
		Amino acid sequencing by UPLC-ESI-MS/MS	Calibration	SB
		N-terminal sequencing by UPLC-ESI-MS/MS	Calibration	SB
		C-terminal sequencing by UPLC-ESI-MS/MS	Calibration	SB
		Peptide mapping by UPLC-ESI-MS/MS	Calibration	SB
		Disulfide bond analysis by UPLC-ESI-MS/MS	Calibration	SB
		Free sulfhydryl group quantification by FLR	System suitability ^b	SB
		Methionine oxidation by UPLC-ESI-MS/MS	Calibration	SB
		Deamidation by UPLC-ESI-MS/MS	Calibration	SB
	Glycan profile	N-linked glycosylation site determination by UPLC-ESI-MS/MS	Calibration	SB
		N-glycan identification by procainamide labeling and UPLC-ESI-MS/MS	Calibration	SB
		N-glycan profile analysis by 2-AB labeling and HILIC-UPLC	Method qualified	SB
		Fc-specific glycan profile by HILIC-UPLC	System suitability	SB
		O-glycan site by LC-ESI-MS/MS	Calibration	SB
		O-glycan profile by β-elimination and HILIC-UPLC	System suitability	SB
	Charge variants	Charge heterogeneity analysis by icIEF	Method qualified	SB
	Biophysical properties	Protein secondary structure analysis by CD (Far-UV)	System suitability	(b) (4)
		Protein tertiary structure analysis by intrinsic fluorescence spectroscopy	System suitability	
		Protein folding analysis by extrinsic fluorescence spectroscopy	System suitability	
		Protein secondary structure analysis by FTIR spectroscopy	System suitability	
		Protein tertiary structure analysis by H/DX-MS	Calibration	
		Thermal stability analysis by DSC	System suitability	
		Aggregates characterization analysis by SEC/MALLS	System suitability	

Tier	Category	Test and Analytical Method	Suitability	Testing Site
		Aggregates characterization analysis by SV-AUC	System suitability	(b) (4)
		Protein size characterization analysis by DLS	System suitability	
		Subvisible particles analysis by MFI	System suitability	
		Extinction coefficient determination	System suitability	
	Fc-related biological activity	FcγRIa binding assay by FRET	Method qualified	SB
		FcγRIIa binding assay by SPR	Method qualified	SB
		FcγRIIb binding assay by SPR	Method qualified	SB
		FcγRIIIa binding assay (158V/V) by SPR	Method qualified	SB
		FcγRIIIa binding assay (158F/F) by SPR	Dose dependent signal ^c	SB
		FcγRIIIb binding assay by SPR	Dose dependent signal ^c	SB
		FcRn binding assay by SPR	Method qualified	SB
		C1q binding assay by ELISA	Dose dependent signal ^c	SB
		ADCC assay	Dose dependent signal ^c	SB
		CDC assay	Dose dependent signal ^c	SB
	Additional biological activity	TNF-α binding on different species	Dose dependent signal ^c	SB
		Apoptosis assay	Dose dependent signal ^c	SB

^a Calibration: Calibration is conducted using the analyte mass to be compensated based on the accurate mass of exact internal calibrant. Also, calibrant is analyzed with sample in every 15 seconds whenever needed.

^b System suitability: The system suitability of the assays is evaluated using controls, standards, and/or instrument calibrations.

^c Appropriateness qualified through control samples and/or dose-response demonstration

Reviewer Comment: The evaluation of TNF-α binding activity and TNF-α neutralization activity by Tier 1 is acceptable because these quality attributes are relevant to the MoA of US-licensed Enbrel for the indications US-licensed Enbrel is approved for. Several of the quality attributes that were evaluated by Tier 3 should be evaluated by Tier 2. Because of a potential clinical impact, it's the Agency's expectation that levels of afucosylated, high mannosylated, and α-galactosylated N-linked glycan species, glycans with terminal N-acetylglucosamine (tGalNAc), and charge forms be evaluated according to a Tier 2 statistical approach for biosimilars to US-licensed Enbrel. Differences in the content of these quality attributes may impact efficacy, PK, immunogenicity, and/or safety. The Agency's expectation was communicated to Samsung, and it was requested that additional data be provided to allow for a meaningful evaluation of these quality attributes by Tier 2 quality range analysis (IR dated December 19, 2017). Although Samsung disagreed with placing these quality attributes into Tier 2, quantitative data from additional US-licensed Enbrel and EU-approved etanercept batches were provided to allow for analysis of afucosylated and high mannosylated N-linked glycan content and charge variant content per icIEF by quality ranges (IR response, January 12, 2018, Seq. 0020). While no additional data were provided for tGalNAc and α-galactose N-linked glycan content, it was determined that a meaningful conclusion regarding the similarity of these quality attributes can

be made based on the data provided in the original submission (see below for further discussion).

The qualification and verification reports for the test methods used in the analytical similarity assessment were reviewed by Dr. Jennifer Swisher (OBP/DBRR I) during inspection of the Samsung Bioepis Co., Ltd. testing facility (November 2 – 6, 2017). It was determined that the information and data in the reports are acceptable to support that the test methods are suitable for their intended purpose and performed in a well-controlled manner.

Lots used in the Analytical Similarity Assessment

SB4, US-licensed Enbrel, and EU-approved etanercept batches were used in the analytical similarity assessment. The SB4 batches (26 batches) used in the analytical similarity assessment included DS and DP batches derived from Process A (16 batches) and Process B (10 batches) DS (Table 6, see below). Although multiple DP batches were used in the clinical studies, these batches were derived from a common DS batch (12-602-001). A representative clinical DP batch (i.e., 12L11 or SB4-13B01) was included in the evaluation of each of the quality attributes. Twenty-four SB4 batches were used in the Tier 1 and Tier 2 evaluations with exceptions noted below (e.g., protein concentration), Tier 3 evaluations included the analysis of data from 2 – 18 SB4 batches.

Table 6: Information of SB4 Used for the Similarity Assessment

Type	DS Manufacturing Process	Development Stage	Batch Number	Description	DS Batch used	Manufacturing Information		Used for Similarity Assessment		
						Date	Site	Tier 1	Tier 2	Tier 3
DS (50 mg/mL)	Process A	Pilot batch	PUR-C12-04 P2	· Process development	N/A ^a	May 2012	(b) (4)	O	O ^b	-
			PUR-R12-01	· Stability study	N/A	Jul 2012		O	O ^b	-
			PUR-C12-06	· Process scale-up verification	N/A	Jun 2012		O	O ^b	-
			PUR-C12-07	· Process scale-up verification	N/A	Aug 2012		O	O ^b	-
			PUR-C12-08	· Process scale-up verification	N/A	Sep 2012		O	O ^b	-
		Clinical batch	12-602-001	· Stability study	N/A	Nov 2012		-	- ^c	-
			12-602-002	N/A	N/A	Dec 2012		O	O	-
			12-602-003	· Manufactured for use in clinical study, but pending use	N/A	Dec 2012		O	O	-
		PVR batch	13-602-001	· Process validation	N/A	Dec 2013		O	O	O ^b
			13-602-006	· Process validation	N/A	Feb 2014		O	O	O ^b
	Process B	PVR batch	15-602E-004	· Process validation	N/A	Aug 2015		O	O ^b	-
			15-602E-005	· Process validation	N/A	Sep 2015		O	O ^b	-
		Commercial batch	HP5-16-602E-008	N/A	N/A	Oct 2016		O	O ^b	-
			HP5-16-602E-009	N/A	N/A	Oct 2016		O	O ^b	-
			HP5-16-602E-010	N/A	N/A	Nov 2016		O	O ^b	-
			HP5-16-602E-011	N/A	N/A	Nov 2016		O	O ^b	-
			HP5-16-602E-012	N/A	N/A	Nov 2016		O	O ^b	-

Type	DS Manufacturing Process	Development Stage	Batch Number	Description	DS Batch used	Manufacturing Information		Used for Similarity Assessment		
						Date	Site	Tier 1	Tier 2	Tier 3
DP (50 mg/mL)	Process A	Pilot batch	PDR-112-12-137	· Stability study · Non-clinical study	PUR-C12-05	May 2012	(b) (4)	O	O ^b	-
		Clinical batch	12L11	· Stability study · Clinical study	12-602-001	Dec 2012		O	O	-
			SB4-13B01	· Clinical study	12-602-001	Feb 2013		-	-	O ^b
		PVR batch	SB4-14C20	· Process validation · Stability study	13-602-002	Mar 2014		O	O	O
			SB4-14C26	· Process validation · Stability study	13-602-003	Mar 2014		O	O	O ^b
			SB4-14C28	· Process validation · Stability study	13-602-004	Mar 2014		O	O	O ^b
	Process B	PVR batch	00001	· Process validation · Stability study	15-602E-001	Sep 2015		O	O	O ^b
			00002	· Process validation · Stability study	15-602E-003	Oct 2015		O	O	O ^b
			00003	· Process validation · Stability study	15-602E-002	Oct 2015		O	O	O ^b

^a Not applicable

^b Batch which was not tested for all test items included in the respective Tier.

^c 12-602-001 was only used for HIC SAR study (Section 2.3.2.1).

Reviewer Comment: A sufficient number of SB4 batches were provided to allow for meaningful comparisons to US-licensed Enbrel and EU-approved etanercept. Samsung combined the analysis of DS and DP batches from different manufacturing process campaigns together for the analytical similarity assessment. Based on the data provided in the BLA that support comparability of the SB4 materials (Sections 3.2.S and 3.2.P), this approach is acceptable. However, the Agency's expectation for the analytical similarity assessment is that each value for each quality attribute being assessed is contributed by an independent DP or DS batch of the proposed biosimilar. The original analysis of SB4 data included several DP batches (e.g., several clinical DP batches) that were generated from one DS batch. The Agency does not consider different DP batches produced from the same DS batch to be independent for analyses of quality attributes that are impacted by the DS manufacturing process, but not by the DP manufacturing process. It was communicated to Samsung to include in the analytical similarity assessment DP batches manufactured from independent DS batches, and for multiple DP batches manufactured from a single DS batch, include either the DS batch or one DP batch that is representative of all those batches (IR dated December 19, 2017). In response to the IR (January 12, 2018, Seq. 0020), Samsung updated its analysis to only include data generated from independent SB4 DP and DS batches; Table 6 (see above) was updated to reflect the final SB4 batches used in the analytical similarity assessment. Although Table 6 shows that two clinical DP batches (12L11 and SB4-13B01) generated from DS batch 12-602-001 are included in the analytical similarity assessment, DP batches 12L11 and SB4-3B01 were not tested together for the same product quality attribute. Because the updated information shows that the SB4 batches used in the analytical similarity assessment are appropriate, it was unnecessary to remove any additional SB4 batch data from the re-analysis performed by Samsung.

A total of 51 and 56 US-licensed and EU-approved etanercept batches (50 mg/PFS and 25/mg PFS), respectively, were used in the analytical similarity assessment as comparators to SB4. These batches were analyzed between March 2012 and July 2016, before their expiry dates (May

2012 to October 2018). Tier 1 evaluations included the analyses of 47 – 51 US-licensed Enbrel and 44 – 54 EU-approved etanercept batches. Tier 2 evaluations included the analyses of 23 – 51 US-licensed Enbrel and 23 – 56 EU-approved etanercept batches. Tier 3 evaluations included the analyses of at least one batch each of US-licensed Enbrel and EU-approved etanercept. US-licensed Enbrel (1034016) and EU-approved etanercept (G75422, G86367, H78852, and G47931) batches that were used in the clinical studies were also evaluated in the analytical similarity assessment for Tier 1 and Tier 2 evaluations.

Reviewer Comment: *A sufficient number of US-licensed Enbrel and EU-approved etanercept batches were provided to allow for the establishment of meaningful similarity acceptance criteria. The US-licensed Enbrel and EU-approved etanercept batches used in the analytical similarity assessment were selected across the product shelf-life; therefore, it's likely that the expected range of variability for these products is captured in the analytical similarity testing.*

Reference Standards used in the Analytical Similarity Assessment

The RRS was used to determine the relative activity of SB4, US-licensed Enbrel, and EU-approved etanercept batches per analyses by TNF- α binding assay, TNF- α neutralization assay, LT α 3 binding assay, TNF- α binding from different species assay, and apoptosis assay.

Reviewer Comment: *Because more than one RRS was used during the development of SB4 (Section 3.2.S.5), it was requested that Samsung indicate which RRS was used for each batch of SB4, US-licensed Enbrel, and EU-approved etanercept tested by the methods that require comparison to a reference material (IR dated December 19, 2017). It was also requested that Samsung describe how the data were interpreted for the analytical similarity assessment if more than one reference standard was used for a particular method. In response to the IR (January 12, 2018, Seq. 0020), Samsung stated that the testing by the TNF- α binding, TNF- α neutralization, and apoptosis assays included the use of multiple RRS, i.e., EBS-034, EBS-052, and EBS-127 RRS. The data provided in Section 3.2.S.5 support that the three RRS used in the analytical similarity assessment are comparable (e.g., TNF- α binding and TNF- α neutralization quality attributes); therefore, are appropriate to be used in the analytical similarity assessment for their intended purpose.*

Similarity Assessment Results for Tier 1

Equivalence testing was used to evaluate the similarity of TNF- α binding activity and TNF- α neutralization activity among SB4, US-licensed Enbrel, and EU-approved etanercept. US-licensed Enbrel exerts its primary MoA by binding to soluble TNF- α and neutralizing its activity by preventing the binding of TNF- α to TNFR2 and the subsequent activation of TNFR-mediated cellular pathways. Assays were developed to assess soluble TNF- α binding and TNF- α neutralization among SB4, US-licensed Enbrel, and EU-approved etanercept. For each quality attribute, data were reported as relative activity to the RRS.

The quality attributes were tested against the null hypothesis ($H_0: \mu_B - \mu_R \leq -\delta$ or $\mu_B - \mu_R \leq \delta$), whereby mean responses of SB4 (or EU-approved etanercept) and US-licensed Enbrel (or EU-approved etanercept) batches are denoted by μ_B and μ_R , respectively, and the equivalence margin is shown as $\delta > 0$. The equivalence margin (δ) was defined as $1.5 \times \sigma_R$, whereby σ_R is the variability of n batches of the comparative product. Analytical similarity was accepted for the quality attribute if the (1-2)100% two-sided confidence interval of the mean difference was within the equivalence margin ($-\delta, \delta$). The confidence interval of the mean difference was calculated according to the formula listed below:

$$(\bar{X}_B - \bar{X}_R) \pm t_{1-\alpha, df^*} \times \sqrt{\frac{S_B^2}{n_B} + \frac{S_R^2}{n_R^*}}$$

Reviewer Comment: The equivalence testing approach used was based on FDA draft guidance and will be evaluated by CMC stats.

TNF- α Neutralization Assay: The inhibitory activity of SB4 (24 total batches, including one clinical and 10 commercial batches), US-licensed Enbrel (47 batches), and EU-approved etanercept (44 batches) on soluble TNF- α signaling pathways was measured through a TNF- α neutralizing assay using a 293-NF κ B-Luc cell line. The 293-NF- κ B-Luc cell line contains a NF- κ B binding sequence upstream to the luciferase reporter gene. The binding of TNF- α to cell surface TNFR leads to a signal cascade activating NF- κ B, which in turn activates the expression of the luciferase reporter gene. By measuring luciferase activity, the ability of the samples to inhibit potency was assessed. The range of %relative potency values shown in Figure 2 (see below) are 87 – 121% (100% mean), 82 – 116% (99% mean), and 83 – 123% (103% mean) for SB4, US-licensed Enbrel, and EU-approved etanercept, respectively. Only one SB4 batch (commercial) and one EU-approved etanercept batch (G13149) were outside the %relative potency range for US-licensed Enbrel.

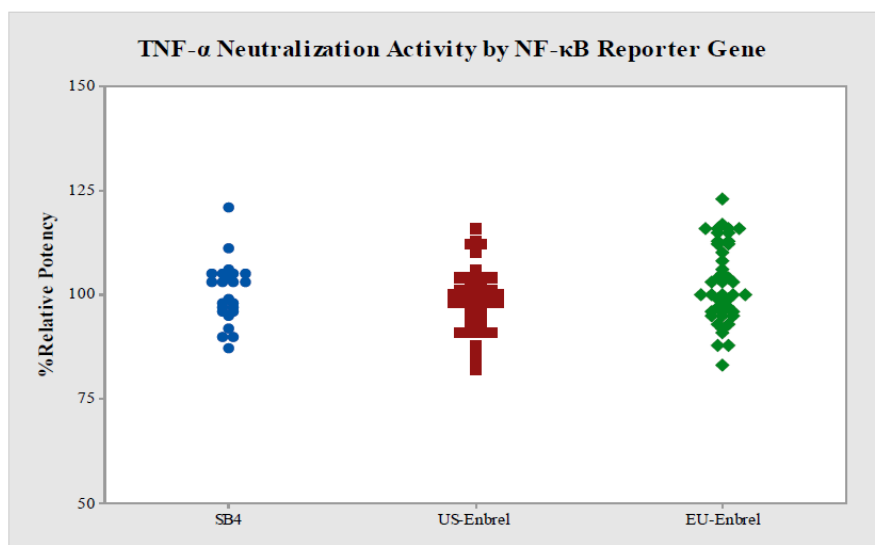


Figure 2: Result of TNF- α Neutralization Activity of SB4 and Enbrel®

Results from the equivalence test demonstrate that the two-sided confidence intervals of the mean differences of SB4 and US-licensed Enbrel, SB4 and EU-approved etanercept, and EU-approved etanercept and US-licensed Enbrel for TNF- α neutralization activity are within the equivalence acceptance criteria (Table 11, see below).

Table 11: Equivalence Test of TNF- α Neutralization Activity by NF- κ B Reporter Gene

Product	Number of Batches	Comparator Product	Number of Batches	Significance Level (α)	(1-2 α)% Confidence Interval	EAC ^a	Statistical Equivalence
SB4	24	US Enbrel [®]	47	0.05	(-1.55, 4.98)	(-11.09, 11.09)	Yes
SB4	24	EU Enbrel [®]	44	0.05	(-6.02, 1.27)	(-14.17, 14.17)	Yes
EU Enbrel [®]	44	US Enbrel [®]	47	0.05	(1.12, 7.06)	(-11.09, 11.09)	Yes

^a Equivalence acceptance criterion

TNF- α Binding Assay: The TNF- α binding activity of SB4 (24 total batches, including one clinical and 10 commercial batches), US-licensed Enbrel (51 batches), and EU-approved etanercept (54 batches) was determined by FRET-based competitive inhibition binding assay. The relative potency values shown below in Figure 3 (see below) are 99 – 112% (104% mean), 93 – 108% (101% mean), and 95 – 117% (104% mean) for SB4, US-licensed Enbrel, and EU-approved etanercept, respectively. Two batches of SB4 and six batches of EU-approved etanercept were outside the %relative binding range for US-licensed Enbrel.

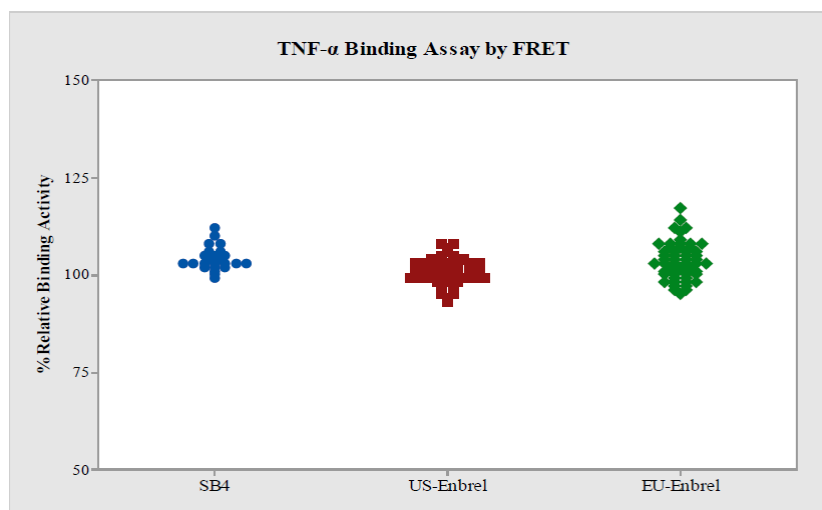


Figure 3: Result of TNF- α Binding Activity of SB4 and Enbrel[®]

Results from the equivalence test demonstrate that the two-sided confidence intervals of the mean differences of SB4 and US-licensed Enbrel, SB4 and EU-approved etanercept, and EU-approved etanercept and US-licensed Enbrel for TNF- α binding activity are within the equivalence acceptance criteria (Table 14, see below).

Reviewer Comment: The Tier 1 evaluations of the TNF- α binding activity and TNF- α neutralization activity conducted by Samsung support statistical equivalence; however, an independent analysis performed by CMC stats will be used to verify that the data support a

demonstration of highly similar between SB4 and US-licensed Enbrel and the establishment of analytical bridges among SB4, US-licensed Enbrel, and EU-approved etanercept.

US-licensed Enbrel can also bind to membrane TNF- α and TNF- β (also referred as LT α 3); however, it's unclear whether the cellular pathways downstream of these molecules are mainly involved in the diseases that US-licensed Enbrel is approved to treat. Samsung developed an apoptosis assay for Tier 3 evaluation to determine the similarity of SB4, US-licensed Enbrel, and EU-approved etanercept to neutralize the activity of transmembrane TNF- α . Additionally, Samsung developed a binding assay by Tier 2 evaluation to determine the similarity of SB4, US-licensed Enbrel, and EU-approved etanercept to bind to LT α 3. This approach is acceptable, and the results from these evaluations are discussed later in the review (Tier 3 and Tier 2, respectively).

Similarity Assessment Results for Tier 2

Quality ranges were used to evaluate the quality attributes identified as lower clinical risk and were defined as $X_R \pm xS_R$, whereby X_R is the mean value of the reference batches, S_R is the standard deviation of the reference batches, and x is the standard deviation multiplier (SDM). Quality attributes analyzed by an assay with low variability (coefficient of variation lower than 15%) were assigned a SDM value of 3, while quality attributes analyzed by an assay with higher variability (coefficient of variation higher than 15%) were assigned a SDM value of 2.5. Some quality attributes were evaluated by one-side quality ranges, while others were evaluated by two-sided quality attribute ranges (Table 4).

Reviewer Comment: All quality attributes analyzed by quality ranges included a SDM value of three. Intermediate precision analyses (Table 3) of the quality attributes evaluated by Tier 2 demonstrate coefficient of variation values ranging from 0.3 to 4.7%, which supports the use of a SDM value of three for quality range analysis. It's the Agency's expectation that two-sided quality ranges be used for Tier 2 evaluation. Because Samsung used one-sided quality ranges for several of the Tier 2 evaluations, the reviewer calculated two-sided quality ranges (mean $\pm$ 3SD) based on the data provided from Samsung (Table 1, prepared by the reviewer; see below).

Table 1: Calculation of the Tier 2 Two-sided Quality Ranges

Quality Attribute	US-licensed Enbrel				EU-approved etanercept			
	n	Mean	SD	Quality Range	n	Mean (%)	SD	Quality Range
Physicochemical properties								
%HMW by SEC	51	2.7%	0.3	1.8 – 3.6%	55	3.3%	0.4	2.1 – 4.5%
%Peak 1 by HIC	51	1.5%	0.3	0.6 – 2.4%	56	1.7%	0.3	0.8 – 2.6%
%Peak 2 by HIC	51	83.1%	1	80.1 – 86.1%	56	84.4%	1.3	80.5 – 88.3%
%Peak 3 by HIC	51	15.4%	1	12.4 – 18.4%	56	13.9%	1.2	10.3 – 17.5%
%main by rCE-SDS	50	98.2%	0.9	95.5 – 100%	49	98.2%	0.8	95.8 – 100%
%main by nrCE-SDS	50	98.7%	0.5	97.2 – 100%	53	98.4%	0.4	97.2 – 99.6%
%TSA content by HPLC	51	15.3%	0.4	14.1 – 16.5%	54	15.4%	0.3	14.5 – 16.3%

Protein concentration	23	50.1%	0.9	47.4 – 52.8%	23	50.0%	0.7	47.9 – 52.1%
%acidic by icIEF*	24	23.3%	2.4	16 – 30.4%	23	23.8%	2.8	15.6 – 32.1%
%main by icIEF*	24	48.9%	1.7	43.8 – 54.1%	23	51.3%	2.2	44.8 – 57.8%
%basic by icIEF*	24	27.9%	1.9	22.1 – 33.6%	23	24.8%	2.7	16.7 – 33.0%
Biological Activities								
%LTα3 binding (relative activity)	49	100%	6	82 – 118%	51	102%	5	87 – 117%
Glycan Profile								
%afucose by HILIC-UPLC*	31	4.7%	0.5	3.1 – 6.3%	36	5.2%	0.4	3.9 – 6.5%
%high mannose by HILIC-UPLC*	31	3.6%	0.5	2 – 5.2%	36	2.8%	0.4	1.7 – 3.9%
% α-galactose by HILIC-UPLC*	NP	0	0	N/A	NP	0	0	N/A
tGalNAc by HILIC-UPLC*	3	0.2 [^]	0	N/A	3	0.2 [^]	0	N/A

*Not evaluated in this section of the review, refer to the section of the review discussing the Tier 3 evaluations.
N/A = not applicable, NP = not provided, [^] = average number per single chain

Reviewer Comment: The analyses generated from the Tier 2 evaluations of the quality attribute data support a demonstration of highly similar between SB4 and US-licensed Enbrel and establishment of analytical bridges between SB4, US-licensed Enbrel, and EU-approved etanercept. Although a sufficient percentage of SB4 batches didn't fall within the two-sided quality ranges established for a given quality attribute, justification and data were provided to support that the observed differences do not preclude a demonstration of highly similar between SB4 and US-licensed Enbrel and the establishment of analytical bridges among the comparators. These data, analyses, and justifications are discussed below.

%HMW by SEC: The determination of highly similar between SB4 and US-licensed Enbrel and the establishment of analytical bridges among SB4, US-licensed Enbrel, and EU-approved etanercept with respect to HMW content by SEC were made based on the evaluation of data from 24 batches of SB4 (one clinical and 10 commercial batches) by separate two-sided quality ranges generated from analysis of data from 51 batches of US-licensed Enbrel and 55 batches of EU-approved etanercept. The analysis of the data from the 51 batches of US-licensed Enbrel and 55 batches of EU-approved etanercept are presented in Tables 102 and 104 of the Appendix, respectively, while the data from the SB4 batches are tabulated in Table 16. For presentation purposes, data from three representative US-licensed Enbrel and EU-approved etanercept batches that were tested side-by-side with the 24 batches of SB4 were provided. The HMW content in SB4 batches (0.6 – 2.2%) was generally lower than that in US-licensed Enbrel (2.0 – 3.4%, n=51) and EU-approved etanercept (2.6 – 4.4%, n=55). Nineteen percent (5/26) of the SB4 batches fell within the two-sided quality range for US-licensed Enbrel (1.8 – 3.6%), and 7% (2/26) of SB4 batches fell within the two-sided quality range for EU-approved etanercept (2.1 – 4.6%). Fifty eight percent (32/55) of the EU-approved etanercept batches fell within the two-sided quality range for US-licensed Enbrel. The data from the side-by-side testing are graphed in Figure 6 (see below), and the quality ranges are superimposed on the bar graph.

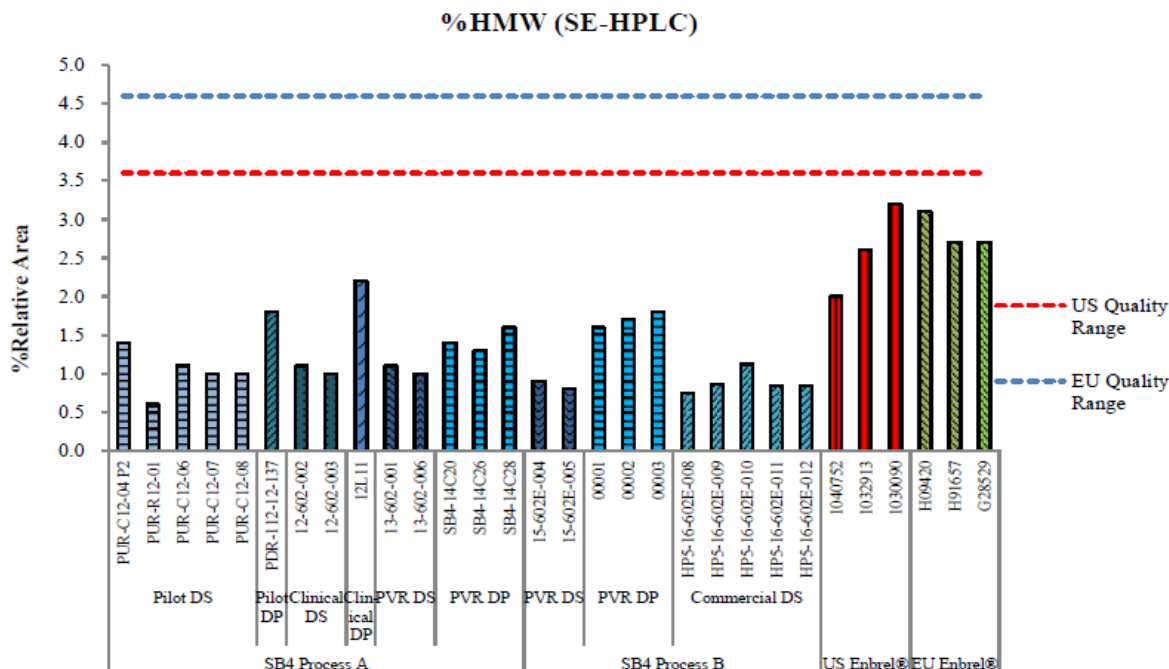


Figure 6: Similarity of %HMW between SB4 and Enbrel® by SEC

*Figure shows the one-side quality range determined by Samsung. The lower limits for the quality ranges calculated by the reviewer are not shown.

The chromatogram peak profile of SB4, US-licensed Enbrel, and EU-approved etanercept (Figure 5) supports that HMWs levels are lower in SB4 in comparison with US-licensed Enbrel and EU-approved etanercept. The SEC chromatograms showed that US-licensed and EU-approved etanercept have an additional HMW peak, which was not observed in the SB4 chromatograms (refer to Tier 3 testing by SEC-MALLS and SV-AUC for additional discussion concerning the additional HMW peak in US-licensed Enbrel and EU-approved etanercept chromatograms). Despite this observation, the SB4 chromatogram peak pattern was similar to that of US-licensed Enbrel and EU-approved etanercept, and no new/unexpected peaks appeared in the SB4 chromatograms.

Reviewer Comment: Samsung did not report values for %monomer and %LMWs by SEC as part of the analytical similarity assessment. As discussed in Sections 3.2.S.4.2 and 3.2.S.4.3, the SEC method cannot always resolve the LMW peak from the monomer; therefore, %LMW and %monomer are often calculated together. The analytical similarity assessment of LMW content is evaluated by %peak 1 by HIC and monomer is evaluated by several purity methods, i.e., HIC (%peak 2) and CE-SDS (%main peak; see below).

The differences in HMWs levels between US-licensed Enbrel and EU-approved etanercept are likely contributed to batch-to-batch variability. Although most of the SB4 batches fell outside the two-sided quality ranges, the lower levels of HMWs in SB4 do not preclude a demonstration of highly similar between SB4 and US-licensed Enbrel and the establishment of analytical bridges among SB4, US-licensed Enbrel, and EU-approved etanercept. The magnitude of differences and the expected assay variability are not great enough to indicate a potential for clinical impact.

Hydrophobic Variants by HIC: The determination of highly similar between SB4 and US-licensed Enbrel and the establishment of analytical bridges among SB4, US-licensed Enbrel, and EU-approved etanercept with respect to peak 1, peak 2, and peak 3 content by HIC were made based on the evaluation of data from 24 batches of SB4 (one clinical and 10 commercial batches) by separate two-sided quality ranges generated from analysis of data from 51 batches of US-licensed Enbrel and 55 batches of EU-approved etanercept. The analysis of the data from the 51 batches of US-licensed Enbrel and 55 batches of EU-approved etanercept was presented in Tables 102 and 104 of the Appendix, respectively, while the data from the SB4 batches are tabulated in Table 17. For presentation purposes, data from three representative US-licensed Enbrel and EU-approved etanercept batches that were tested side-by-side with the 24 batches of SB4 were provided. Chromatograms from the side-by-side testing are shown in Figure 8. Although HIC peak 3 was noticeably smaller in the SB4 chromatograms, the chromatograph peak pattern was similar among SB4, US-licensed Enbrel, and EU-approved etanercept. No new/unexpected peaks were observed in the SB4 chromatographs. Data from the side-by-side testing are graphed in Figures 9 – 11 (see below) with the quality ranges superimposed on the bar graphs.

The peak 1 content in SB4 batches (1.4 – 4.1%) was generally higher than that in US-licensed Enbrel (1.1 – 2.1%, n=51) and EU-approved etanercept (1.3 – 2.6%, n=55). Sixty five percent (17/26) of SB4 batches fell within the two-sided quality range for US-licensed Enbrel (0.5 – 2.5%), and 58% (15/26) of SB4 batches fell within the two-sided quality range for EU-approved etanercept (0.8 – 2.6%). Over 90% of the EU-approved etanercept batches fell within the two-sided quality range for US-licensed Enbrel.

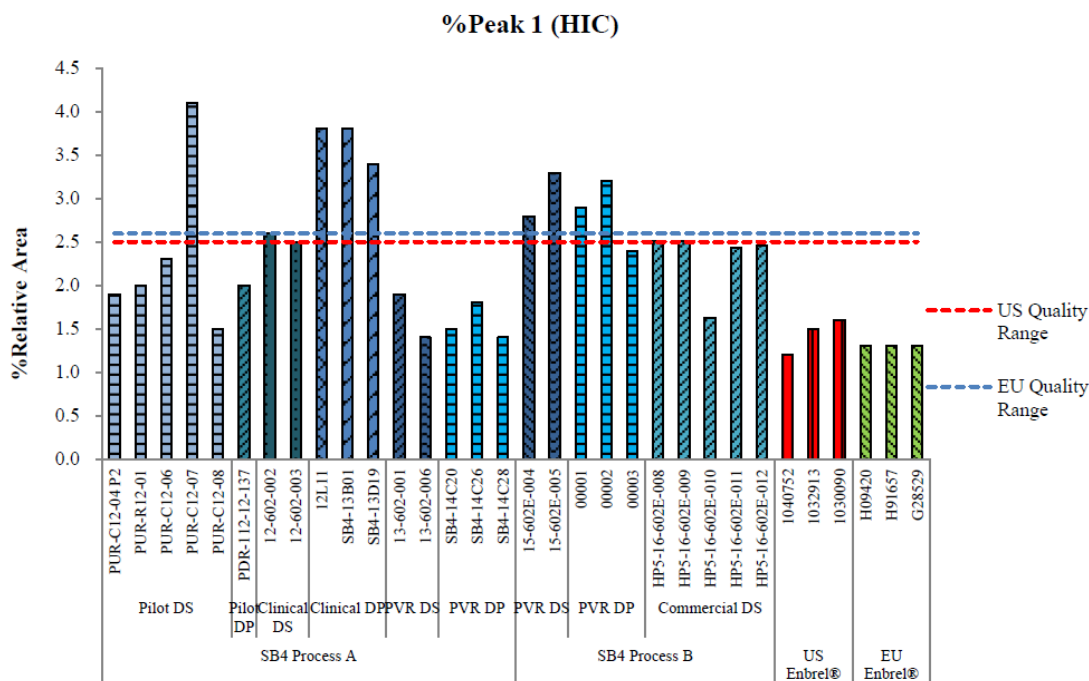


Figure 9: Similarity of %Peak 1 between SB4 and Enbrel® by HIC

*Figure shows the one-side quality ranges determined by Samsung. The lower limits for the quality ranges calculated by the reviewer are not shown.

The peak 2 content in SB4 batches (91.0 – 94.8%) was significantly higher than that in US-licensed Enbrel (80.6 – 86.0%, n=51) and EU-approved etanercept (81.0 – 87.6%, n=55). None of the SB4 batches fell within the two-sided quality ranges for US-licensed Enbrel (80.1 – 86.1%) and EU-approved etanercept (80.5 – 88.3%). Eighty six percent (48/56) of the EU-approved etanercept batches fell within the two-sided quality range for US-licensed Enbrel.

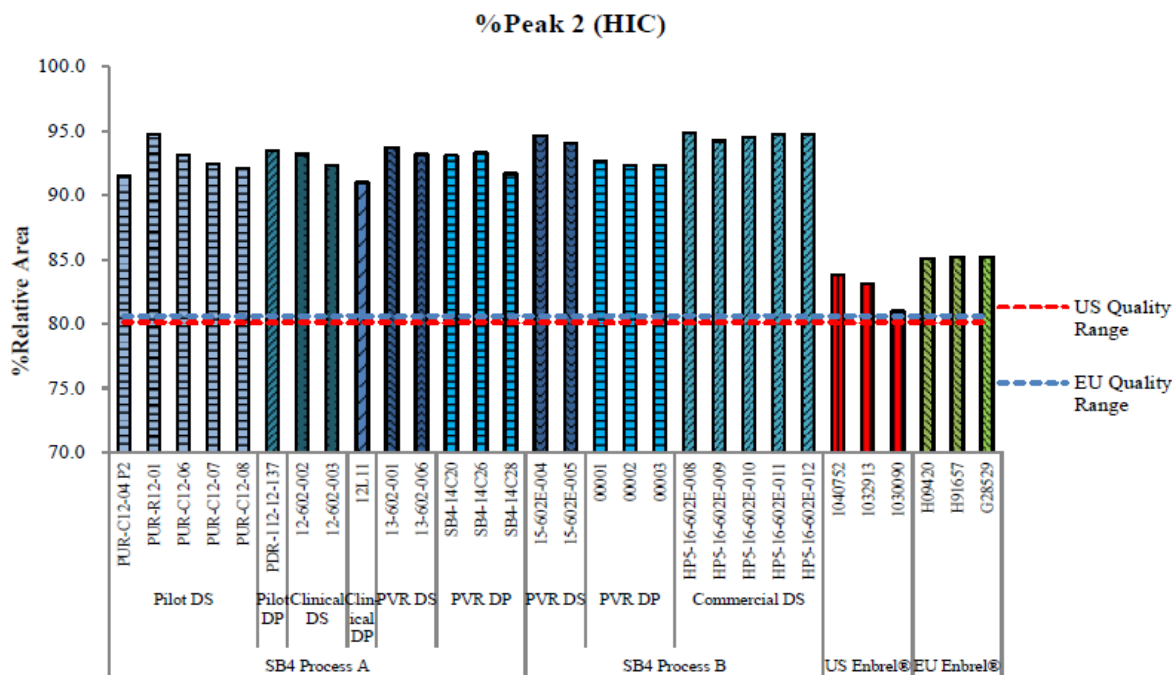


Figure 10: Similarity of %Peak 2 between SB4 and Enbrel® by HIC

*Figure shows the one-side quality ranges determined by Samsung. The upper limits for the quality ranges calculated by the reviewer are not shown.

The peak 3 content in SB4 batches (2.5 – 6.9%) was significantly lower than that in US-licensed Enbrel (12.5 – 18.2%, n=51) and EU-approved etanercept (10.7 – 16.9%, n=55). None of the SB4 batches were within the two-sided quality ranges for US-licensed Enbrel (12.4 – 18.3%) and EU-approved etanercept (10.3 - 17.5%). Eighty eight percent (49/56) of EU-approved etanercept batches were within the two-sided quality range for US-licensed Enbrel.

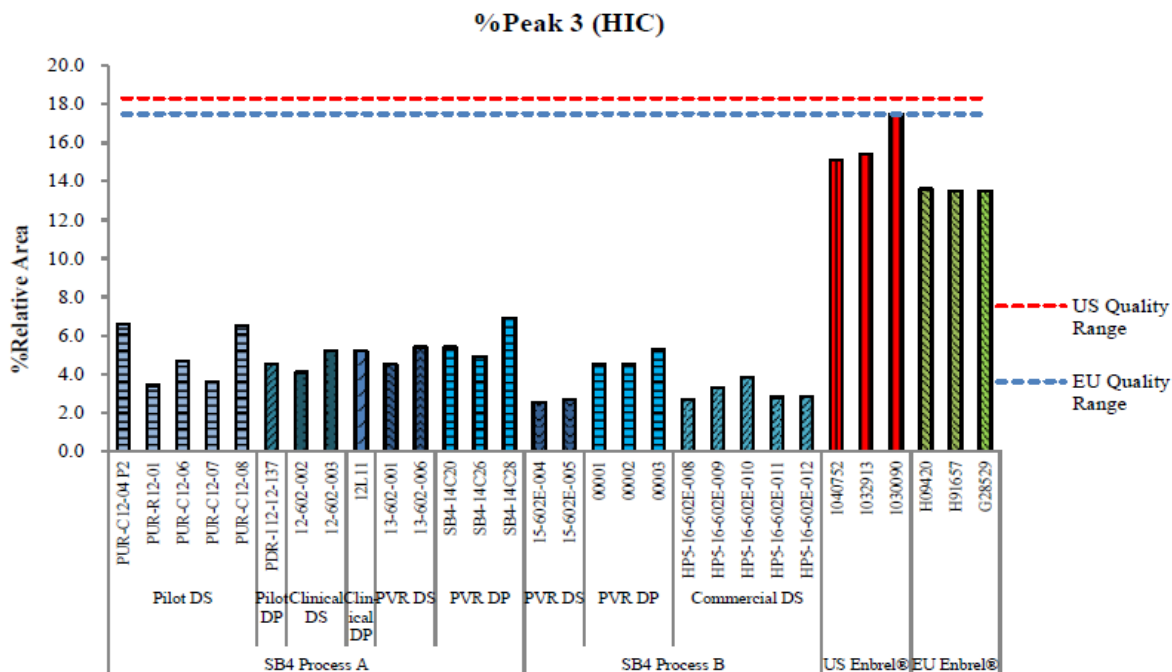


Figure 11: Similarity of %Peak 3 between SB4 and Enbrel® by HIC

*Figure shows the one-side quality ranges determined by Samsung. The lower limits for the quality ranges calculated by the reviewer are not shown.

Reviewer Comment: The differences in HIC peak content at the levels detected in the Tier 2 evaluation did not result in a rejection of statistical equivalence of TNF- α binding activity and TNF- α neutralization activity among the comparator groups by Tier 1 evaluation. Published literature supports that incorrect disulfide bridging in US-licensed Enbrel and EU-approved etanercept (in HIC peak 3) is reversible under serum-like redox conditions, restoring potency to normal levels (Lamanna WC et. al, 2017). Therefore, differences in HIC peak 3 may not be clinically relevant due to potential refolding in vivo. Taken together, the differences in the HIC peak profile between SB4 and US-licensed Enbrel and EU-approved etanercept does not preclude a demonstration of highly similar between SB4 and US-licensed Enbrel or impact the establishment of the analytical bridge among the three products.

Samsung evaluated the differences in HIC peak 1, peak 2, and peak 3 levels between SB4 and US-licensed Enbrel or EU-approved etanercept by performing additional studies, referred as structure-activity-relationship (SAR) studies. Because a determination of highly similar between SB4 and US-licensed Enbrel and the establishment of analytical bridges among SB4, US-licensed Enbrel, and EU-approved etanercept were confirmed and the purpose of these additional studies was for characterization purposes, it was acceptable for Samsung to use one batch of EU-approved etanercept or US-licensed Enbrel in comparison with SB4 material. The results of these characterization studies are discussed below.

SAR Study 1

The first SAR study was performed to determine the identity and function of each HIC peak. An in-process SB4 sample (batch EBP-120-HX001) was fractionated by HIC (Figure 12, see below). All eight HIC fractions (peak 1, late peak 1, early peak 2, peak 2, peak 2 tail, early peak 3, peak

3, and peak 3 tail) were characterized by HIC, SEC, TSA, intact protein mass, and TNF- α binding assay analyses.

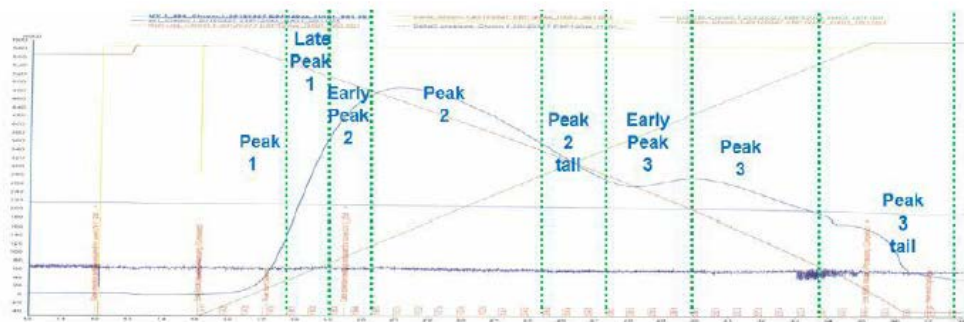


Figure 12: Fractionation of In-Process Sample (EBP-120-HX-001)

HIC analysis determined that the relative content of peak 1 (98.1%) was the highest in the peak 1 fraction, peak 2 (85.9%) was the highest in the peak 2 fraction, and peak 3 (89.0%) was the highest in the peak 3 tail fraction (Figure 13, see below).

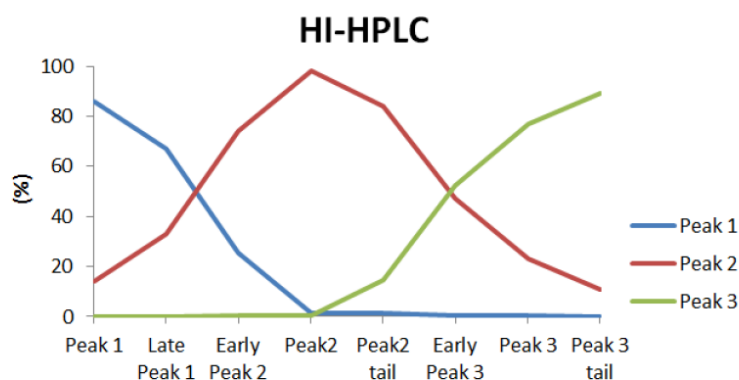


Figure 13: Relative Content of Peak 1, Peak 2, and Peak 3 for Each Fraction from SB4 Pilot In-process Sample

SEC analysis demonstrated that the content of LMWs was the highest in peak 1 (87.6%) and late peak 1 (69.5%) fractions, while the content of HMWs was the highest in peak 3 (8.4%) and late peak 3 (16.3%) fractions (Figure 14). Fractionated peak 2 contained the highest level of the main peak (97.4%).

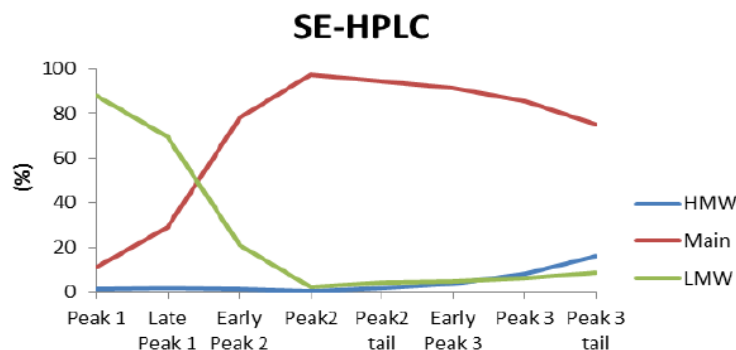


Figure 14: Relative Content of HMW, Main, and LMW for Each Fraction from SB4 Pilot In-process Sample

The intact mass results by LC-MS analysis supports smaller forms of SB4 in fractions with abundant peak 1. TSA levels were generally comparable among the fractions. TNF- α binding assay analysis shows that fractions only with peak 2 have robust activity (early peak 2 fraction: 84% relative activity; peak 2 fraction: 117% relative activity; and peak 2 tail fraction: 69% relative activity), while fractions containing (1) peak 1 with minimal peak 2 (peak 1 fraction: 18% relative activity and late peak 1 fraction: 37% relative activity) and (2) peak 3 with minimal peak 2 (peak 3 and peak 3 tail fractions: 15% relative activity) are relatively inactive.

Reviewer Comment: The results from SAR study #1 support that HIC peak 2 is the active form of SB4 with high TNF- α binding activity, while HIC peak 1, which consists mainly of LMWs, and peak 3, which mainly consists of HMWs (and disulfide scrambled variants, see SAR study #3 below), are less active forms of SB4 with low TNF- α binding activity. Data from SAR study #3 also show that HIC peak 1 and peak 3 have low TNF- α neutralization activity, which correlates with the TNF- α binding data from SAR study #1.

SAR Study 2

A second SAR study was performed to compare the characteristics of HIC peak 2 and peak 3 in SB4 (clinical batch, 12-602-001) and EU-approved etanercept (F45454). Because the quantity of HIC peak 1 was too low for analysis, comparative analysis between SB4 and EU-approved etanercept was not performed for HIC peak 1. Three fractions were generated through HIC analysis, and the HIC content of each fraction is visualized in Figure 17. Pool 1 contains only HIC peak 2, while pool 2 contains HIC peak 2 with a portion of the HIC peak 3 left tail. Pool 3 only contains HIC peak 3. Data from this study are tabulated in the table below (Table 19).

Table 19: Summary of Physicochemical and Biological Characterization for Each Fraction from SB4 Clinical DP and EU Enbrel®

Sample Name		TSA (mol/mol chain)	TNF- α Binding (% Rel. Activity)	%HMW by SEC
EU Enbrel® (F45454), non-fractionated		15.4	100	3.9
EU Enbrel® (F45454), pool 1	Peak 2 only (main peak)	17.0	112	0.2
EU Enbrel® (F45454), pool 2	Peak 2 + Peak 3 (main peak with tailing)	14.0	122	0.2
EU Enbrel® (F45454), pool 3	Peak 3 only (inactive form)	15.7	16	7.3
SB4 (12-602-001), non-fractionated		15.4	109	1.3
SB4 12-602-001, pool 1	Peak 2 only (main peak)	17.2	113	0.2
SB4 12-602-001, pool 2	Peak 2 + Peak 3 (main peak with tailing)	14.0	123	0.3
SB4 12-602-001, pool 3	Peak 3 only (inactive form)	16.2	32	12.4

Reviewer Comment: Data support that the HIC fractions for SB4 and EU-approved etanercept exhibit similar trends in TNF- α binding activity and TSA and HMW content. The similar levels of TNF- α binding activity between non-fractionated and pools containing peak 2 for SB4 and EU-approved etanercept suggest that the content of peak 1 and peak 3 did not significantly impact TNF- α binding activity, although additional data were not provided to investigate further. The higher TNF- α binding activity in the peak 3 pool for SB4 in comparison to the corresponding pool for EU-approved etanercept is likely because the peak 3 pool for SB4 contains some of the tail of peak 2 (Figure 17).

SAR Study 3

The third SAR study was performed to examine the biological activity of each peak and to confirm previous SAR study results. Four fractions (peak 1, peak 2, peak 2 tail, and peak 3) of an in-process SB4 sample (prior to HIC purification; Process A PVR DS batch) were collected and analyzed by TSA, intact protein mass, disulfide bond mapping, TNF- α binding assay, and TNF- α neutralization assay. The trends observed for TSA, intact protein mass, and TNF- α binding from the first SAR study were verified. Similar to TNF- α binding activity, TNF- α neutralization activity was mainly attributed to HIC peak 2 (114%, peak 2 fraction; 99%, peak 2 tail fraction), while reduced TNF- α neutralization activity was detected in the peak 1 fraction (32%) and the peak 3 fraction (18%).

Reviewer Comment: Data support that TNF- α binding and TNF- α neutralization activities correlate across HIC fraction samples.

Disulfide bond analysis of the HIC peak 3 fraction from SB4 (Process A PVR DS batch, 13-602-002) and US-licensed Enbrel was performed. Peak 3 fractions collected from SB4 and US-licensed Enbrel were digested under non-reducing conditions and analyzed by LC-MS analysis.

The chromatograms (Figure 19) and a list of ten scrambled forms that were detected (Table 21) were provided.

Reviewer Comment: Because the data provided in the original submission were not sufficiently clear, it was communicated to Samsung to update the submission to clearly show which mismatched forms were detected in the SB4 and US-licensed Enbrel batches and to provide the mass of each mismatched peptide that was detected (IR dated December 19, 2017). In the IR response (January 12, 2018, Seq. 0020), Samsung updated Figure 19 (see below) to show that each mismatched form was detected in the SB4 and US-licensed Enbrel HIC peak 3 chromatograms. Additionally, the mass of each mismatched peptide was provided (Table 21). Although the masses provided were not delineated between SB4 and US-licensed Enbrel, comparison of the chromatograms support the conclusion that all ten mismatched forms are detected in SB4 and US-licensed Enbrel.

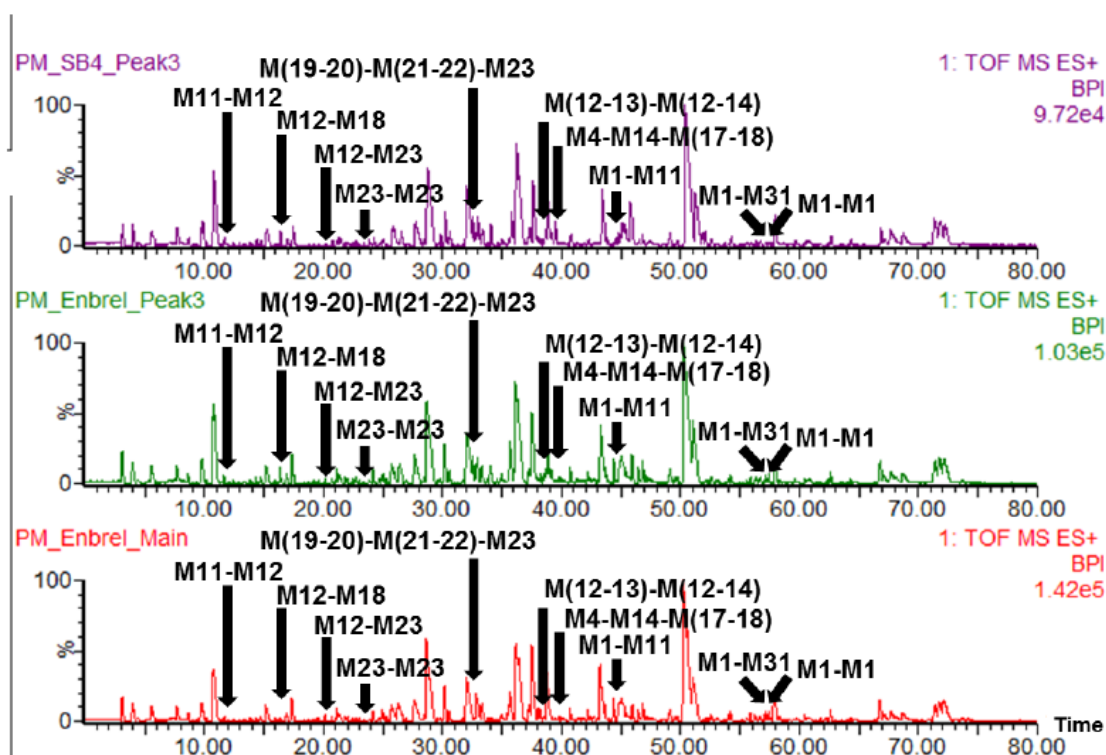


Figure 9: Mass Chromatogram for 10 Mismatched Peptides

Table 14: Mass Information for 10 Mismatched Peptides

Mismatched Form	Peptide Sequence	Detected Mass (Da)	Detected RT (min)
M1-M1	LPAQVAFTPYAPEPGST ~~CR~~ =LPAQVAFTPYAPEPGST ~~CR~~	4005.94	57.4
M1-M11	LPAQVAFTPYAPEPGST ~~CR~~ = ~~CSS~~	2297.05	44.4
M1-M31	LPAQVAFTPYAPEPGST ~~CR~~ =TPEVT ~~C~~ VVV	2947.45	57.1
M4-M14-M(17-18)	DQTAQM ~~C~~ CSK= ~~ICT~~ CRPGWY ~~C~~ ALSK= ~~K~~ CRPGFGVARPGTETS	4370.96	39.6
M11-M12	~~CSS~~ =DQVETQA ~~CTR~~	1442.57	11.7
M(12-13)-M(12-14)	DQVETQA ~~CTR~~ QNR=DQVETQA ~~CTR~~ EQNR ~~ICT~~ CR	3927.75	38.7
M12-M18	DQVETQA ~~CTR~~ = ~~CR~~	1424.56	16.4
M12-M23	DQVETQA ~~CTR~~ =DAV ~~CT~~ STSPTR	2284.01	20.1
M(19-20)-M(21-22)-M23	P ~~C~~ APGTFSDTTSST=D ~~IC~~ RPHQ ~~I~~ NVVAIPGDASM=DAV ~~CT~~ STSPTR	4641.09	32.6
M23-M23	DAV ~~CT~~ STSPTR=DAV ~~CT~~ STSPTR	2271.01	23.4

Purity (main peak) by reducing CE-SDS: The determination of highly similar between SB4 and US-licensed Enbrel and the establishment of analytical bridges among SB4, US-licensed Enbrel, and EU-approved etanercept with respect to purity (main peak) by reducing CE-SDS were made based on the evaluation of data from 24 batches of SB4 (one clinical and 10 commercial batches) by separate two-sided quality ranges generated from analyses of data from 50 batches of US-licensed Enbrel and 49 batches of EU-approved etanercept. The data from the analysis of the 50 batches of US-licensed Enbrel and 49 batches of EU-approved etanercept was presented in Tables 102 and 104 of the Appendix, respectively, while the data from the SB4 batches are tabulated in Table 22. For presentation purposes, data from three representative US-licensed Enbrel and EU-approved etanercept batches that were tested side-by-side with the 24 batches of SB4 were provided. Chromatograms from the side-by-side testing appear similar among three comparator groups and no additional/unexpected peaks were observed in the SB4 chromatograms (Figure 21). Data from the side-by-side testing are graphed in Figure 22 with the quality ranges superimposed on the bar graphs. The main peak content in SB4 (97.7 – 99.3%), US-licensed Enbrel (96.0 – 99.1%, n=50), and EU-approved etanercept (96.6 – 99.0%, n=49) was similar. All SB4 batches were within the US-licensed Enbrel (95.4 – 100%) and EU-approved etanercept (95.9 – 100%) two-sided quality ranges. All EU-approved etanercept batches were within the two-sided quality range for US-licensed Enbrel. The chromatograms from the three groups look similar, and no additional/unexpected peaks were observed in the SB4 chromatograms (Figure 21).

Purity (main peak) by non-reducing CE-SDS: The determination of highly similar between SB4 and US-licensed Enbrel and the establishment of analytical bridges among SB4, US-licensed Enbrel, and EU-approved etanercept with respect to purity (main peak) by non-reducing CE-SDS were made based on the evaluation of data from 20 batches of SB4 (one clinical and 10 commercial batches) by separate two-sided quality ranges generated from analyses of data from 50 batches of US-licensed Enbrel and 53 batches of EU-approved etanercept. The data from the analysis of the 50 batches of US-licensed Enbrel and 53 batches of EU-approved etanercept was presented in Tables 102 and 104 of the Appendix, respectively, while the data from the SB4 batches are tabulated in Table 23. For presentation purposes, data from three representative US-licensed Enbrel and EU-approved etanercept batches that were tested side-by-side with the 20 batches of SB4 were provided. Chromatograms from the side-by-side testing appear similar among three comparator groups and no additional/unexpected peaks were observed in the SB4

chromatograms (Figure 24). Data from the side-by-side testing are graphed in Figure 25 with the quality ranges superimposed on the bar graphs. The main peak content of SB4 (98.0 – 99.3%), US-licensed Enbrel (97.4 – 99.5%, n=50), and EU-approved etanercept (97.7 – 99.3%, n=53) was similar. All SB4 batches were within the US-licensed Enbrel and EU-approved etanercept two-sided quality ranges (97.2 - 100%), and all EU-approved etanercept batches were within the US-licensed Enbrel two-sided quality range. The chromatograms from the three groups look similar, and no additional/unexpected peaks were observed in the SB4 chromatograms (Figure 24).

Total Sialic Acid (TSA): The determination of highly similar between SB4 and US-licensed Enbrel and the establishment of analytical bridges among SB4, US-licensed Enbrel, and EU-approved etanercept with respect to total sialic acid content (NANA and NGNA species) were made based on the evaluation of data from 24 batches of SB4 (one clinical and 10 commercial batches) by separate two-sided quality ranges generated from analyses of data from 50 batches of US-licensed Enbrel and 53 batches of EU-approved etanercept. The data from the analysis of the 50 batches of US-licensed Enbrel and 53 batches of EU-approved etanercept was presented in Tables 102 and 104 of the Appendix, respectively, while the data from the SB4 batches are tabulated in Table 24. For presentation purposes, data from three representative US-licensed Enbrel and EU-approved etanercept batches that were tested side-by-side with the 24 batches of SB4 were provided. Data from the side-by-side testing are displayed in Figure 28 with the quality ranges superimposed on the bar graphs. The TSA content (NANA and NGNA) for SB4 batches (14.6 – 15.9 mol/mol chain), US-licensed Enbrel (14.8 – 15.9 mol/mol chain, n=50), and EU-approved etanercept (14.6 – 16.1 mol/mol chain, n=53) was similar. All SB4 batches fell within the two-sided quality ranges for US-licensed Enbrel (14.3 – 16.3 mol/mol chain) and EU-approved etanercept (14.4 – 16.4 mol/mol chain), and all EU-approved etanercept batches fell within the two-sided quality range for US-licensed Enbrel. Chromatograms from the side-by-side testing appear similar among three comparator groups and no additional/unexpected peaks were observed in the SB4 chromatograms (Figure 27)

With respect to individual species of sialic acid, NANA and NGNA were only evaluated in the batches that were tested side-by-side. The NANA and NGNA levels were similar among SB4 (14.5 – 15.7 mol/mol chain and 0.1 – 0.2 mol/mol chain, respectively), US-licensed Enbrel (15.7 – 16.2% and 0.1%, respectively, n=3), and EU-approved etanercept (15.6 – 15.8% and 0.1%, respectively, n=3).

Reviewer Comment: *The evaluation of NANA and NGNA as performed by Samsung is acceptable because NANA and NGNA are not listed as quality attributes designated for Tier 2 evaluation.*

Quantity (Protein Concentration): Protein concentration was determined using UV_{280} and the extinction coefficient $1.14 \text{ ml/mg} \cdot \text{cm}$ (determined from the innovator's patent). The determination of highly similar between SB4 and US-licensed Enbrel and the establishment of analytical bridges among SB4, US-licensed Enbrel, and EU-approved etanercept with respect to protein concentration by UV_{280} were made based on the evaluation of data from seven batches of SB4 (one clinical and three commercial batches) by separate two-sided quality ranges generated from analyses of data from 23 batches of US-licensed Enbrel and 23 batches of EU-approved

etanercept. The data from the analysis of the 23 batches of US-licensed Enbrel and 23 batches of EU-approved etanercept was presented in Tables 102 and 104 of the Appendix, respectively, while the data from the SB4 batches are tabulated in Table 23. For presentation purposes, data from three representative US-licensed Enbrel and EU-approved etanercept batches that were tested side-by-side with the seven batches of SB4 were provided. Data from the side-by-side testing are graphed in Figure 29 with the quality ranges superimposed on the bar graphs. The protein concentration content in SB4 (46.4 – 49.7 mg/ml) was slightly lower than that in US-licensed Enbrel (48.5 – 52.6 mg/ml) and EU-approved etanercept (48.7 – 51.6 mg/ml). Eighty eight percent (8/9) and 44% (4/9) of SB4 batches were within the two-sided quality ranges for US-licensed Enbrel (47.3 – 52.9 mg/ml) and EU-approved etanercept (48.1 – 52.0 mg/ml), respectively. All 23 batches of EU-approved etanercept were within the two-sided quality range for US-licensed Enbrel.

Reviewer Comment: *Although there are differences in protein concentration between SB4 and US-licensed Enbrel and EU-approved etanercept, this can be resolved by addressing a manufacturing issue related to the filling of the SB4 DP batches and does not preclude a demonstration of highly similar between SB4 and US-licensed Enbrel and the establishment of analytical bridges among SB4, US-licensed Enbrel, and EU-approved etanercept. Refer to Section 3.2.P.5.3 for further information.*

LTα3 binding: LTα3 (TNF-β) binding activity was determined by a FRET assay that follows a similar procedure as used for the TNF-α binding FRET assay. The determination of highly similar between SB4 and US-licensed Enbrel and the establishment of analytical bridges among SB4, US-licensed Enbrel, and EU-approved etanercept with respect to LTα3 binding activity by FRET assay were made based on the evaluation of data from 19 batches of SB4 (one clinical and 10 commercial batches) by separate two-sided quality ranges generated from analyses of data from 49 batches of US-licensed Enbrel and 51 batches of EU-approved etanercept. The data from the analysis of the 49 batches of US-licensed Enbrel and 51 batches of EU-approved etanercept was presented in Tables 103 and 105 of the Appendix, respectively, while the data from the SB4 batches are tabulated in Table 26. For presentation purposes, data from three representative US-licensed Enbrel and EU-approved etanercept batches that were tested side-by-side with the 24 batches of SB4 were provided. Data from the side-by-side testing are graphed in Figure 30 with the quality ranges superimposed on the bar graphs. The relative LTα3 binding activity of SB4 (98 – 115%), US-licensed Enbrel (88 – 117%, n=49), and EU-approved etanercept (91 - 114%, n=51) were similar; nearly all SB4 batches were within the range of US-licensed Enbrel and EU-approved etanercept batches and all EU-approved etanercept batches were within the range of US-licensed Enbrel batches. Data from all SB4 batches were within the quality ranges for US-licensed Enbrel (83 – 118%) and EU-approved etanercept (87 – 118%), and the data from all the EU-approved etanercept batches were within the quality range for US-licensed Enbrel.

Similarity Assessment Results for Tier 3

Tier 3 evaluation of quality attributes included the comparison of raw data and graphical representations of raw data generated from SB4, US-licensed Enbrel, and EU-approved etanercept. For the analysis of quality attributes that produced quantitative data, quality ranges (i.e., mean ± 3 SD) were also used to provide a statistical evaluation of the similarity data. The

quality attributes evaluated by Tier 3 were tested side-by-side and categorized into six groups, i.e., (i) primary structure and micro-heterogeneities, (ii) glycan profile, (iii) biophysical properties, (iv) Fc-related biological activities, and (v) additional biological activities. All batches used in the Tier 3 evaluation were used in the Tier 1 and Tier 2 evaluations.

Reviewer Comment: *The analytical similarity assessment of additional Tier 2 quality attributes, i.e., afucosylated, high mannosylated, and α -galactosylated N-linked glycans, glycans with tGalNAc, and charge variants by icIEF, were evaluated in this section. The data generated from Tier 3 and additional Tier 2 quality attribute testing (discussed below) support a demonstration of highly similar between SB4 and US-licensed Enbrel and the establishment of analytical bridges among SB4, US-licensed Enbrel, and EU-approved etanercept.*

1. Primary Structure and Micro-Heterogeneities

Molecular weight and tGalNAc: SB4 is a highly glycosylated fusion protein containing three N-linked glycosylation sites and 13 potential O-linked glycosylation sites on each single chain. Among the 13-potential O-linked glycans, an average of 8 – 10 sites are occupied with GalNAc-Gal core glycan structures that are either mono- or di-sialylated. The molecular weight of SB4 (9 batches, including one clinical and three commercial batches), US-licensed Enbrel (three batches), and EU-approved etanercept (three batches) was determined using mass spectrometry (UPLC-ESI-MS) after removal of N-linked glycans and terminal sialic acids on O-linked glycans and subsequent reduction with dithiothreitol. The molecular weights of the reduced, N-deglycosylated, and O-desialylated single chain of SB4, US-licensed Enbrel, and EU-approved etanercept were similar and within 5 Da of the theoretical masses for each single chain with either 8, 9, or 10 O-linked glycan structures (Table 27). The average number of O-glycans per chain was slightly lower in SB4 (8.4 mean, 8.1 – 8.5) in comparison with US-licensed Enbrel (9.3 mean, 9.2 – 9.4) and EU-approved etanercept (9.3 mean, 9.2 – 9.4; Table 28). The average number of tGalNAc per chain in the SB4 was 0.24 (0.1 – 0.4, n=7) and in US-licensed/EU-approved etanercept was 0.2 (n=3 each; Table 28).

Reviewer Comment: *Although there is a slight difference in the number of O-linked glycans per chain between SB4 and US-licensed and EU-approved etanercept, the content of sialic acid, which can impact the PK and immunogenicity of the product, and potency were similar between SB4 and US-licensed and EU-approved etanercept (see above). Additionally, the average number of tGalNAc, which can impact product clearance, per chain is similar among SB4 and EU-approved etanercept. The observed difference in O-glycan occupancy between SB4 and US-licensed/EU-approved etanercept is not expected to have a clinical impact and do not preclude a demonstration of similarity between SB4 and US-licensed Enbrel and the establishment of analytical bridges among SB4, US-licensed Enbrel, and EU-approved etanercept.*

Amino Acid Sequence: SB4 (three batches, including one clinical and one commercial batch), US-licensed Enbrel (one batch), and EU-approved etanercept (one batch) were digested with trypsin, Lys-C, and Asp-N proteases, and the digested peptides were analyzed using UPLC-ESI-MS/MS. Peptide coverage maps were provided (Figures 34 – 38), and the experimental molecular mass of each digested peptide was reported (Table 29). Complete coverage was observed with all tested samples. No additional peptides or missing peptides were detected among SB4, US-licensed Enbrel, and EU-approved etanercept batches. The experimental peptide

masses of SB4, US-licensed Enbrel, and EU-approved etanercept were within a 0.08 Da difference with respect to the corresponding theoretical peptide masses.

N- and C-terminal sequencing: SB4 (nine batches, including one clinical and three commercial batches), US-licensed Enbrel (three batches), and EU-approved etanercept (three batches) were digested with trypsin and Lys-C for N-terminal and C-terminal analysis, respectively, and the digested peptides were separated, sequenced, and analyzed by UPLC-ESI-MS/MS. The relative contents were calculated from the extracted ion chromatograms and presented as percentages of the integrated intensity.

N-terminal variants

The intact N-terminal form (1-LPA) and Leu-deleted (1-PA) and Leu-Pro-deleted (1-A) forms were identified across the comparator groups. Representative spectra for the N-terminal sequence of SB4, US-licensed Enbrel, and EU-approved etanercept were provided in Figure 39 for the intact form, Figure 40 for the Leu-deleted form, and Figure 41 for the Leu-Pro-deleted form. The N-terminal sequences of the three forms were identical among SB4, US-licensed Enbrel, and EU-approved etanercept. The content of the intact form in SB4 (55.4 – 76.4%) was lower than that in US-licensed Enbrel (87.2 – 90.0%) and generally lower than that in EU-approved etanercept (67.5-79.7%; Table 30). The content of the Leu-deleted form in SB4 (22.2-42.2%) was higher than that in US-licensed Enbrel (3.8-4.9%) and EU-approved etanercept (11.7-18.7%). The content of the Leu-Pro-deleted form in SB4 (1.2-2.5%) was lower than that in US-licensed Enbrel (5.9-7.9%) and EU-approved etanercept (8.6-13.8%).

C-terminal variants

The intact C-terminal form (GK-467) and a Lys-deleted form (G-466) were identified across the comparator groups. Representative spectra for the C-terminal sequence of SB4, US-licensed Enbrel, and EU-approved etanercept were provided in Figure 43 for the intact form and Figure 44 for the Lys-deleted form. The C-terminal sequences of the three forms were identical among SB4, US-licensed Enbrel, and EU-approved etanercept. The content of intact form in SB4 (0.2-0.7%) was lower than that in US-licensed Enbrel (8.4-9.8%) and EU-approved etanercept (6.4-8.1%), whereas the content of the Lys-deleted form in SB4 (99.3 – 99.7%) was higher than that in US-licensed Enbrel (90.2 – 91.6%) and EU-approved etanercept (91.9 – 93.6%).

Reviewer Comment: *The higher levels of the C-terminal intact form (with lysine) in US-licensed and EU-approved etanercept in comparison with those in SB4 correlate with higher levels of basic charge variants. Published studies support that the impact of C-terminal lysine variants do not impact on the biological function and PK of monoclonal antibodies and Fc fusion proteins. Characterization studies, discussed below, demonstrated that N-terminal (Tables 98 and 99) and C-terminal (Tables 93 and 94) variation had no impact on TNF- α neutralization activity and TNF- α binding activity of SB4, US-licensed Enbrel, and EU-approved etanercept. The observed differences in N-terminal and C-terminal variant content between SB4 and US-licensed Enbrel and EU-approved etanercept are not expected to have a clinical impact and do not preclude a demonstration of similarity between SB4 and US-licensed Enbrel and the establishment of analytical bridges among SB4, US-licensed Enbrel, and EU-approved etanercept.*

Peptide Mapping: Peptide mapping using UPLC coupled to ESI-MS/MS was performed to assess the primary structure of SB4 (three batches, including one clinical and one commercial batch) process A batches, one process B batch), US-licensed Enbrel (one batch), and EU-approved etanercept (one batch). Prior to peptide mapping, samples were digested with different proteases (trypsin, Lys-C, and Asp-N), and N-linked glycans and terminal sialic acids on O-linked glycans were removed by Peptide-N-Glycosidase F (PNGase F) and sialidase A treatments, respectively. When Asp-N was used as a digestion enzyme, samples were treated with PNGase F only. The digested peptides were analyzed with respect to their PTMs, sequence variants, and whole sequence. Chromatograms for SB4, US-licensed, and EU-approved etanercept samples after treatment with trypsin, Lys-C, and Asp-N were provided (Figures 45, 46, and 47, respectively).

Reviewer Comment: *The chromatograms show similar peak patterns among SB4, US-licensed Enbrel, and EU-approved etanercept.*

Disulfide bond analysis: The disulfide bonds in SB4 (three batches, including one clinical and one commercial batch), US-licensed Enbrel (one batch) and EU-approved etanercept (one batch) were analyzed using UPLC-ESI-MS/MS. Samples were denatured with 8M urea, alkylated with N-ethylmaleimide, digested with trypsin, and treated with PNGase F and sialidase A to remove N-linked glycans and terminal sialic acids on O-linked glycans, respectively. After Asp-N treatment, peptides were analyzed. Disulfide-linked peptide peaks of samples were detected under non-reducing conditions, and peaks containing cysteine (Cys) residues were detected after samples were reduced with DTT. Chromatograms were provided showing the peptides with disulfide bonds for SB4, US-licensed Enbrel, and EU-approved etanercept material (Figure 48).

Reviewer Comment: *The peak pattern profiles in the non-reduced (red) and reduced (green) chromatograms for the SB4 Process B batch did not appear to be identical to those in the corresponding SB4 Process A, US-licensed Enbrel, and EU-approved etanercept chromatograms. It was requested for Samsung to provide justification for any differences seen in the peak profiles (December 19, 2017). In the IR response (January 12, 2018, Seq. 0020), Samsung indicated that the SB4 Process B batch was not run side-by-side with the other batches and that most differences were the result of the SB4 Process B DS batch not being run side-by-side. The unique peaks present in the SB4 Process B non-reduced chromatogram, as shown in Figure 48, were identified (e.g., peptides without cysteine residues, miscleaved peptide, and a mismatched peptide; Table 19, Section 1.11.1). When the SB4 Process DS batch was run side-by-side with a US-licensed Enbrel batch (Figure 14, Section 1.11.1), the differences observed in Figure 48/Table 19 were not detected. It's likely that the differences were a result of assay variability (e.g., digestion efficiency and miscleavage by trypsin) and are not critical to the analysis of the analytical similarity data.*

Based on the chromatograms provided in Figure 48, nine peptides were detected that contain disulfide linkages, and the experimental masses of these peptides in SB4, US-licensed Enbrel, and EU-approved etanercept were similar and within the assay variability of 30 ppm of the theoretical masses (Table 32). The data support that SB4, US-licensed Enbrel, and EU-approved etanercept have 16 disulfide linkages formed by 29 Cys residues (11 intra-chain disulfide bonds

are present in the TNFR region, two intra-chain disulfide bonds are located in the Fc region, and three inter-chain disulfide bonds are present in the hinge region).

Table 32: Detected Disulfide Linked Peptides and Experimental Masses of Representative SB4 and Enbrel®

Region	Type	Disulfide-linked Peptides	No. of Disulfide Bonds	Theoretical m/z (Charge State)	Detected m/z				
					SB4 Process A		SB4 Process B	Enbrel®	
					Clinical DP	PVR DP	PVR DP	US	EU
					SB4-13B01	SB4-14C20	00001	1040752	H09420
TNFR region	Intra-chain	M*1(1-19)-M4(25-34)-M6(43-47)	2	742.94 (+5)	742.94	742.94	742.94	742.94	742.94
		M5(35-42)-M8(50-53)	1	631.27 (+2)	631.27	631.27	631.27	631.27	631.27
		M9(54-57)-M10(58-77)-M12(81-90)	2	789.33 (+5)	789.33	789.33	789.34	789.34	789.33
		M11(78-80)-M14(95-108)-M16(114-119)-M15(109-113)	3	788.86 (+4)	788.88	788.87	788.87	788.88	788.88
		M18(121-135)-M19(136-148)-M21(155-170)-M23(175-185)	3	818.25 (+7)	818.25	818.25	818.25	818.24	818.26
Hinge region	Inter-chain	M27(239-240)-M27(239-240)	1	415.10 (+1)	415.09	415.09	415.10	415.08	415.09
		M29(243-268)-M29(243-268)	2	780.26 (+7)	780.26	780.26	780.26	780.26	780.27
Fc region	Intra-chain	M31(276-284)-M42(341-342)	1	597.30 (+2)	597.30	597.30	597.30	597.30	597.29
		M50(381-390)-M59(437-459)	1	641.81 (+6)	641.81	641.81	641.80	641.81	641.81

* Multi digested peptide number, which was automatically enumerated by software digested with trypsin and Asp-N enzyme

Free Thiols: Quantitation of free thiols in SB4 (nine batches, including one clinical and three commercial batches), US-licensed Enbrel (three batches), and EU-approved etanercept (three batches) was performed by fluorescence analysis of sample and standard solutions loaded onto a microplate and mixed with thiol quantitation reagent solution. The concentration of free thiol group was determined according to a standard curve. The molar concentration of free thiol content in SB4, US-licensed Enbrel, and EU-approved etanercept was 0.3-0.8 μM (0.2 – 0.4%), 0.1-0.2 μM (0.1%), and 0.2-0.5 μM (0.1%), respectively.

Reviewer Comment: *Despite this minor difference in content, the relative percentage of free thiols was very low ($< 0.4\%$) in all samples. These data and the data derived from the disulfide bond analysis suggest that nearly all 58 Cys residues were linked by disulfide bonds with very few free Cys residues. Data from hydrogen/deuterium exchange (H/DX) and differential scanning calorimetry (DSC) analyses support structural integrity and similarity among SB4, US-licensed Enbrel, and EU-approved etanercept (see below).*

Methionine Oxidation: Met₁₈₇ is located in the TNF- α binding region of US-licensed Enbrel, and its oxidation has the potential to affect TNF- α binding activity. Met₂₇₂ is located in the FcRn binding region of US-licensed Enbrel, and its oxidation has the potential to affect the Fc binding capacity. It is noted that oxidation of Cys residues was not analyzed because free Cys residues are at extremely low levels (NMT 0.4%). SB4 (nine batches, including one clinical and three commercial batches), US-licensed Enbrel (three batches), and EU-approved etanercept (three batches) were digested with trypsin, and the digested peptides were separated and quantitated by UPLC-ESI-MS/MS. The relative contents were calculated from the extracted ion chromatograms and were presented as percentages of the integrated intensity (Table 34). The Met₁₈₇ oxidation content of SB4 (1.9-3.4%) was similar, but included some batches that were higher in content, than that in US-licensed Enbrel and EU-approved etanercept (1.9-2.1% and 2.0-2.2%,

respectively). The Met₂₇₂ oxidation content of SB4 was 5.9-16.3%, which was slightly wider than that of US-licensed Enbrel and EU- Etanercept (7.9-12.1% and 10.5-14.8%, respectively).

Reviewer Comment: *Some batches of SB4 showed oxidation levels at Met₁₈₇ and Met₂₇₂ to be slightly higher than the ranges established for US-licensed Enbrel and EU-approved etanercept. No differences were observed with TNF- α binding and TNF- α neutralization activities and FcR binding activity. The differences in oxidation are likely not great enough to have a potential clinical impact; therefore, they do not preclude a demonstration of highly similar between SB4 and US-licensed Enbrel and the establishment of analytical bridges among SB4, US-licensed Enbrel, and EU-approved etanercept. The impact of oxidation on stability was evaluated as part of the stability comparisons with SB4, US-licensed Enbrel, and EU-approved etanercept (see below).*

Deamidation: Seven Asn residues (Asn₃₃₅, Asn₃₈₁, Asn₄₀₄, Asn₄₀₉, Asn₄₁₀, Asn₄₄₁, and Asn₄₅₄) that are located in the FcRn binding region were analyzed. SB4 (nine batches, including one clinical and three commercial batches), US-licensed Enbrel (three batches), and EU-approved etanercept (three batches) were digested with trypsin, and the digested peptides were separated and quantitated by UPLC-ESI-MS/MS. The relative contents of deamidated Asn residues were calculated from the extracted ion chromatograms and presented as percentages of the integrated intensity (Table 35). The data from these studies are summarized below:

- The Asn₃₃₅ deamidation content in SB4 (2.2-5.2%) was similar, but included batches that were slightly lower in content, than that in US-licensed Enbrel (3.9-4.9%) and EU-approved etanercept (4.4-6.3%).
- The Asn₃₈₁ deamidation content in SB4 (0.6-1.3%) was similar to that in US-licensed Enbrel (1.0-1.2%) and EU-approved etanercept (1.1-2.1%).
- The Asn₄₀₄, 409, or 410 deamidation content in SB4 (2.6-7.1%) was similar, but included batches that were slightly lower in content, than that in US-licensed Enbrel (5.0-10.6%) and EU-approved etanercept (5.3-10.3%).
- The Asn₄₄₁ or 454 deamidation content of SB4 (2.2-6.6%) was similar, but included batches that were slightly lower in content, than that in US-licensed Enbrel (4.5-5.7%) and EU-approved etanercept (5.2-5.6%).

Reviewer Comment: *In addition to the residues evaluated for oxidation and deamidation, etanercept has additional Met residues (Met₃₀, 174, 223, 378, 448) and Asn residues (Asn₆₆, 93, 149, 164, 171, 296, 306, 317, 345), which some are included in the TNFR and Fc regions. It was requested that Samsung provide the content of oxidized Met and deamidated Asn residues at these positions for SB4, US-licensed Enbrel, and EU-approved etanercept (IR dated December 19, 2017). In the IR response (January 12, 2018, Seq. 0020), Samsung provided the requested data (Table 15, Section 1.11.1); however, could not provide an evaluation of oxidation/deamidation at certain residues (Met₂₂₃, Met₃₇₈, Asn₃₁₇, and Asn₃₄₅) because of method limitations. The additional residues analyzed showed similar content of oxidation and deamidation among SB4, US-licensed Enbrel, and EU-approved etanercept.*

2. Glycan Profile

SB4 was characterized with respect to its glycosylation profile (N-linked and O-linked glycosylation), which was compared to that of US-licensed Enbrel and EU-approved etanercept.

Identification of N-linked Glycosylation Sites: SB4 (two batches, including one clinical batch), US-licensed Enbrel (one batch), and EU-approved etanercept (one batch) were denatured with detergent, treated with PNGase F for deglycosylation, digested with Asp-N, and analyzed by peptide mapping by UPLC-ESI-MS/MS. Because the sequences of SB4 Process A and Process B materials are identical, Process B material was not analyzed in this study. During PNGase F treatment, the glycan-linked Asn is converted to Asp, which is the target site for Asp-N. Treatment of all samples with PNGase F resulted in the conversion of three glycosylated peptides D7 (Asn₁₄₉ to Asp₁₄₉), D8 (Asn₁₇₁ to Asp₁₇₁), and D15 (Asn₃₁₇ to Asp₃₁₇). The Asp-containing peptides were digested by Asp-N, which generated six peptides (D7:1, D8:1, D8:2, D15:1, and D15:2). The molecular masses of these digested peptides were similar across the different groups and were no more than 0.01 Da different than the theoretical masses (Table 36). Peptide D7:2 (DTTSST) was not detected in any of the samples because it was too small and hydrophilic to bind to the chromatography column. The MS/MS spectrum of each sample treated with (Figure 49) or without (Figure 50) PNGase F was provided. The MS/MS spectra support that the cleavage by Asp-N targeted Asn₁₄₉, Asn₁₇₁, and Asn₃₁₇ residues and that the major N-glycopeptides detected in the chromatograms of the non-PNGase F-treated samples were identical among SB4, US-licensed Enbrel, and EU-approved etanercept.

Reviewer Comment: *The chromatograms of deglycosylated (Figure 49) and glycosylated (Figure 50) peptides appear similar among SB4, US-licensed Enbrel, and EU-approved etanercept. The data support that SB4, US-licensed Enbrel, and EU-approved etanercept have three N-linked glycosylation sites, i.e., Asn₁₄₉ and Asn₁₇₁ in the TNFR domain and Asn₃₁₇ in the CH2 region of the Fc domain.*

Identification of N-linked Glycans: N-linked glycans in SB4 (two batches, including one clinical batch), US-licensed Enbrel (one batch), and EU-approved etanercept (one batch) were identified using UPLC-ESI-MS/MS. N-linked glycans were labeled with procainamide and separated using a UPLC system equipped with an UPLC BEH glycan column. The signal was detected using a FLR detector coupled to ESI-MS/MS. The SB4, US-licensed Enbrel, and EU-approved etanercept chromatograms show a similar display pattern of the N-linked glycan peaks (Figure 51). The same N-linked glycan structures (M3G0F, G0, G0F, M5, G1, G1', G1F, G1F', G1F+GluNAc, M4G1F, G2, SG1F, G2F, SG1F', SG2, SM4G1F, SG2', SG2F, SG2F', SM3G1, G2FS2, and SG3F) identified in US-licensed Enbrel and EU-approved etanercept were identified in SB4 with the exception of G1F + GluNAc (peak 9). The mass of each N-linked glycan peak was similar between all samples and matches the corresponding theoretical mass (Table 37).

Reviewer Comment: *Although peak 9 (G1F + GluNAc N-linked glycan) was not detected in any of the SB4 chromatograms, it was detected at very low levels in the US-licensed Enbrel and EU-approved etanercept chromatograms. Similarly, peak 12 (SG1F) was not consistently detected because of relatively low levels of the peak. For example, peak 12 was only detected in one out of three SB4 chromatograms and the US-licensed Enbrel batch chromatogram. The N-linked glycan peak profile was similar among SB4, US-licensed Enbrel, and EU-approved etanercept*

chromatograms. The quantification of N-linked glycans is discussed below and reported in groups.

Quantification of N-linked Glycans: The determination of highly similar between SB4 and US-licensed Enbrel and the establishment of analytical bridges among SB4, US-licensed Enbrel, and EU-approved etanercept with respect to N-linked glycan species content by HILIC-UPLC were made based on the evaluation of data from seven batches of SB4 (one clinical and three commercial batches) by separate two-sided quality ranges (mean $\pm$ 3 SD) generated from analyses of data from 31 batches of US-licensed Enbrel and 36 batches of EU-approved etanercept. Samples were denatured with SDS and DTT and treated with PNGase F to release the N-glycans. The released N-glycans were labeled with 2-AB, injected onto a UPLC BEH glycan columns, and detected by a fluorescence detector. N-glycan profiles of SB4, US-licensed Enbrel, and EU-approved etanercept are categorized into four different groups according to structural compositions: afucosylated glycans (%afucose), neutral galactosylated glycans (%galactose), charged glycans (%charged), and high mannosylated glycans (%HM). Definitions for calculating these groups of N-linked glycans were provided.

The analysis of the data from the seven batches of SB4, 31 batches of US-licensed Enbrel, and 36 batches of EU-approved etanercept was presented in Tables 3, 5, and 6 (Section 1.11.1; Seq. 0020, January 12, 2018). For presentation purposes, data from three representative US-licensed Enbrel and EU-approved etanercept batches that were tested side-by-side with the seven batches of SB4 were provided. Chromatograms show a similar N-linked glycan profile among the comparator groups (Figure 53). Data from the side-by-side testing are graphed in Figures 54 – 57 with the quality ranges superimposed on the bar graphs. The SB4 analyzed by the quality ranges are summarized below.

%Afucose species

- SB4: 8.7 – 10.3%
- US-licensed Enbrel: 3.6 – 6.0% (quality range of 3.1 - 6.3%)
- EU-approved etanercept: 4.4 – 6.0% (quality range of 3.9 – 6.5%)

%Charged species

- SB4: 34.0 – 36.8%
- US-licensed Enbrel: 44.0 – 50.0% (quality range of 43.5 – 53.0%)
- EU-approved etanercept: 45.4 – 49.3% (quality range of 41.6 – 53.0%)

%Galactose species

- SB4: 69.4 – 73.1% [SB4-14C28 data point removed (49.4%), suspected error]
- US-licensed Enbrel: 48.1 – 55.7% (quality range of 43.3 – 57.6%)
- EU-approved etanercept: 48.3 – 57.0% (quality range of 47.3 – 60.9%)

%High Mannose species

- SB4: 1.8 – 3.1%
- US-licensed Enbrel: 2.4 – 4.4% (quality range of 2 – 5.2%)

- EU-approved etanercept: 1.9 – 3.2% (quality range of 1.7 – 3.9%)

Reviewer Comment: *The %afucose and %high mannose species were analyzed by quality ranges per the Agency's expectations for Tier 2 evaluation. Because quality ranges were provided for all glycan groups, %galactose and %charged species were also analyzed by quality ranges (mean $\pm$ 3SD) despite their designation for Tier 3 evaluation. The data suggest that in comparison with US-licensed Enbrel and EU-approved etanercept, SB4 contains slightly higher levels of afucosylated N-linked glycans, higher levels of galactosylated N-linked glycans, lower levels of charged N-linked glycans, and similar levels of high mannosylated N-linked glycans.*

Differences in levels of afucosylated N-linked glycans can impact ADCC activity. As discussed below, although SB4 showed a slightly higher level of ADCC activity (2 – 5% relative to ADCC activity of Remicade) in comparison to ADCC activity of US-licensed Enbrel and EU-approved etanercept (0 – 1% relative to ADCC activity of Remicade), the overall ADCC activity is low, and this difference is likely not to be clinically relevant. Despite significant differences in levels of galactosylated N-linked glycans between SB4 and US-licensed Enbrel and EU-approved etanercept, no differences were seen in C1q binding and CDC activity (see below). As discussed above, α -galactose, which can impact immunogenicity, is recommended for Tier 2 evaluation; however, a formal presentation of data was not provided in the analytical similarity assessment. This is acceptable, because Samsung clarified that α -galactose was not detected in SB4, US-licensed Enbrel, and EU-approved etanercept. Despite a difference in charged N-linked glycans, the overall charge contribution from N-linked glycan is low (25%) in comparison to that from O-linked glycans (75%). Furthermore, the content of TSA was shown to be similar between SB4, US-licensed Enbrel, and EU-approved etanercept. Differences in levels of high mannose may impact PK. Based on the analysis by the clinical pharmacology and clinical teams, there were no significant differences in the PK and safety between the comparative groups (refer to these reviews for more information). Because the differences in the N-linked glycan species content at the levels observed during the assessment did not lead to an impact on potency (see above, Tier 1 evaluations) and are not likely to be clinically relevant, differences at these levels do not preclude a demonstration of highly similar between SB4 and US-licensed Enbrel and the establishment of analytical bridges among SB4, US-licensed Enbrel, and EU-approved etanercept.

Because there were differences in N-linked glycan species between SB4 and US-licensed Enbrel/EU-approved etanercept, additional studies, referred as glyco-structure-activity-relationship (Glyco-SAR) studies, were performed to verify the impact on potency. Because a determination of highly similar between SB4 and US-licensed Enbrel and the establishment of analytical bridges among SB4, US-licensed Enbrel, and EU-approved etanercept were confirmed and the purpose of these additional studies was to verify the impact on potency, it was acceptable for Samsung to use one batch of EU-approved etanercept in comparison with SB4 material. The results of this characterization study are discussed below.

Glyco-SAR Study #1

A glyco-structure activity relationship study (Glyco-SAR) was performed to assess the impact of glycan structures on the biological activity of SB4 (one batch) and EU-approved etanercept (one batch). Samples were treated with mannosidase, sialidase, and galactosidase to prepare species without high mannose [Man(-)], sialic acid [Sial(-)], and galactose [Gal(-)], respectively. In the

case of Gal(-) samples, samples were also treated with sialidase. After digestion, samples were purified by Protein A affinity and analyzed for N-linked glycan content and TNF- α neutralization activity. Chromatograms and the quantification of different types of N-linked glycans confirm proper digestion by the exo-glycosidases (Figure 60 and Table 39, respectively). Results from the TNF- α neutralization assay are graphed below in Table 61.

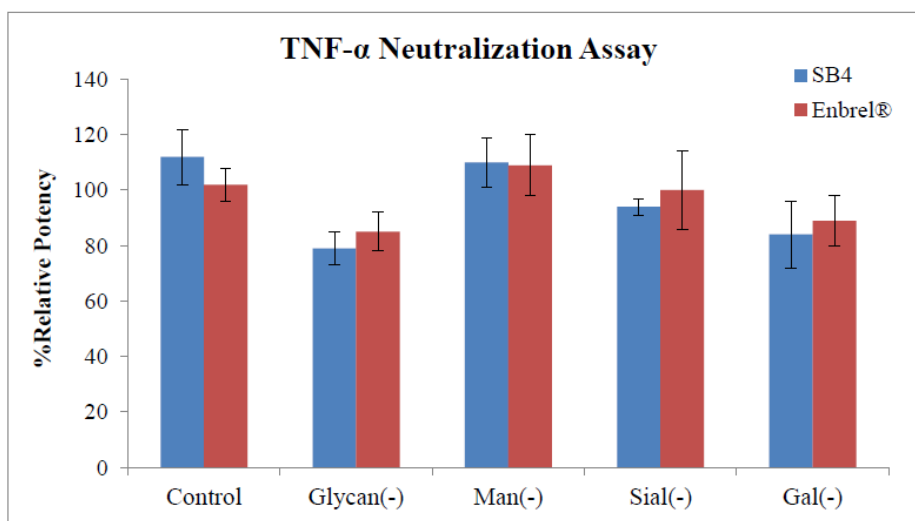


Figure 61: Similarity of TNF- α Neutralization Potency of Glyco-SAR Study Samples

Reviewer Comment: The data suggest that removal of mannose, sialic acid, and galactose species in SB4 and EU-approved etanercept does not significantly impact TNF- α neutralization activity considering deviation within the samples per group and assay variability. Removal of all glycans showed the largest reduction in TNF- α neutralization activity. Because there are two N-linked glycan sites in the TNFR region, it's possible that the removal of N-linked glycans may impact TNF- α binding activity. Samsung did not provide data analyzing the N-linked glycosylation of the TNFR region separated from the Fc region for more in-depth analysis. However, despite the reduction in relative TNF- α neutralization activity when N-linked glycans were removed, there was no significant difference in relative potency between SB4 (112% to 79%) and EU-approved etanercept (102% to 85%).

Fc-specific Glycan Profile: Glycosylation in the Fc region can facilitate Fc receptor-mediated effector functions such as ADCC and CDC and clearance. To determine the relative content of N-linked glycan in the Fc region (Asn₃₁₇) of SB4 (seven batches, including one clinical batch and three commercial batches), US-licensed Enbrel (three batches), and EU-approved etanercept (three batches), samples were treated with papain, which separates the fusion protein into Fc and TNFR regions. After digestion, the separated Fc region of etanercept was collected using protein A column purification. The collected Fc region was analyzed by HILIC-UPLC as described above. The range of values for each glycan group is shown below for SB4, US-licensed Enbrel, and EU-approved etanercept, and the quality ranges (mean $\pm$ 3SD) of the US-licensed Enbrel and EU-approved etanercept values for each glycan group is shown below (Table 41). Chromatograms show a similar N-linked glycan profile among the comparator groups (Figure 63).

Afucose species

- SB4: 5.9 – 7.8%
- US-licensed Enbrel: 2.5 – 2.7% (quality range of 2.3 – 3.0%)
- EU-approved etanercept: 2.6 – 2.8% (quality range of 2.3 – 3.0%)

Charged species

- SB4: 0.6 – 3.4% (Process A: 0.6 – 1.8%, Process B: 3.3 – 3.4%)
- US-licensed Enbrel: 1.1 – 1.4% (quality range of 0.8 – 1.7%)
- EU-approved etanercept: 1.5 – 1.6% (quality range of 1.4 – 1.7%)

Galactosylated species

- SB: 54.5 – 59.5% [SB4-14C28 data point removed (25.6%), suspected error]
- US-licensed Enbrel: 42.5 – 45.0% (quality range of 39.3 – 47.5%)
- EU-approved etanercept: 43.6 – 45.6% (quality range of 41.1 – 48.0%)

Reviewer Comment: Similar trends were detected with glycan analysis of the Fc region of the molecule as seen with the intact molecule. Refer above for comments concerning the differences between SB4 and US-licensed Enbrel and EU-approved etanercept.

Identification of O-linked Glycosylation Sites: The O-linked glycosylation sites of SB4 (two batches, including one clinical batch), US-licensed Enbrel (one batch), and EU-approved etanercept (one batch) were determined by tryptic peptide mapping using UPLC-ESI-MS/MS. Because the sequences of SB4 Process A and Process B materials are identical, Process B material was not analyzed in this study. Independent investigations have published that there are between 12 and 13 potential O-linked glycosylation sites (Gur et al., 2010 and Houel et al., 2014). As shown in Table 42, the 13 potential O-linked glycosylation sites were identified among five tryptic peptides [T01 (1 site), T13 (1 site), T14 (3 sites), T15 (7 sites), and T17 (1 site)]. The experimental masses of the O-glycosylated peptides were similar between all samples and match the theoretical masses (Table 43). MS/MS spectra for each tryptic peptide were provided and were similar among the comparators.

Quantification of O-linked Glycans: The O-glycan profile of SB4 (four batches, including one clinical batch), US-licensed Enbrel (three batches), and EU-approved etanercept (three batches) was determined by HILIC-UPLC. Samples were dialyzed and treated with OrelaTM and acetic acid to separate the O-glycans. The released O-glycans were labeled with 2-AB and injected onto a UPLC BEH glycan columns and detected by a fluorescence detector. Chromatograms were provided (Figures 72 and 73). The chromatograms show three major O-glycan forms [peak 1 (mono-sialylated, represents product derived from the pretreatment of β -elimination), peak 2 (mono-sialylated), and peak 3 (di-sialylated)] followed by N-glycan forms. Quantification of the peaks is shown in Table 44 and summarized below:

Peak 1 (mono-sialylated)

- SB4: 32.8 – 37.2%
- US-licensed Enbrel: 24.5 – 29.7% (quality range is 19.4 – 35.1%)
- EU-approved etanercept: 28.4 – 31.6% (quality range of 25.3 – 35.0%)

Peak 2 (mono-sialylated)

- SB4: 42.5 – 52.0%
- US-licensed Enbrel: 57.4 – 59.1% (quality range of 55.7 – 61.0%)
- EU-approved etanercept: 55.8 – 58.2% (quality range of 53.3 – 61.4%)

Peaks 1 and 2 (mono-sialylated)

- SB4: 76.0 – 85.0%
- US-licensed Enbrel: 86.1 – 88.8% (quality range of 75.2 – 96.0%)
- EU-approved etanercept: 86.2 – 89.9% (quality range of 81.6 – 93.5%)

Peak 3 (di-sialylated)

- SB4: 15.0 – 24.0% (range with a mean of 18.3)
- US-licensed Enbrel: 11.2 – 18.1% (quality range of 4.0 – 24.8%)
- EU-approved etanercept: 10.2 – 13.8% (quality range of 6.5 – 18.4%)

Reviewer Comment: *It's acceptable that SB4 process B material was not evaluated in this study because previous studies demonstrate comparability between Process A and Process B materials with respect to O-glycosylation sites, O-glycopeptide content, and TSA content. The minor differences observed in mono-sialylated and di-sialylated content is expected not to have a clinical impact; likewise, data support that SB4, US-licensed Enbrel, and EU-approved etanercept are similar with respect to TSA content (see above), which may suggest that the slightly higher amount of di-sialylated O-glycan compensates the slightly lower level of O-glycan occupancy (see above) for SB4.*

3. Charge Variants

The similarity of charge variants was assessed by CEX-HPLC (Tier 3) and iCIEF (Tier 2) methods. Because of highly sialylated O-glycan forms, proteinaceous charge variants are only detected after removal of sialic acids. Therefore, samples were pretreated with sialidase prior to running the samples.

Reviewer Comment: *Charge variants by iCIEF were analyzed per Tier 2 analysis, while charge variants by CEX-HPLC were not because of the superiority of the former method to resolve acidic and basic peaks from the main peaks.*

CEX-HPLC: The relative contents of acidic, basic, and main peaks were determined in desialylated SB4 (four batches, including one clinical batch), US-licensed Enbrel (three batches), and EU-approved etanercept (three batches). For all samples, the relative contents of acidic and main peaks were reported together because the main and acidic peaks could not be resolved. The basic charge peak profile between SB4 and US-licensed/EU-approved etanercept appears

different (Figure 77). The basic peak in SB4 chromatograms show very low levels of basic charge variants (20.6 – 22.8%), while the chromatograms of US-licensed Enbrel (42.0 – 43.0%) and EU-approved etanercept (37.3 – 40.9%) show higher levels that consist of two prominent basic peaks (Table 44). As a result, SB4 had higher peak area for %acidic variants + %main (77.2 – 79.4%) in comparison to that in US-licensed Enbrel (57.0 – 58.0%) and EU-approved etanercept (59.1 – 62.7%).

icIEF: Charge variants were further analyzed by icIEF, an orthogonal method to CEX-HPLC. The determination of highly similar between SB4 and US-licensed Enbrel and the establishment of analytical bridges among SB4, US-licensed Enbrel, and EU-approved etanercept with respect to charge variant content (acidic, main, and basic species) by icIEF were made based on the evaluation of data from seven batches of SB4 (one clinical and three commercial batches) by separate two-sided quality ranges (mean $\pm$ 3 SD) generated from analyses of data from 24 batches of US-licensed Enbrel and 23 batches of EU-approved etanercept. The analysis of the data from the seven batches of SB4, 24 batches of US-licensed Enbrel, and 23 batches of EU-approved etanercept was presented in Table 4 (Section 1.11.1; Seq. 0020, January 12, 2018). For presentation purposes, data from three representative US-licensed Enbrel and EU-approved etanercept batches that were tested side-by-side with the seven batches of SB4 were provided. Data from the side-by-side testing are graphed in Figures 81 – 83 (acidic, main, and basic species, respectively) with the quality ranges superimposed on the bar graphs. The acidic variant content in SB4 batches (40.4 – 44.4%) was higher than that in US-licensed Enbrel (17.8 – 26.6%, n=24) and EU-approved etanercept (19.6 – 30.1%, n=23). The main peak content in SB4 batches (48.8 – 52.7%) was similar to that in US-licensed Enbrel (47.9 – 51.7%) and EU-approved etanercept (46.8 – 55.4%). The basic variant content in SB4 batches (6.1 – 8.4%) was lower than that in US-licensed Enbrel (24.9 – 30.5%) and EU-approved etanercept (18.0 – 29.2%). All the SB4 batches fell outside the US-licensed Enbrel and EU-approved etanercept quality ranges for acidic (16.0 – 30.4% and 15.6 – 32.1%, respectively) and basic (22.1 – 33.6% and 16.7 – 33.0%, respectively) variants. All SB4 batches fell within the US-licensed Enbrel and EU-approved etanercept quality ranges for the main species (43.8 – 54.1% and 44.8 – 57.8%, respectively)

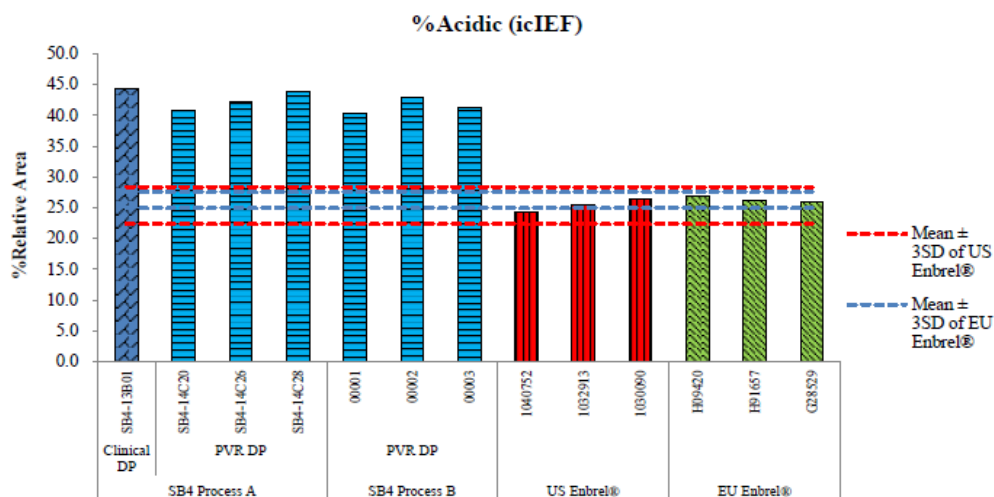


Figure 81: Similarity of %Acidic between SB4 and Enbrel® by icIEF

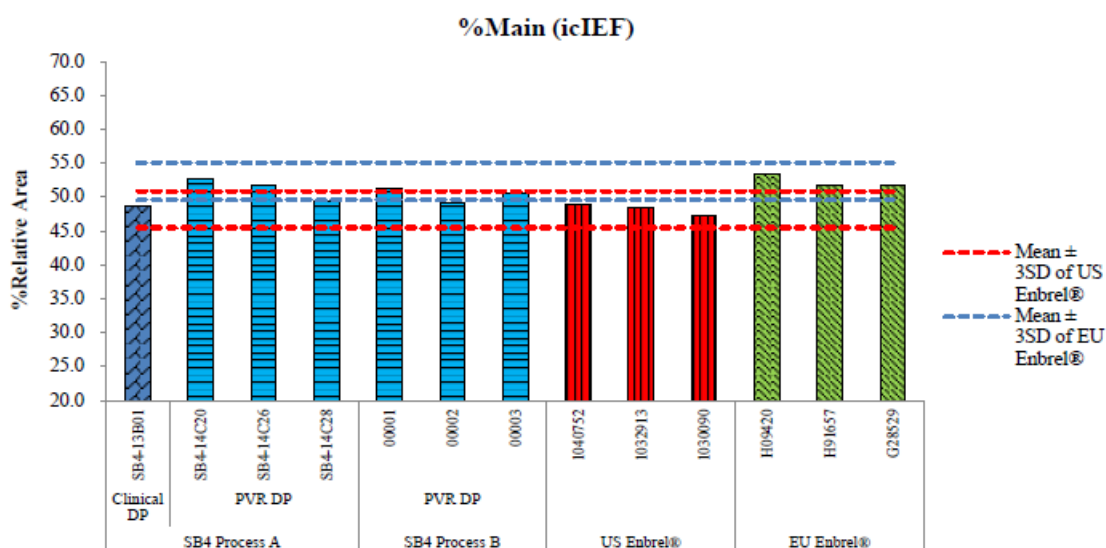


Figure 82: Similarity of %Main between SB4 and Enbrel® by icIEF

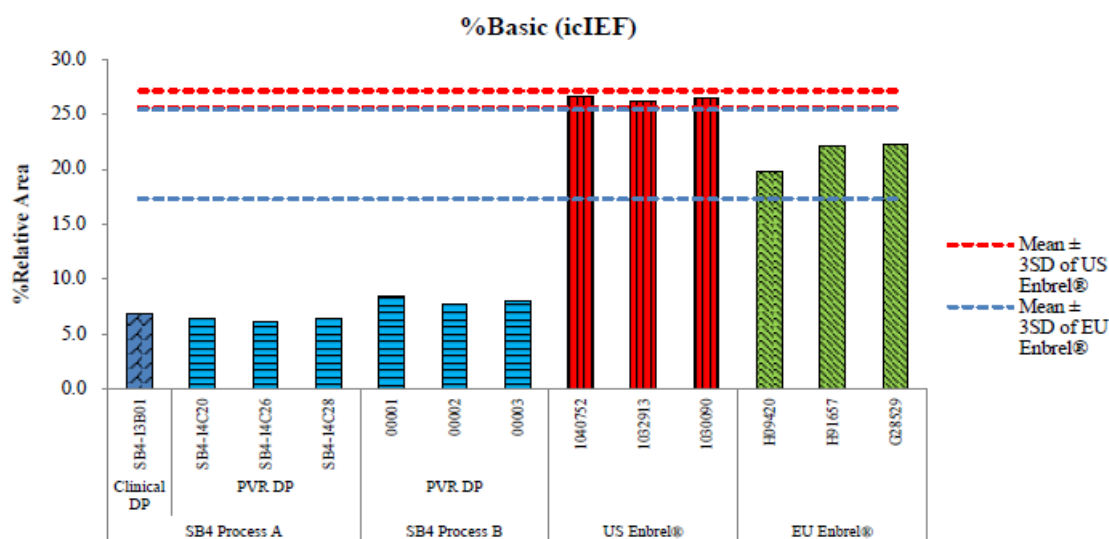


Figure 83: Similarity of %Basic between SB4 and Enbrel® by icIEF

Representative electropherograms were provided from each comparative group. The main peak in the SB4 electropherograms was split into two peaks, which is different than the one main peak observed in US-licensed Enbrel and EU-approved etanercept electropherograms (Figure 88, see below for example and discussion). Besides this difference, the electropherograms for SB4, US-licensed Enbrel, and EU-licensed etanercept appear similar in peak pattern. The pI for the main form of SB4, US-licensed Enbrel, and EU-approved etanercept was 7.4.

Reviewer Comment: Because the differences in the acidic and basic species content at the levels observed during the assessment did not lead to an impact on potency (see above, Tier 1 evaluations), these differences at these levels do not preclude a demonstration of highly similar

between SB4 and US-licensed Enbrel and the establishment of analytical bridges among SB4, US-licensed Enbrel, and EU-approved etanercept.

Because there were differences in acidic and basic species and the main peak profile between SB4 and US-licensed Enbrel/EU-approved etanercept, additional studies were performed to verify the impact on potency and characterize the peaks. Because a determination of highly similar between SB4 and US-licensed Enbrel and the establishment of analytical bridges among SB4, US-licensed Enbrel, and EU-approved etanercept were confirmed and the purpose of these additional studies is for characterization and verification purposes, it was acceptable for Samsung to use one batch of EU-approved etanercept in comparison with SB4 material. The results of these studies are discussed below.

Characterization of Charge Variants: The differences in the charge profile between SB4 and EU-approved etanercept were investigated by fractionating SB4 (SB4-14C20) and EU-approved etanercept (H63237) into different charge variant fractions and characterizing each fraction. Samples were desialylated and separated using a liquid phase IEF Rotofor system and a WCZ-10 semi-preparation column to create iCIEF and CEX-HPLC fractions, respectively.

iCIEF fraction study

Desialylated SB4 and EU-approved etanercept were fractionated using liquid phase IEF (Rotofor system, Bio-Rad), which separates proteins by pI. The results of the iCIEF analysis of each fraction are shown below in Figure 84. Based on the iCIEF analysis, fractions 5 and 6 were defined as the acidic variants, fraction 7 as the main form, and fractions 8 and 9 as the basic variants (Figure 84).

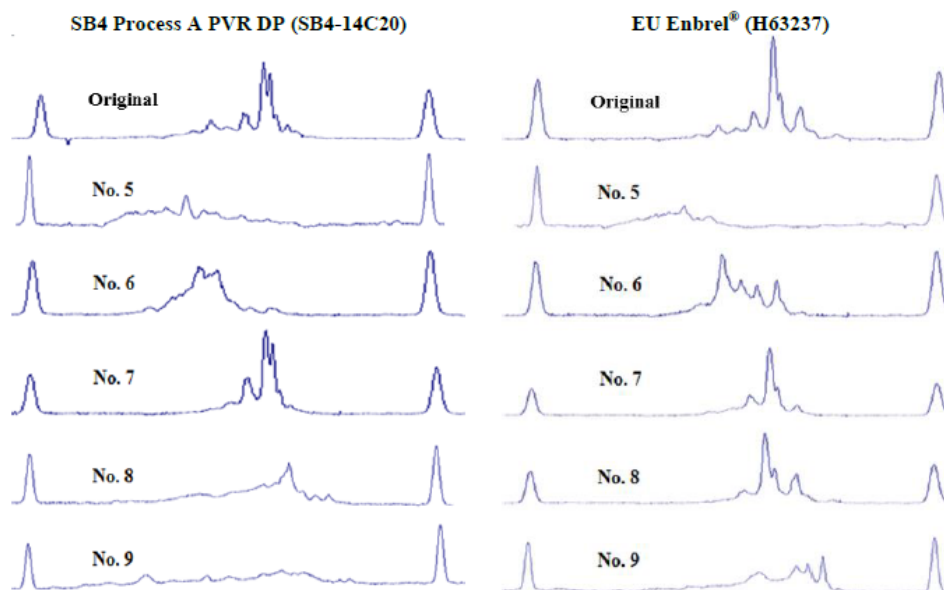


Figure 84: iCIEF Analysis of Rotofor Fractions

Each fraction was analyzed by intact mass analysis to determine O-glycan occupancy and other post-translational modifications (i.e., fragmentation, glycation, and N-terminal leucine clipping)

and peptide mapping analysis to determine sialylation, oxidation, deamidation, and C-terminal lysine content. Peptide analysis was not performed on SB4 fraction 9 because of an inadequate sample amount after intact mass analysis. Chromatograms related to intact mass and peptide mapping analyses were provided in Figure 86 and Figure 87, respectively. The data from these studies are tabulated in Table 47 (see below).

Table 47: Results from Characterization of Rotofor Fractions

Sample			Intact Mass		Peptide Mapping				
			O-glycan Occupancy	N-terminal Variant (Leu-clipping form)	Relative Level of C-terminal Lysine Variant (%)		Relative Level of Oxidized Met Residue (%)		Relative Level of Deamidation (%)
					Lys-deleted Form	Intact Form	Met ₁₈₇	Met ₂₇₂	Asn ₃₃₅
SB4 Process A	Acidic	No.5 ^a	8.8	20.5	99.5	0.5	8.2	5.4	2.8
		No.6	8.7	21.3	99.7	0.3	4.3	5.1	1.5
	Main	No.7	8.7	21.4	99.8	0.2	N/D ^b	4.5	1.2
	Basic	No.8	8.7	24.1	99.8	0.2	7.8	4.6	2.0
		No.9	8.7	28.3	N/T ^c	N/T ^c	N/T ^c	N/T ^c	N/T ^c
EU Enbrel [®]	Acidic	No.5	9.0	14.9	95.1	4.9	2.2	1.6	2.0
		No.6	9.2	12.6	96.1	3.9	3.9	1.9	1.9
	Main	No.7	9.2	11.8	93.2	6.8	3.7	1.7	1.1
	Basic	No.8	9.2	13.8	84.7	15.3	2.5	1.6	1.5
		No.9	9.2	22.6	N/T ^c	N/T ^c	N/T ^c	N/T ^c	N/T ^c

^a Fraction number from Rotofor fractionation by chamber

^b Not detected

^c Not tested. Sufficient amount of fraction sample No.9 was not obtained to perform both of intact mass and peptide mapping analysis.

Reviewer Comment: The N-terminal Leu-deleted form was elevated in SB4 fractions, especially in basic fraction 9, in comparison to corresponding EU-approved etanercept fractions. The C-terminal intact form was elevated in EU-approved etanercept fractions, especially basic fraction 9, in comparison to corresponding SB4 fractions, and vice versa for the C-terminal Lys-deleted form. Oxidation of Met₁₈₇ and Met₂₇₂ was slightly higher in the SB4 fractions in comparison to that in the corresponding EU-approved etanercept fractions. Samsung stated that glycation and fragments were not observed in any of the fractions; however, no data were provided. In response to the IR sent on December 19, 2017, oxidation analysis at different Met residues was provided, which demonstrated that the content of oxidized Met₃₀ and Met₄₄₈ was similar in the SB4 fractions (0.6 – 1.1% and 0.2 – 1.1%, respectively) and the EU-approved etanercept fractions (0.3 - 1.2% and 0.0 – 0.4%, respectively; Table 16, Section 1.11.1).

The decrease in basic variants in SB4 can partially be explained by a lower amount of the C-terminal lysine intact form in SB4 in comparison to that in EU-approved etanercept. Likewise, carboxypeptidase B treatment of non-fractionated material significantly diminished the amount of the basic peaks in SB4 (9.1% to 5.0%) and EU-approved etanercept (23.3% to 6.8%; Figure 88) to comparable levels as determined by icIEF. A difference in basic variants that is mainly C-terminal variants is not expected to have a clinical impact.

CEX-HPLC fraction study

CEX-HPLC was used to separate desialylated SB4 and EU-approved etanercept to create fractions based on charge profile (Figure 89).

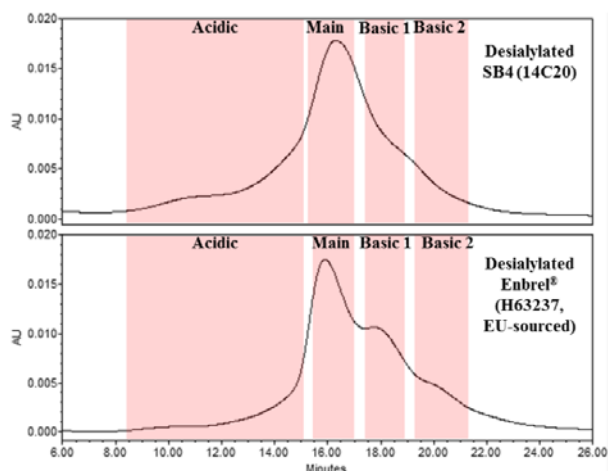


Figure 89: Fractionated Charge Variant Peaks from Desialylated SB4 and EU Enbrel®

The CEX-HPLC fractions were characterized according to the same test methods used for the analysis of the Rotofor fractions with the exception that the CEX-HPLC fractions were also evaluated for TNF- α binding activity. The results from these studies are tabulated in Table 48 and displayed in Figure 95 (see below).

Table 48: Characterization Results of CEX-HPLC Fractions

Sample		Intact Mass		Peptide Mapping				
		O-glycan Occupancy	N-terminal Variant (Leu-clipping form)	Relative Level of C-terminal Lysine Variant (%)		Relative Level of Oxidized Met Residue (%)		Relative Level of Deamidation (%)
				Lys-deleted Form	Intact Form	Met187	Met272	Asn335
SB4 Process A	Acidic	8.8	19.7	99.9	0.1	1.3	3.8	0.2
	Main	8.5	20.5	99.9	0.1	1.0	4.4	0.3
	Basic 1	8.3	20.2	99.7	0.3	1.8	6.4	0.3
	Basic 2	8.1	23.3	99.6	0.4	2.9	8.4	0.4
EU Enbrel®	Acidic	9.5	5.5	97.8	2.2	0.8	2.6	0.4
	Main	9.2	6.9	94.5	5.5	1.9	3.5	0.4
	Basic 1	9.0	8.0	86.1	13.9	N/Da	2.1	N/D
	Basic 2	8.9	6.9	79.2	20.8	0.8	3.4	0.4

^a Not detected

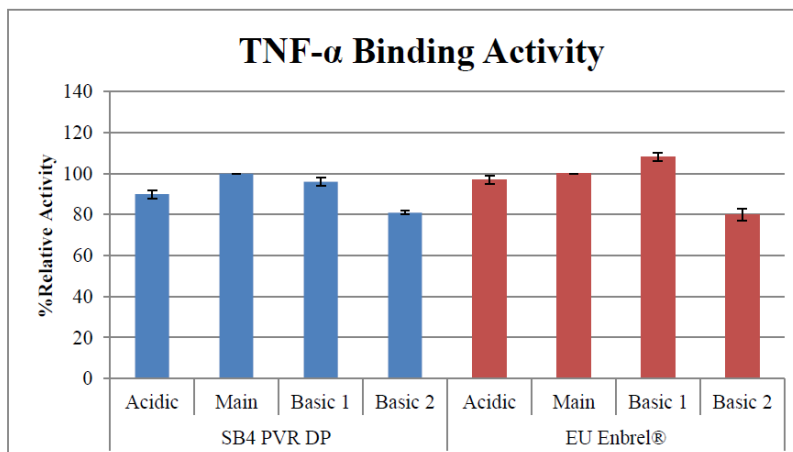


Figure 95: Relative TNF-α Binding Activity of CEX-HPLC Fraction

Reviewer Comment: With respect to the Rotofor fractions, similar trends were observed for N-terminal and C-terminal variants, and deamidation at Asn₃₅₅, while the CEX-HPLC fractions showed a decrease in O-glycan occupancy from acidic to basic fractions and the difference in oxidation at Met187 and Met272 across the CEX-HPLC fractions was less clear in SB4 and EU-approved etanercept. TNF-α binding data showed that TNF- binding activity was less in the basic 2 fraction (~81%) in comparison to that in the main fraction (~100%); however, this difference is within assay variability and the TNF-α binding activity across the fractions between SB4 and EU-approved etanercept was similar.

Additional studies were performed where non-fractionated SB4 and EU-approved etanercept were treated with or without carboxypeptidase to remove the C-terminal lysine intact variant. The amount/presence of C-terminal lysine intact variant was shown not to impact TNF-α binding activity (Figure 93) and TNF-α neutralization activity (Figure 94).

Reviewer Comment: The data from the fraction studies support that charge variants between SB4 and EU-approved etanercept share comparable physiochemical properties and biological activities.

Peak Splitting in the Main Region by icIEF analysis. Different degrees of peak splitting of the main region were observed for SB4, US-licensed Enbrel, and EU-approved etanercept using icIEF analytical methods (example shown above in Figure 84). In order to evaluate the possible impact of the difference in the degree of peak splitting, the different icIEF charge variant fractions were further analyzed to elucidate the cause of peak splitting and their impact on biological activities.

Higher degree of peak splitting of the main region was observed for SB4 compared to EU-approved etanercept. Samsung hypothesized that the cause of higher peak splitting of the main region for SB4 is because of differences in the manufacturing process. A study was performed where EU-approved etanercept was exposed to (b) (4) obtained during the SB4 manufacturing process. Treatment of EU-approved etanercept with the SB4 (b) (4) induced peak splitting of the main region to a similar extent to that was observed in SB4

(Figure 80). Additionally, levels of the N-terminal Leu-deleted form increased in EU-approved etanercept from 5.8% to 27.6%, which is comparable to the level present in SB4 (23.6%).

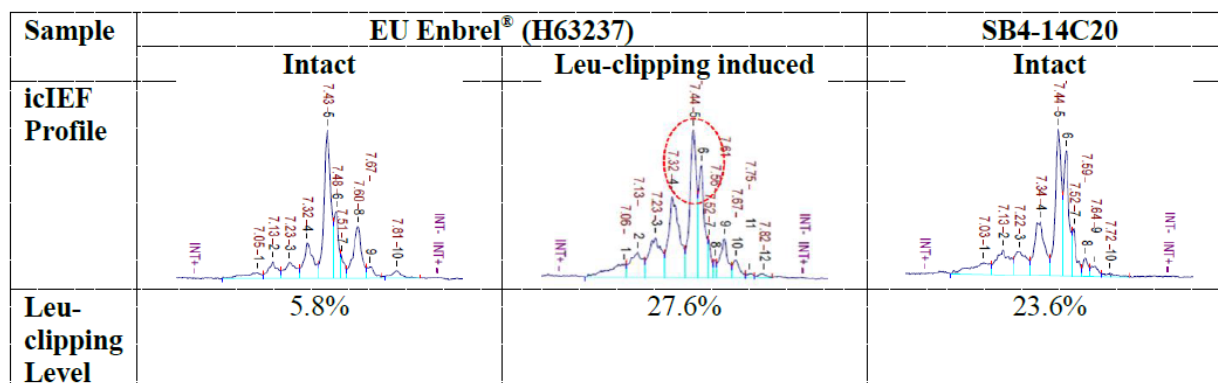


Figure 97: icIEF Electropherograms for EU Enbrel® and SB4

The impact of the splitting of the main peak region and the increased level of the N-terminal Leu-deleted form on the biological activities of EU-approved etanercept was investigated. Results demonstrate that the splitting of the main peak region and the increase of N-terminal Leu-deleted variant in EU-approved etanercept did not impact TNF- α binding activity and TNF- α neutralization activity (Table 49).

Reviewer Comment: The data support that the splitting of the main peak in SB4 electropherograms is contributed to N-terminal leucine clipping, (b) (4)

When EU-approved etanercept material was subject to main peak splitting, there was an increase in the level of the N-terminal Leu-deleted form, but no impact on the biological activity of the (b) (4) treated EU-approved etanercept material.

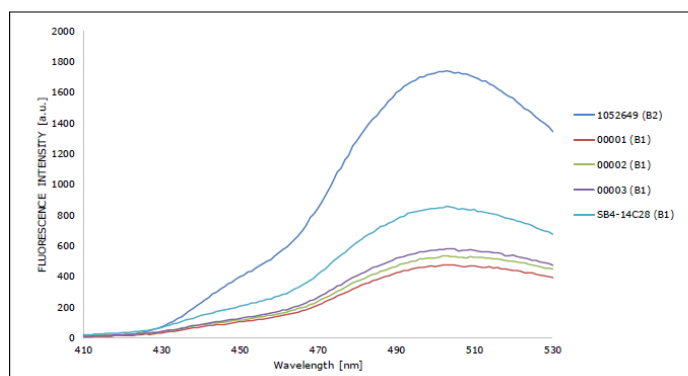
4. Biophysical properties

Circular Dichroism (CD) Spectroscopy: Far-UV (190-250 nm) CD spectroscopy was used to assess the similarity of the secondary structure among SB4 (six batches, including three commercial batches), US-licensed Enbrel (four batches), and EU-approved etanercept (six batches). The far-UV CD profiles, which are characteristic of beta-sheet structures, are shown as overlays in Figures 100 and 101. The spectra for SB4, US-licensed Enbrel, and EU-approved etanercept are nearly overlapping across the Far-UV region.

Intrinsic Fluorescence (ITF) Spectroscopy: ITF spectroscopy was used as an indirect method to assess the similarity of the tertiary structure among SB4 (six batches, including three commercial batches), US-licensed Enbrel (four batches), and EU-approved etanercept (six batches). Spectra overlays were provided in Figures 102 and 103, and spectra data (i.e., emission maxima and maximum fluorescence intensity) were provided in Table 50. The SB4 spectra, including emission maxima and maximum fluorescence intensity, are within the variation of the corresponding US-licensed Enbrel and EU-approved etanercept data, which are similar.

Extrinsic Fluorescence Spectroscopy: The similarity of surface hydrophobicity among SB4 (six batches, including three commercial batches), US-licensed Enbrel (four batches), and EU-approved etanercept (six batches) was evaluated by characterizing the binding interactions of

samples with an extrinsic fluorescent dye [1-Anilinonaphthalene-8-Sulfonate (ANS)] via fluorescent spectroscopy. The ANS fluorescence intensity is a result of hydrophobic interactions between ANS and the protein molecule. The emission maximum was similar among SB4 (502-507), US-licensed Enbrel (503-506), and EU-approved etanercept (504); however, the peak intensities were significantly lower in SB4 (476 – 1056 au) in comparison with US-licensed Enbrel (2018 – 22293 au) and EU-approved etanercept (1751 – 2409 au; Figures 104 – 105 and Table 51). A representation of the difference in peak intensities between SB4 and US-licensed Enbrel is shown below.



*SB4 Process A PVR: SB4-14C28; SB4 Process B PVR: 00001, 00002, and 00003; US Enbrel®: 1052649

Figure 105: Extrinsic Fluorescence Emission Spectra of SB4 Process B and Enbrel®

The difference in fluorescence intensity was further evaluated to determine an impact on potency. One commercial SB4 batch was stressed by heating at 40°C for 3 days, which resulted in an increase of hydrophobicity as shown by an increase of the emission maximum by 25 times in comparison to the unstressed sample (Figure 106).

Reviewer Comment: *Because of differences in formulation, which can impact hydrophobic interactions, it is reasonable for the extrinsic fluorescent spectra to be different between SB4 and US-licensed/EU-approved etanercept. It is not expected that the observed differences would result in a clinical impact.*

Fourier Transform Infrared (FTIR) Spectroscopy: The similarity of the secondary structure among SB4 (six batches, including three commercial batches), US-licensed Enbrel (four batches), and EU-approved etanercept (six batches) was evaluated by FTIR, where infrared radiation is absorbed, and after Fourier transformation, data were converted into spectra. The analysis of protein secondary structure by FTIR is based on contributions from the amide bands, particularly the Amide I region between 1,600 – 1,700 cm^{-1} and Amide II region between 1480 – 1,600 cm^{-1} . Beyond 2,000 cm^{-1} , non-protein related contributions from buffer components to the spectra can be observed. The FTIR spectra of SB4, US-licensed Enbrel, and EU-approved etanercept are similar; spectra overlays are provided in Figures 107 – 110. A broad peak with a minimum near 1640 cm^{-1} was observed in second derivative batch, which suggests that the samples are dominated by β -sheet conformation. Minor differences in the 1660-1700 cm^{-1} spectra region were observed among sample groups.

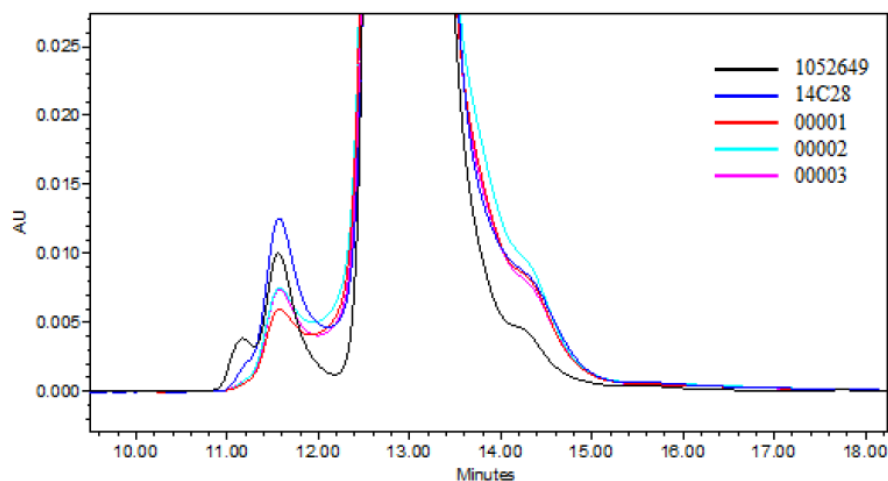
Hydrogen/Deuterium Exchange (H/DX): H/DX coupled with mass spectrometry analysis was performed to assess the similarity of the tertiary structure and conformational dynamics among SB4 (three batches, including one clinical and commercial batch), US-licensed Enbrel (one batch), and EU-approved etanercept (one batch). The H/DX method relies on the exchange of the protein backbone amide hydrogens with deuterium in solution. By measuring hydrogen and deuterium exchange rates, information on protein dynamics and the tertiary structure can be obtained. Because samples are digested and analyzed by mass spectrometry, the location of conformational differences can be identified. Coverage maps were provided from each analysis showing that the digested peptides provide adequate coverage of the etanercept sequence (92.5% coverage; Figure 111) and 94.5% coverage (analysis 2; Figure 112). The deuterium uptake plots for each individual peptide (Figures 113 and 114) generally show overlapping kinetic curves among SB4, US-licensed Enbrel, and EU-approved etanercept. The deuterium uptake butterfly plots (Figures 115 to 118) show that the dynamics of deuterium uptake for SB4 is similar to that of US-licensed Enbrel and EU-approved etanercept.

Differential Scanning Calorimeter (DSC): DSC was performed to assess the similarity of the heat-induced protein denaturation pattern among SB4 (six batches, including three commercial batches), US-licensed Enbrel (four batches), and EU-approved etanercept (six batches). The sample melting curves (Figure 120), which are nearly overlapping among the samples, show three thermal transitions (T_{m1} , T_{m2} , and T_{m3}). The range of T_{m1} values was 56.9 – 58.8°C for SB4, 56.7 – 56.8°C for US-licensed Enbrel, and 56.7 – 56.9°C for EU-approved etanercept. The range of T_{m2} values was 69.3 – 70.8°C for SB4, 69.5 – 69.6°C for US-licensed Enbrel, and 69.6°C for EU-approved etanercept. The range of T_{m3} values were 82.0 – 82.9°C for SB4, 82.5°C for US-licensed Enbrel, and 82.6 °C for EU-approved etanercept.

Reviewer Comment: *The SB4 T_m values were more variable than the US-licensed and EU-approved etanercept T_m values; however, the values are generally similar and differences are likely to be within method variability.*

Size Exclusion Chromatography/Multi-Angle Laser light Scattering (SEC/MALLS). SEC/MALLS was used to support the analysis by SEC and provide additional information with respect to similarity of size-related product variants. SB4 (five batches, including one clinical and three commercial batches), US-licensed Enbrel (one batch), and EU-approved etanercept (one batch) were analyzed by SEC/MALLS for an assessment of the similarity of HMW and monomer/LMW content and relative molecular weight. Chromatograms appear similar among samples besides differences in HMW content. For all SB4, US-licensed Enbrel, and EU-approved etanercept chromatograms, a main peak was detected near 13.1-13.2 min and small peaks representing HMW and LMW species were detected near 11-12 min and 14.5 min, respectively. In the HMW region, two peaks are observed in the US-licensed Enbrel and EU-approved etanercept chromatograms, whereas only one peak is observed in the SB4 chromatogram (Figures 121 – 122, excerpt of Figure 122 is shown below). The average content of monomer + LMW species was similar among SB4 (97.8 – 98.6%), US-licensed Enbrel (96.9%), and EU-approved etanercept (97.8%), while the average content of HMW species in SB4 samples (1.4 – 2.2%, 1.8% average) was generally lower than in US-licensed Enbrel (3.1%) and EU-approved etanercept (2.1%). While the monomer molecular weight in SB4 (124 – 146 kDa) was similar to that in US-licensed and EU-approved etanercept (146 kDa), the HMW

molecular weight in SB4 (235-305 kDa) was lower than that in US-licensed Enbrel (390 kDa) and EU-licensed Etanercept (405 kDa).



*SB4 Process A PVR: SB4-14C28; SB4 Process B PVR: 00001, 00002, and 00003; US Enbrel®: 1052649

** Top: Full Chromatogram, Bottom: Zoom-in

Figure 122: MALLS Scattering Data of SB4Process B and Enbrel®

Reviewer Comment: The difference in the HMW molecular weight between SB4 and US-licensed/EU-approved etanercept is likely because of poor resolution of the main HMW peak (11.9 minutes) with the additional HMW peak (11.0 minutes) present in US-licensed/EU-approved etanercept; the molecular weight of the main HMW peak included a portion of the additional HMW peak, which resulted in a higher HMW molecular weight value for US-licensed/EU-approved etanercept. Because of the molecular weight of the main peak, the main HMW peak and additional HMW peak, present in US-licensed and EU-approved etanercept, are considered to a dimer and tetramer, respectively, of the dimeric protein. The higher HMW content in US-licensed/EU-approved etanercept is contributed by the additional HMW peak (11.0 minutes) and higher levels of the main HMW peak (11.9 minutes).

Sedimentation Velocity-Analytical Ultracentrifugation (SV-AUC): SV-AUC was used as an orthogonal method to SEC and SEC/MALLS to assess the similarity of purity and HMW content among SB4 (four batches, including one clinical batch), US-licensed Enbrel (three batches), and EU-approved etanercept (three batches). Monomer and HMW content, monomer molecular weight, and the frictional coefficient values were reported in Tables 54 and 55. Similar to analysis by SEC and SEC-MALLS, the HMW content in SB4 (N/D – 0.2%) was lower and the monomer content (99.5 – 99.8%) in SB4 was higher in comparison to those in US-licensed Enbrel (0.5 – 1.1% and 97.8 – 99.5%, respectively) and EU-approved etanercept (0.9 – 2.4% and 97.6 – 98.9%, respectively). The molecular weight values of the monomer in SB4 were more uniform by SV-AUC detection (151-156 kDa) in comparison with corresponding SEC-MALLS values (124 – 146 kDa) and comparable to monomer molecular weight SV-AUC values in US-licensed Enbrel (152-153 kDa) and EU-approved etanercept (152-154 kDa). The frictional coefficient, a value which represents deviation from a globular shape, was similar among SB4 (2.15 – 2.21), US-licensed Enbrel (2.21 – 2.22), and EU-approved etanercept (2.20 – 2.22).

Reviewer Comment *The levels of the dimeric fusion protein, HMW species, and LMW species analyzed by SEC-MALLS and SV-AUC test methods support the SEC analysis. Aggregates in the nm- and μ m-size ranges were characterized by the dynamic light scattering (DLS) and micro-flowing imaging (MFI) methods, respectively (see below).*

Dynamic Light Scattering (DLS): SB4 (seven batches, including one clinical and three commercial batches), US-licensed Enbrel (three batches), and EU-approved etanercept (three batches) were analyzed by DLS to measure subvisible aggregates in the nanometer size range and to determine particle size distribution. Monodisperse samples have polydispersity values close to zero, while broader distributions have larger values. The main results (Table 56) from the study are discussed below:

- As shown in the chromatograms (Figures 124 – 125 and Table 125), one main peak was detected at 13.9-15.2 nm for all samples. Due to the detection of an additional peak between 2000 – 6000 nm for several US-licensed Enbrel and EU-approved etanercept batches, the main peak intensity of these batches was 96.83-100.00% and 97.87-100.00%, respectively, while that of SB4 was 100.00%. The main peak diameter was similar among SB4 (13.89 – 15.20), US-licensed Enbrel (14.59 – 14.72), and EU-approved etanercept (14.76 – 15.17).
- The Z-average diameter values were similar among SB4 (12.82 – 14.48 nm), US-licensed Enbrel (13.14 – 13.73 nm), and EU-approved etanercept (13.09 – 13.71 nm). The polydispersity values diameter values were similar, considering assay variability, between SB4 (0.4 – 0.12), US-licensed Enbrel (0.11 – 0.19), and EU-approved etanercept (0.12 – 0.17).

Micro-flow imaging (MFI): MFI was performed for the quantification, visualization, and characterization of sub-visible particles in the micron size range by passing test fluid through the focal plane of a microscope and obtaining high-speed images. The MFI results show that SB4 samples (seven batches, including one clinical and three commercial batches) contain fewer SVPs ($\geq 1 \mu\text{m}$, $\geq 2 \mu\text{m}$, $\geq 10 \mu\text{m}$, and $\geq 25 \mu\text{m}$) than US-licensed Enbrel (three batches) and EU-approved etanercept (three batches). Results are tabulated in Table 57 and displayed in Figures 126 – 130). Results from DLS testing showed that there were no sub-visible particles between 0.1 – 1.0 μm in any of the samples.

Extinction Coefficient: The extinction coefficients of SB4 (one batch), US-licensed Enbrel (one batch), and EU-approved etanercept (one batch) were experimentally determined by two methods (AUC-IF/UV-Vis and SEC/LS/UV/DRI). Results for AUC-IF/UV-VIS demonstrate that the average extinction coefficient for SB4, US-licensed Enbrel, and EU-approved etanercept are $1.068 (\text{mg/ml})^{-1}\text{cm}^{-1}$, $1.106 (\text{mg/ml})^{-1}\text{cm}^{-1}$, and $1.185 (\text{mg/ml})^{-1}\text{cm}^{-1}$, respectively. Results for SEC/LS/UV/DRI demonstrate that the average extinction coefficient for SB4, US-licensed Enbrel, and EU-approved etanercept are $0.932 (\text{mg/ml})^{-1}\text{cm}^{-1}$, $0.898 (\text{mg/ml})^{-1}\text{cm}^{-1}$, and $0.898 (\text{mg/ml})^{-1}\text{cm}^{-1}$, respectively (Tables 58 and 59). The average value of the two extinction coefficients by the two different methods was identical or similar among SB4 (1.00), US-licensed Enbrel (1.00), and EU-approved etanercept (1.04; Table 60).

Reviewer Comment: It was requested for Samsung to provide an explanation for why the experimentally determined extinction coefficient values are different than the extinction coefficient value from the innovator patent, which was used for routine QC testing and for the analytical similarity assessment (IR dated December 19, 2017). Additionally, it was asked for Samsung to clarify whether the experimentally determined extinction coefficient values were ever used to calculate protein concentration for any of the SB4, US-licensed Enbrel, and EU-approved etanercept batches. In the IR response (January 12, 2018, Seq. 0020), Samsung provided acceptable reasons for why the extinction coefficient values were different, citing inherent assay variability, formulation differences (i.e., buffer solution properties), and limitations of assays. Samsung also reiterated that these experimentally determined extinction coefficients were not used to determine protein concentration of any SB4, US-licensed Enbrel, and EU-approved etanercept batches.

5. Fc-related Activities

Fc receptor and C1q Binding Assays: SB4 (seven batches, including one clinical and three commercial batches), US-licensed Enbrel (three batches), and EU-approved etanercept (three batches) were analyzed in a variety of SPR assays that detect binding to FcγRIa, FcγRIIa, FcγRIIb, FcγRIIIa, FcγRIIIa (158V/V), FcRIIIa (158F/F), FcγRIIIb, FcRn, and C1q (Tables 61 – 67). Data from US-licensed Enbrel and EU-approved etanercept were used to create two-sided quality ranges for evaluation of data generated from SB4 (and EU-approved etanercept for evaluation with the US-licensed Enbrel quality ranges). Data representative of SB4 binding to FcγRIa, FcγRIIa, FcγRIIb, FcRn, and C1q were within the US-licensed Enbrel and EU-approved etanercept quality ranges, while data representative of SB4 binding to FcγRIIIa (158V/V), FcRIIIa (158F/F), and FcγRIIIb were lower than that of US-licensed Enbrel and EU-approved etanercept and generally outside the US-licensed Enbrel and EU-approved etanercept quality ranges.

Antibody-dependent cell-mediated cytotoxicity (ADCC) Assay: The ADCC assay was performed using a stable mouse cell line that overexpresses 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. Data were analyzed using PLA software, and the relative biological activity was calculated. In addition to analysis of SB4 (seven batches, including one clinical and three commercial batches), US-licensed Enbrel (three batches), and EU-approved etanercept (three batches), Remicade (batch 2RMKA82304), which is known to induce ADCC activity as part of its MoA, was used as a positive control. The results from these experiments (Table 69 and Figure 139) show that SB4, US-licensed Enbrel, and EU-approved etanercept induce only 0 – 5% of cell lysis in comparison to cell lysis induced by Remicade.

Reviewer Comment: Although the levels are low, it appears that ADCC activity of SB4 (2 – 5% relative cell lysis) is slightly higher than that of US-licensed Enbrel and EU-approved etanercept (0 – 2% relative cell lysis). While these results do not correlate with FcγR binding (see above, the slightly higher, albeit low, ADCC activity of SB4 correlates with the minor increase of %afucose N-linked glycan species in SB4 in comparison to corresponding levels in US-licensed and EU-approved etanercept (see above). However, these minor differences in ADCC activity

are likely not to have a clinical impact, e.g., ADCC activity is not a presumed MoA of US-licensed Enbrel in the indications SB4 is sought for.

Complement-dependent Cytotoxicity (CDC) Assay: The CDC activity of SB4 was analyzed by an enzyme reaction-based CDC assay, using a cell line over-expressing human transmembrane TNF- α on the cell surface (Jurkat-mTNF- α cell). Human serum was used as a complement source. Data were analyzed using PLA software and the relative biological activity was calculated. In addition to analysis of SB4 (seven batches, including one clinical and three commercial batches), US-licensed Enbrel (three batches), and EU-approved etanercept (three batches), Remicade (batch 2RMKA82304), which is known to induce CDC as part of its MoA, was used as a positive control. Because SB4, US-licensed Enbrel, and EU-approved etanercept are engineered not to express the CH1 domain of IgG-Fc, which contains the C3 binding region, it's expected that CDC activity of these products to be limited. Results from this study demonstrate that SB4, US-licensed Enbrel, and EU-approved etanercept induce about 21 - 36% of CDC activity, which is lower than that induced by Remicade (55%; Table 70 and Figure 140). Moreover, CDC activity among SB4 (21 – 31%), US-licensed Enbrel (29 – 36%), and EU-approved etanercept (21 – 33%) was similar.

6. Additional Biological Activities

TNF- α binding of different species: The ability of SB4 (two batches), US-licensed Enbrel (one batch), and EU-approved etanercept (one batch) to bind to TNF- α from different species (i.e., human, mouse, rat, and monkey) was evaluated. There were no noticeable differences in binding activity (94 – 107%) among SB4, US-licensed Enbrel, and EU-approved etanercept to human, monkey, mouse, and rat TNF- α . Similar trends were observed in different species such as monkeys, mice, and rats, which show that there were no differences across species.

Apoptosis assay: Caspases (i.e., caspases 3 and 7) are a family of proteases essential to the induction of apoptosis, which is a biological effect of transmembrane TNF- α signaling of TNFR2 in T cells (and macrophages). The ability of SB4 (seven batches, including one clinical and three commercial batchess), US-licensed Enbrel (three batches), and EU-approved etanercept (three batches) was evaluated for apoptosis activity by measuring caspase activity in Jurkat cells constitutively expressing membrane bound TNF- α . Data were analyzed using PLA software, and the relative biological activity was calculated with respect to the RRS. The measured signal is proportional to apoptosis activity. The %relative apoptosis values for SB4 (92 – 114%) were generally similar to the values for US-licensed Enbrel (97 – 102%) and EU-approved etanercept (101 – 106%; Table 72). In addition, quality ranges (mean $\pm$ 3SD) were established by analyzing three batches each of US-licensed Enbrel and EU-approved etanercept. Although several SB4 batches were outside the US-licensed Enbrel (92 – 107%) and EU-approved etanercept (95 – 112%) quality ranges, the narrow quality ranges for this method is likely because of a limited number of samples used to create the quality ranges.

Reviewer Comment: *It is unclear the role membrane TNF- α binding and activity plays in the indications approved for US-licensed Enbrel. The slight difference is not expected to translate into a clinical impact for the indications sought in this application.*

3.2.R.4.3 Comparative Stability Studies with SB4, US-licensed Enbrel, and EU-approved Etanercept

Comparative stability studies were conducted to investigate the degradation profiles of SB4, US-licensed Enbrel, and EU-approved etanercept when subject to different conditions. The results from these stability studies are discussed below.

Reviewer Comment: *SB4 Process A batches (i.e., pilot, clinical, and PVR campaigns) were used in the stability studies in comparison with US-licensed Enbrel and EU-approved etanercept. Because the different Process A campaigns and the Process B campaign were demonstrated to be analytically comparable (Sections 3.2.S.2.6, 3.2.S.7, and 3.2.P.2.3), it's acceptable that Process A material was used in the comparative stability studies in lieu of the commercial process material. In the original submission, insufficient information was present to determine similarity pertaining to the stability profile of the comparator groups. In response to the IR sent on December 19, 2017, Samsung provided representations of raw data from the initial and last test time-points for each tested sample (January 12, 2018, Seq. 0020). The degradation profiles of SB4, US-licensed Enbrel, and EU-approved etanercept under the tested conditions (discussed below) are similar. The minor differences observed do not preclude a demonstration of highly similar between SB4 and US-licensed Enbrel and the establishment of analytical bridges among SB4, US-licensed Enbrel, and EU-approved etanercept.*

Heat stress Condition: Three separate side-by-side comparative stability studies were performed with SB4, US-licensed Enbrel, and EU-approved etanercept (Table 73) under heat stress conditions ($40\pm 2^{\circ}\text{C}$, $75\pm 5\%$ RH) for up to three or six months. Appearance (color and clarity), pH, visible particles, sub-visible particles, protein concentration, TNF- α binding, TNF- α neutralization, oxidation, and purity/product-related variants by SEC, HIC, reducing CE-SDS, and icIEF were analyzed. Study 3 also included an evaluation of TSA content.

Study 1 (three months)

- Three batches of SB4 (SB4-14C20, SB4-14C26, SB4-14C28; Process A PVR DP)
- One batch of US-licensed Enbrel (1038236)
- One batch of EU-approved etanercept (H09420)

Study 2 (three months)

- One batch of SB4 (12L11; Process A clinical DP)
- One batch of EU-approved etanercept (G50590)

Study 3 (six months)

- One batch of SB4 (PDR-112-12-138; Process A pilot DP)
- One batch of EU-approved etanercept (E76197)

Study Results

Appearance, pH, protein concentration, sub-visible particles, and sialic acid content did not show significant changes in SB4, US-licensed Enbrel, and EU-approved etanercept. Significant changes were observed for %HMW by SEC, %main peak by reducing CE-SDS, HIC peaks, charge variants by icIEF, %relative binding activity by TNF- α binding assay, and %relative

potency by TNF- α neutralization assay. Refer to Figure 143 for analysis of trends for HMWs, purity by reducing CE-SDS, HIC peak 2, TNF- α binding activity, and TNF- α neutralization activity.

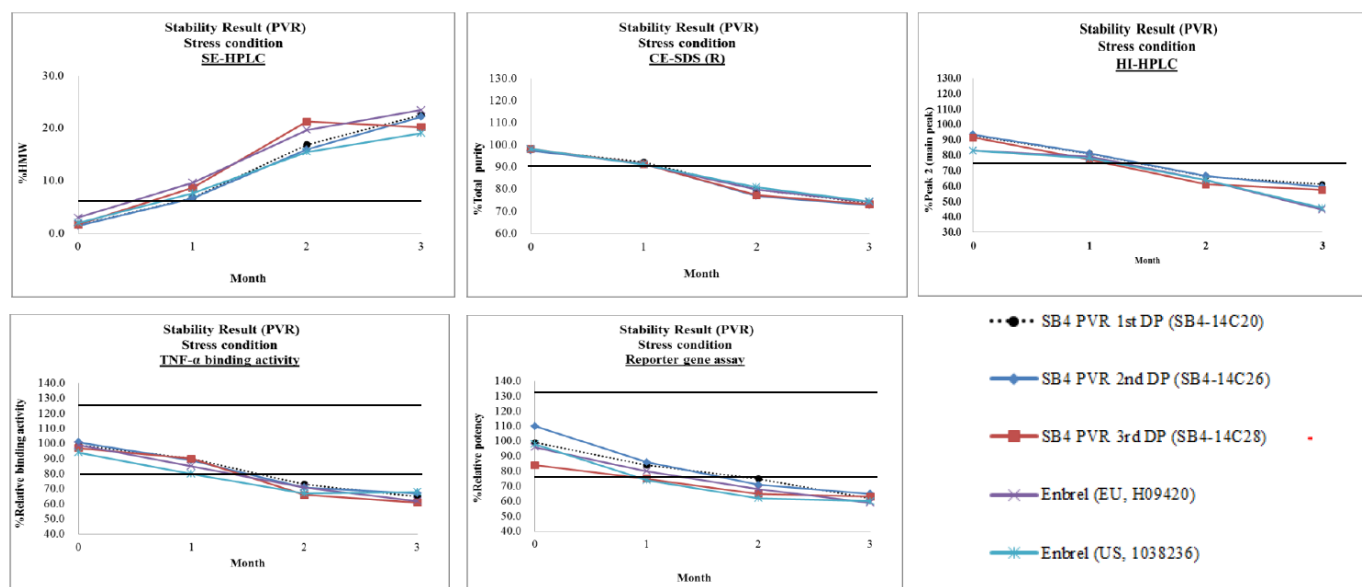


Figure 143: Comparative Stability Result Summary of SB4 PVR DP and Enbrel® under Stress Condition

*Horizontal line in each plot is stability acceptance criteria defined in stability protocol.

Although not shown in Figure 143, the rates of formation for hydrophobic and charge variants are shown below:

HIC Peak 1 (truncated species)

- SB4: 1.0% to 8.9%, 1.4% to 9.3%, and 0.9% to 8.2%
- US-licensed Enbrel: 1.2% to 9.6%
- EU-approved etanercept: 1.2% to 9.2%

HIC Peak 3 (aggregate and scrambled species)

- SB4: 6.3% to 27.4%, 5.1% to 28.5%, and 7.4% to 31.7%
- US-licensed Enbrel: 15.7% to 41.2%
- EU-approved etanercept: 15.7% to 42.7%

Acidic variants by icIEF

- SB4: 37.4% to 73.1%, 39.1% to 73.4%, 42.2% to 75.4%
- US-licensed Enbrel: 26.3% to 67.9%
- EU-approved etanercept: 28.1% to 71.9%

Main by icIEF

- SB4: 54.5% to 22.9%, 53.1% to 21.7%, 50.3% to 19.9%
- US-licensed Enbrel: 47.8% to 26.2%

- EU-approved etanercept: 51.8% to 26.2%

Basic variants by icIEF

- SB4: 8.2% to 3.9%, 7.8% to 4.9%, 7.5% to 4.7%
- US-licensed Enbrel: 25.9% to 5.8%
- EU-approved etanercept: 20.1% to 1.9%

Reviewer Comment: The HIC peak 3 formation rate in SB4 (18% to 23% increase) is slightly lower than that in US-licensed Enbrel and EU-approved etanercept (~37%); however, the levels of HIC peak 3 are significantly reduced in SB4 in comparison to those in US-licensed and EU-approved etanercept after heat stress. An inverse trend was observed for HIC peak 2 degradation, which is supported by the HIC peak 3 formation trend. The acidic content is higher in SB4 in comparison to that in US-licensed and EU-approved etanercept prior to heat stress, and the rate of formation is also higher in SB4 (50% increases vs. 39% increase). The basic variants decreased during stability at a higher rate for US-licensed/EU-approved etanercept (73%) in comparison for SB4 (53%). Despite the differences in charge variation formation rates during heat stress storage, the levels at the end of testing were similar across all comparative groups. The differences in hydrophobic and charge variant rates during stress storage may be because of differences in the initial amount of the variants in each sample prior to heat stress treatment.

Study 2 and Study 3

The trends observed in Study 1 were also observed in studies 2 and 3. Refer to Table 82 and Figure 144 for data from Study 2 and Tables 85 and 86 and Figure 145 for data from Study 3.

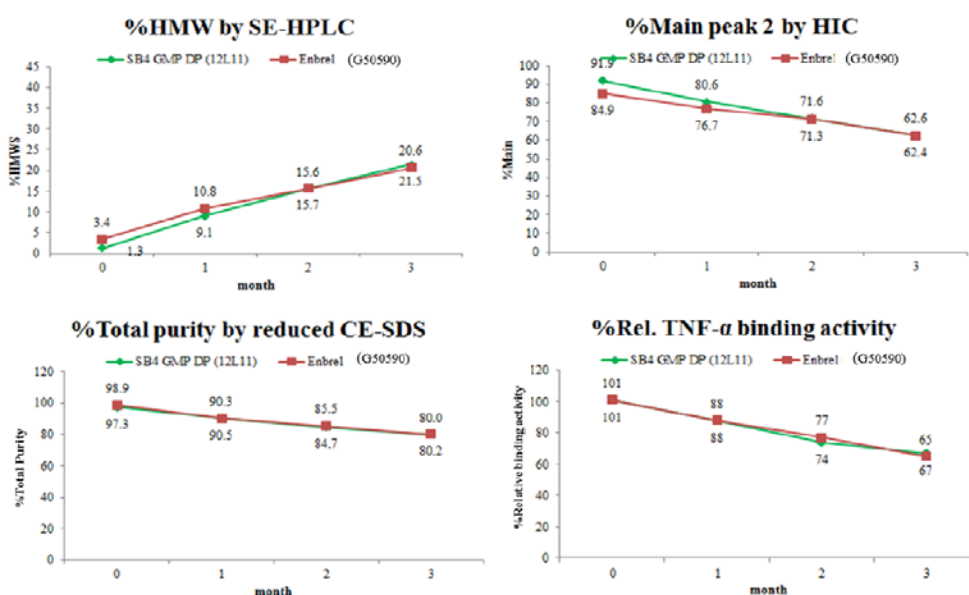


Figure 144: Comparative Stability Result Summary of SB4 Clinical DP and Enbrel® under Stress Condition

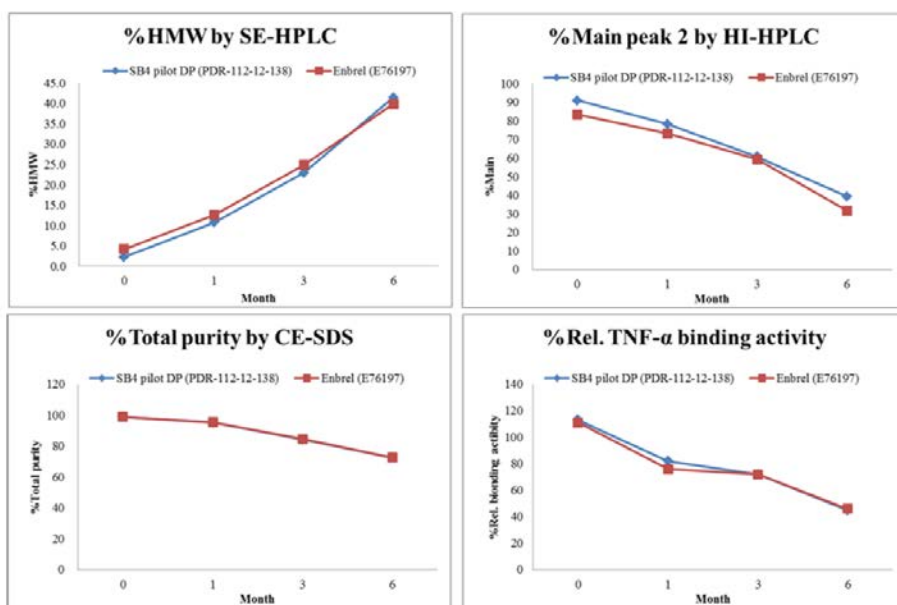


Figure 145: Similarity of Comparative Stability under Heat Stress Condition between SB4 Pilot DP and Enbrel®

Reviewer Comment: Although minor differences may exist with the formation rate of hydrophobic and charge variants, the pathways of degradation are similar among SB4, US-licensed Enbrel, and EU-approved etanercept under heat stress, and no differences in potency were observed between the comparative groups.

Accelerated Condition: The degradation profiles of SB4 (PDR-112-12-138 DP batch, Process A pilot batch campaign) and EU-approved etanercept batch E76197 were evaluated for six months at the accelerated storage condition (25±2°C, 60±5% RH). Appearance, pH, protein concentration, sialic acid, and potency did not significantly change (Tables 89 – 90). The %HMW tested by SEC showed an increase in both SB4 (2.2% to 6.6%) and EU-approved etanercept (4.2% to 6.0%). HIC peak 1 increased in SB4 (2.5% to 5.3%) and EU-approved etanercept (2.0% to 6.0%), while HIC peak 3 increased in SB4 (6.7% to 10.1%). The decrease of total purity by reducing CE-SDS for 6 months was similar between SB4 (98.9% to 95.4%) and EU-approved etanercept (98.8% to 96.4%). The rate of decrease of HIC Peak 2 (active form) in SB4 (90.9% to 84.7%) was higher to that of EU-approved etanercept (83.2% to 80.7%). Trends are shown below in Figure 143.

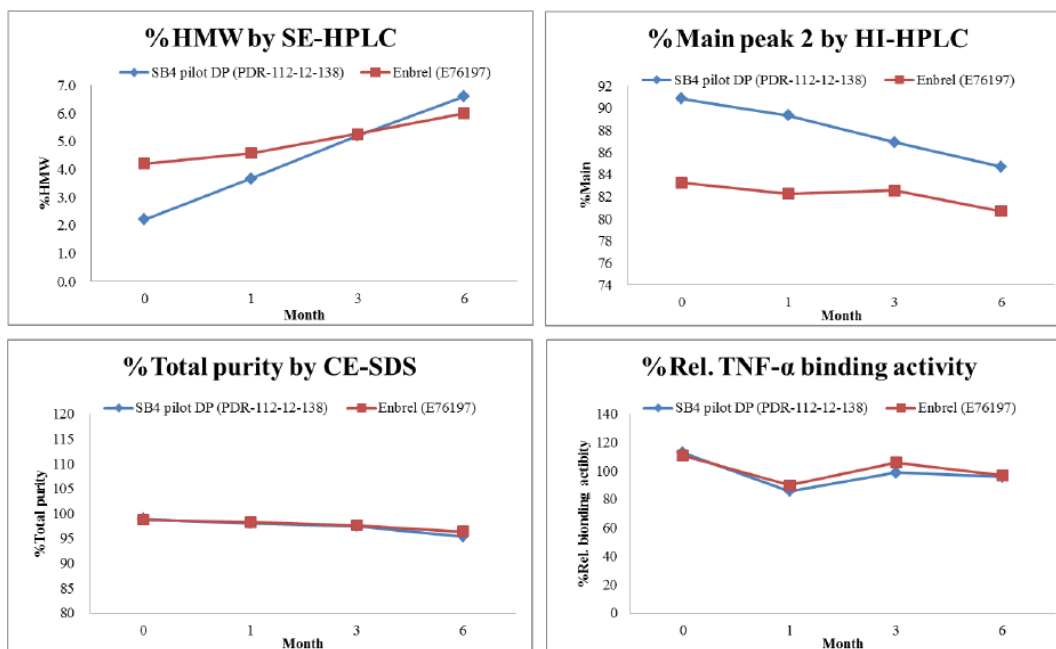


Figure 146: Stability Result Summary of SB4 pilot DP and Enbrel® for Accelerated Condition

Reviewer Comment: The formation of HIC peak 3 in EU-approved etanercept did not increase during accelerated storage conditions, which may be because the HIC peak 3 content in EU-approved etanercept at the time of testing was already high (14.8%). Likewise, the HIC peak 2 content was low at the time of testing, which resulted in a less impactful rate of degradation by HIC analysis. Despite these differences, the stability profile of SB4 and EU-approved etanercept appears similar under accelerated conditions. The use of only EU-approved etanercept is acceptable for this study given the similarity in the degradation profiles between all three products in Study 1 above.

Oxidation Condition: The degradation profiles of SB4 (PUR-C12-05, Process A Pilot DP batch), US-licensed Enbrel (1029314), and EU-approved etanercept (F45454) were evaluated up to three hours under the oxidative condition. Samples were treated with hydrogen peroxidase (final concentration of 0.01%) and stored at 4°C for 1.5 and 3.0 hours until analyzed by peptide mapping for quantification of oxidized methionine residues (Met₃₀, Met₁₇₄, Met₁₈₇, Met₂₂₃, Met₂₇₂, Met₃₇₈, Met₄₄₈). The results show that the oxidative treatment caused oxidation of Met₃₀, Met₁₇₄, Met₁₈₇, and Met₃₇₈ at 1.5 and 3 hours of treatment. The levels of oxidized methionine residues and the rate of oxidation of these residues were similar in all samples (Table 92).

Reviewer Comment: The oxidative stability data provided support that SB4, US-licensed Enbrel, and EU-approved etanercept have similar formation rates for oxidized methionine residues under oxidative conditions.

Freeze-thaw Stability Studies: The degradation profiles of SB4 and US- and EU-approved etanercept were evaluated after exposure to temperature cycling conditions. Samples were stored at -70°C for 24 hours and thawed at 5°C for three hours; this freeze-thaw cycle was repeated

three times. In all samples, test results demonstrate no significant changes to product quality attributes tested by SEC, HIC, CE-SDS, icIEF, and TNF- α binding assay (Table 95).

Reviewer Comment: *The stability profile of SB4, US-licensed Enbrel, and EU-approved etanercept was similar after three freeze-thaw cycles and does not demonstrate product degradation.*

Photostability Studies: Studies were performed to evaluate the effects of light exposure on SB4 (SB4-13-B01, Process A clinical DP batch) and EU-approved etanercept (H00386) in immediate (naked syringe) and commercial (carton) packaging. Control and test samples were evaluated for appearance (color, clarity, and visible particle), pH, quantity, purity and product-related impurities by SEC, HIC, reducing CE-SDS, and icIEF, oxidation, potency (TNF- α binding and TNF- α neutralization assays), and sub-visible particles.

Immediate Packaging

The degradation profiles of SB4 (SB4-13B01, clinical DP) and EU-approved etanercept packaged into the naked PFS were monitored after exposure to at least 1.2 million lux hours of cool white fluorescent lamp light at $25\pm 2^\circ\text{C}$, $60\pm 5\%$ RH. After light exposure, samples were placed in temporary storage at $5\pm 3^\circ\text{C}$ and protected from light. Controls include samples before placement in light chambers (baseline) and filled naked syringes that placed in the light chamber at the same orient as the samples, but were protected from light (dark). No significant changes were observed with the product quality attributes in the dark samples in comparison to baseline control (before placement in light chamber); however, TNF- α binding and TNF- α neutralization did show minor decreases (99% to 94% and 92% to 80%, respectively). Significant changes were detected in the SB4 and EU-approved etanercept test samples. For example, increases of HMWs by SEC (2.3% to 17.8% and 3.1% to 9.6%), %peak 3 by HIC (6.0% to 25.9% and 14.2% to 24.3%), acidic variants by icIEF (47.4% to 54.6% and 25.6% to 29.9%), oxidized Met₁₈₇ (2.5% to 7.9% and 0.7% to 2.7%) oxidized Met₂₇₂ (6.9% to 33.8% and 4.6% to 14.7%) and decreases of %peak 2 by HIC (91.3% to 71.0% and 84.5% to 74.5%) were observed in test samples (SB4 and EU-approved etanercept, respectively) in comparison to the respective dark controls. Minor decreases in %relative TNF- α binding activity (94% to 82% and 95% to 91%) and %relative TNF- α neutralization activity (80% to 71% and 110% to 89%) for SB4 and EU-approved etanercept, respectively, were minor and within method variability.

Commercial Packaging

The degradation profiles of SB4 (SB4-14C20, Process A PVR DP batch) and US-licensed Enbrel (J13793) in commercial packaging (carton) were monitored after exposure to at least 1.2 million lux hours of cool white fluorescent lamp light and at least 200 watt hours/square meter of near ultraviolet lamp light at $25\pm 2^\circ\text{C}$, $60\pm 5\%$ RH. After photo exposure, samples were placed in temporary storage at $5\pm 3^\circ\text{C}$ and protected from light. In comparison to dark control samples, which were not exposed to light but placed in the light chamber at the same orientation as test samples, test samples did not show any significant changes in product quality attributes.

Overall summary and conclusions of the analytical similarity assessment

Reviewer Comment: *The analytical similarity data support a conclusion that SB4 is highly similar to US-licensed Enbrel and the establishment of the analytical portion of the scientific*

bridges among SB4, US-licensed Enbrel, and EU-approved etanercept. The analytical similarity assessment showed differences in the content of product-related impurities, glycan species, and charge variants for SB4 in comparison with US-licensed Enbrel and EU-approved etanercept; however, TNF- α binding and TNF- α neutralization activities were similar. The observed differences included slightly lower levels of HMWs, HIC Peak 3 forms, intact N-terminal and C-terminal forms, charged N-linked glycans, O-glycan occupancy (but higher levels of disialylated O-linked glycans), and basic charge variants in SB4, while levels of HIC Peak 1 forms, afucosylated and galactosylated (but not α -galactose) N-linked glycans, and acidic variants are higher in SB4. These differences were determined to be not clinically relevant and do not preclude a determination of highly similar between SB4 and US-licensed Enbrel or the establishment of the analytical portion of the scientific bridges among SB4, US-licensed Enbrel, and EU-approved etanercept. Additional studies were performed and verified that these differences do not impact potency. Data from comparative stability studies demonstrate that the stability profiles of SB4, US-licensed Enbrel, and EU-approved etanercept are similar despite differences in initial levels of hydrophobic and charge variants.

5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

Samsung evaluated the immunogenicity of SB4 and EU-approved etanercept in healthy subjects (PK study, SB4-G11-NHV) and in patients with Rheumatoid Arthritis (confirmatory efficacy and safety study, SB4-G31-RA). The immunogenicity of SB4 and EU-approved etanercept was also compared to that of US-licensed Enbrel in study SB4-G11-NHV to provide further justification for the use of clinical data obtained from clinical studies using EU-approved etanercept as the comparator to SB4. A multi-tier approach was used to screen, confirm, and titer clinical samples for binding ADAs via a binding antibody assay, and clinical samples that confirmed positive for binding ADAs were analyzed by a neutralizing antibody assay to determine the presence of neutralizing ADAs. The binding and neutralizing antibody assays were developed and validated with reagents based on SB4 and EU-approved etanercept. Because the immunogenicity incidences reported in the BLA are derived from testing of clinical samples with assays that employ reagents based on SB4, the methods and validation studies for these assays are discussed below.

Reviewer Comment: The binding antibody assay was initially developed ((b) (4) Report 8276855) and validated ((b) (4) Report 8276856) for the purpose of testing the SB4-G11-NHV clinical study samples. Because the PK studies were not powered to allow for meaningful conclusions to be drawn about the comparative immunogenicity of SB4, EU-approved etanercept, and US-licensed Enbrel, the method validation studies for the binding antibody assay at this stage in clinical development are not discussed in this review. The binding antibody assay discussed below was developed ((b) (4) Report 8295686) and validated ((b) (4) Report 8295687) to test the clinical samples from study SB4-G31-RA ((b) (4) Reports 8276865 and 8309466), which was designed appropriately to allow for a determination of whether the immunogenicity incidences are similar between the products.

During the review cycle, Samsung was requested to re-analyze the clinical immunogenicity data obtained from study SB4-G31-RA using a cut-point for the binding antibody assay confirmatory analysis based on a more appropriate false positive rate (discussed below) and re-calculate the antibody titers factoring in the sample minimum required dilution (MRD). Given the clinical

binding ADA results (discussed below) and additional support from publicly available information regarding the incidence and nature of ADAs to US-licensed Enbrel, the review team determined that an evaluation of neutralizing ADAs was not necessary to inform for the immunogenicity assessment of SB4 and US-licensed Enbrel; therefore, the neutralizing antibody assay will not be discussed in this review.

Binding Antibody Assay Validation Report ((b) (4) Study Report 8295687)

The binding antibody assay is an electrochemiluminescence (ECL) bridging assay (IC 13-081-V3) that uses Meso Scale Discovery technology and was developed and validated for the detection, confirmation, and titration of binding ADAs directed against SB4 and EU-approved etanercept in human Rheumatoid Arthritis patient serum. Samples are initially evaluated in a screening assay. Samples that test positive in the screening assay are then subjected to a confirmatory assay to demonstrate that the ADA response detected is specific to the drug. Confirmed ADA positive samples are then titered.

Screening Assay

Samples undergo acid dissociation to release ADAs from ADA:drug complexes in the serum. Samples are then neutralized and incubated with a master mix of biotinylated and sulfo-tag labeled SB4 reagents (0.5 µg/ml) to allow ADAs specific to SB4 and EU-approved etanercept bind to the master mix components. The antibody-complex bridge is added to a pre-blocked streptavidin-coated MSD plate, which is washed after an incubation period. Read buffer containing tripropylamine is added, and the sulfo-tag reagent produces a chemiluminescent signal when electrical voltage is applied. The signal is directly proportional to the level of binding ADAs present in the sample.

Confirmatory Assay

The confirmatory assay is run in a competitive binding format and follows the same procedure as the screening assay with the exception that counterpart samples are incubated with an excess of SB4 (100 µg/ml) during the acid dissociation procedure. Percent signal inhibition (%INH) values are calculated from the ECL counts based on the following formula:

$$\text{Percent inhibition} = 100 * [1 - (\text{response with excess drug} / \text{response with no drug})]$$

Reviewer Comment: *Data from developmental studies (Table 21, (b) (4) Study Report 8295686) demonstrate that 100 µg/ml of SB4 is sufficient to inhibit over 99% of assay responses at various ADA levels (i.e., 250 ng/ml and 10,000 ng/ml).*

Titer Assay

The titration assay follows the same procedure as the screening assay with the exception that samples are serially diluted in matrix prior to running of the assay. Sample titer is determined as the reciprocal of the value of the highest serial dilution that yields a response at or above the cut-point.

Reviewer Comment: *Although the clinical study reports (i.e., 8276865 and 8309466) specify that the MRD will be factored into the determination of the clinical SB4-G13-RA sample antibody titers, the reported clinical sample antibody titers did not factor in the MRD. It was requested*

that Samsung determine antibody titer levels by multiplying the sample MRD (see below) by the reciprocal value of the highest serial dilution yielding a response greater at or above the assay cut-point (IR dated November 21, 2017). In response to the IR, Samsung provided the updated titer data (December 11, 2017, Seq. 0017), which are deferred to the clinical and clinical pharmacology teams for review.

Matrix: Pooled human Rheumatoid Arthritis serum was used to prepare the controls. Individual pre-dose patient samples from the SB4-G13-RA study were used for assay cut-point assessment. A MRD of 1:4 was used to dilute the test samples and controls.

Positive Control: An affinity-purified monkey anti-SB4 polyclonal antibody was used as the positive control for assay validation and system suitability testing during clinical sample analysis. Preparations of the positive control at a low concentration [299.54 ng/ml; low positive control (LPC)] and high concentration [10,000 ng/ml; high positive control (HPC)] were used throughout assay validation and for system suitability analysis. An additional positive control, an affinity-purified monkey anti-EU-approved etanercept polyclonal antibody, was used in the drug tolerance and titration experiments.

Negative Control: Pooled human Rheumatoid Arthritis serum was used as the negative control (NC).

Critical Reagents: Critical reagents include commercial and patient matrix samples, positive control antibodies, biotinylated and sulfo-tagged SB4 and EU-labeled reagents, unlabeled SB4, and unlabeled EU-approved etanercept. The biotinylated and sulfo-tagged EU-labeled reagents were used in additional drug tolerance and titration experiments. Appendix 5 of the validation report includes additional information concerning the source, storage, and expiration of each critical reagent.

System Suitability: The upper limit for the negative control must not exceed 77 ECL counts (mean of NC response + 3 x standard deviations). The LPC and HPC ranges must be within 74 and 180 ECL counts (mean of LPC response + 3 x standard deviations) and 1,780 and 10,154 ECL counts (mean of HPC response + 3 x standard deviations), respectively. The HPC response (3 out of 4 duplicate sets) must be greater than the LPC response, and the LPC response (3 out of 4 duplicate sets) must be greater than the assay-cut-point, which must be greater than the NC response for a given run (4 out of 6 duplicate sets). LPC and HPC samples and within sample replicates must have coefficient of variation (CV) values $\leq 25\%$. Additional system suitability requirements for the negative control are described in the method validation protocol (Annex).

Reviewer Comment: System suitability was met during assay validation and clinical immunogenicity sample runs, demonstrating that the assay is capable of producing meaningful data to support the validated state of the assay and the clinical immunogenicity data, respectively.

Screening Assay Cut-point: Data derived from 50 drug-naïve, pre-dose samples from study SB4-G31-RA were analyzed to determine the screening assay cut-point (Annex – Statistics Results Memo SB4 assay). To minimize sources of variability, test samples and controls were

run according to an experimental balanced design, whereby each sample and control were run by two analysts across two plates and two days (VB01 – VB08). Two outliers [i.e., values greater than $Q3 + 1.5 \times IQR$ or less than $Q1 - 1.5 \times IQR$ (where $Q1$ = lower quartile, $Q3$ = upper quartile, and IQR = interquartile range)] were identified and excluded from the data set. After outlier exclusion, Shapiro-Wilks analysis of the dataset demonstrated a departure from normality ($p < 0.05$). A log-transformation was applied to the original dataset and outliers were identified using the previously described method and excluded. After outlier exclusion, Shapiro-Wilks analysis of the dataset demonstrated a departure from normality ($p < 0.05$); therefore, the validation cut-point (59 ECL counts) was determined non-parametrically as the 95th percentile of the raw data set excluding outliers ($n = 185$, mean = 50.0054, standard deviation = 5.3816).

Assay means (ANOVA f-test) and variances (Levene's test) across runs were calculated to determine a suitable cut-point approach (i.e., floating or fixed). Because the assay means were statistically different ($p < 0.001$) and the assay variances were not statistically different ($p = 0.1276$) among runs, a floating cut-point approach was used. The screening cut-point was determined by the addition of the NC mean to the normalization factor, which was determined to be 10 [validation cut-point (59) – NC mean (48.9583)]. For analysis of clinical samples, the screening cut-point was determined as NC mean response + 10 for each plate. The screening cut-point was also used as the titer assay cut-point.

Reviewer Comment: *Sufficient data were provided to support the statistical approach used to determine the screening assay cut-point that was used to analyze the SB4-G31-RA clinical samples. Data were provided to show that sample mean values correlate with negative control mean values across plates ($R^2 = 0.8226$), suggesting that the negative control is appropriate for use as a normalization factor for determining the assay cut-point by the floating cut-point approach. Analysis of the screened positive clinical (SB4-G31-RA) samples that confirmed negative (b)(4) Study Reports 8295687 and 8309466) verified the adequacy of the actual false positive rate.*

Confirmatory Assay Cut-point: Data derived from 30 drug-naïve pre-dose samples, which were used to determine the screening cut-point, were analyzed to determine the confirmatory cut-point (Annex – Statistics Results Memo SB4 assay). To minimize sources of variability, test samples and controls were run according to an experimental balanced design, whereby each sample and control were run by two analysts across two plates and two days (VB01 – VB08). Two outliers [i.e., values greater than $Q3 + 1.5 \times IQR$ or less than $Q1 - 1.5 \times IQR$ (where $Q1$ = lower quartile, $Q3$ = upper quartile, and IQR = interquartile range)] were excluded from the data set. After outlier exclusion, Shapiro-Wilks analysis of the dataset demonstrated that the data are distributed normally ($p \geq 0.05$). Because of the normally distributed data, a parametric method (mean + $3.09 \times$ standard deviation) was used to determine the confirmatory cut-point based on a 0.1% false positive rate. The confirmatory cut-point was calculated as 35.1% signal inhibition ($n = 105$, mean = -3.75223, standard deviation = 12.5773). Clinical samples that show a percent signal inhibition equal or greater than 35.1% would be determined a positive for the presence of binding antibodies.

Reviewer Comment: *The confirmatory cut-point (i.e., 35.1% signal inhibition) was calculated based on a 0.1% false positive rate, which is inappropriate for analysis of the SB4-G31-RA*

clinical samples. A confirmatory cut-point based on a 0.1% false positive rate may underestimate the number of patient samples with low levels of binding ADAs. It was requested that Samsung (i) re-calculate the confirmatory cut-point based on a 1% false positive rate, (ii) re-analyze the SB4-G31-RA clinical samples with the revised cut-point, and (iii) clearly identify in relevant sections of the BLA (e.g., 2.7.2.4) any changes in ADA incidences that are a result of the re-analysis of the clinical samples (IR dated November 21, 2017). In the IR response (December 11, 2017, Seq. 0017; Annex 2, Section 2.5), Samsung re-calculated the confirmatory cut-point based on a 1% false positive rate (i.e., 25.5% signal inhibition) and provided the re-analyzed clinical data, which are deferred to the clinical and clinical pharmacology teams for review.

Sensitivity and LPC: The HPC was diluted by two-fold serial dilutions that expanded past the screening cut-point (10,000 – 2.44 ng/ml). Three independent diluted series were performed and run in duplicate (VB09 – VB12). A linear regression curve was used to back-calculate the positive control antibody concentration at the screening cut-point. The mean and SD of the interpolated antibody concentrations were used to establish the assay sensitivity with a 95% consistency (mean concentration at assay cut-point + $t_{0.05,df}$ x standard deviation). The assay sensitivity was determined as 281.97 ng/ml (Table 4). The concentration for the LPC was determined from data derived from the assay sensitivity experiments and calculated at a concentration to produce a 1% rejection rate (mean concentration at assay cut-point + $t_{0.01,df}$ x standard deviation). The concentration of the LPC was determined as 299.54 ng/ml (rounded up to 300 ng/ml; Table 4).

Reviewer Comment: *The sensitivity of the binding antibody assay was also determined when using EU-approved etanercept-labeled reagents and an anti-EU-approved etanercept positive control antibody. The SB4 and EU-approved etanercept assays showed comparable sensitivities against anti-SB4 (281.97 and 371.53 ng/ml, respectively) and anti-EU-approved etanercept (225.30 and 199.25 ng/ml, respectively; Table 9, Section 2.7.1) positive control antibodies and comparable titration curves against both positive control antibodies (Figure 1, Section 2.7.1). The results from these studies, and additional studies (drug tolerance section, see below), suggest that the binding antibody assay with SB4-labeled reagents can be used to detect ADAs against SB4 and EU-approved etanercept in a comparable manner.*

Precision: Intra-assay and inter-assay precision analyses were performed for the screening, confirmatory, and titer assays. Three sets of controls were analyzed on each plate by at least two analysts over at least two days.

Screening Assay

The intra-assay and inter-assay precision of the screening assay were assessed in analytical runs VB13-VB16, VB23, and VB25-26. Precision was assessed by calculating %CV values from the ECL counts, and the data from these experiments are reported in Table 7. The inter-assay precision of the LPC and HPC across the runs were 14.0% CV and 23.4% CV, respectively, which were within the target criteria of $\leq 25\%$ CV. The intra-assay precision of the LPC and HPC per plate was not greater than 7.9% CV and 6.4% CV, respectively, which were within the target criteria of $\leq 25\%$ CV. The inter-precision of the NC across the runs was 8.9% CV, and the intra-precision of the NC per plate was not greater than 17.2% CV.

Confirmatory Assay

The intra-assay and inter-assay precision of the confirmatory assay were assessed in the same analytical runs that ran the screening assay precision experiments and analytical run VB31. The plate controls were spiked with and without SB4. Precision was assessed by calculating %CV values from the % signal inhibition values, and the data from these experiments are reported in Table 8. The inter-assay precision of the LPC and HPC across the runs were 15.7% CV and 0.3% CV, respectively, which were within the target criteria of $\leq 25\%$ CV. The intra-assay precision of the LPC and HPC per plate was not greater than 10.1% CV and 0.2% CV, respectively, which were within the target criteria of $\leq 25\%$ CV.

Titer Assay

The precision of the titer assay was evaluated using data generated from 12 LPC dilution series from analytical runs VB09 to VB12 (sensitivity and LPC experiments). Titers from these runs were calculated, and the data from these experiments are shown in Table 4. The intra-assay precision of the ECL values for each diluted LPC point per plate was not greater than 17.4% CV, which was within the target criteria of $\leq 25\%$ CV. The inter-assay precision of the back calculated concentration at the cut-point across all runs was 7.7% CV, which was within the target criteria of $\leq 25\%$ CV.

Drug Interference: Analytical runs VB17, VB18, and VB19 evaluated the drug tolerance of the assay. The maximum amount of SB4 or EU-approved etanercept that would not interfere with the ability of the assay to detect ADAs at an appropriate level was evaluated by spiking increasing concentrations of SB4 or EU-approved etanercept (0, 0.5, 1, 1.5, 2.0, and 3.0 $\mu\text{g/ml}$) into matrix samples containing various concentrations of the anti-SB4 positive control antibody (300, 500, 2,000, and 10,000 ng/ml). The results demonstrate that the assay is capable of detecting a positive response at a relative sensitivity of 500 ng/ml ADAs (specific to SB4) in the presence of 2.00 $\mu\text{g/ml}$ of SB4 and 3.00 $\mu\text{g/ml}$ of EU-approved etanercept (Table 10).

Table 10: Anti-SB4 Antibody Drug Tolerance (SB4 Assay)

Analytical Run VB17-VB19							
Analytical Run	SB4 Concentration (µg/mL)	Screening Cut Point	Anti-SB4 Antibody Concentration (ng/mL)				
			0.00	300.00	500.00	2000.00	10000.00
			Observed Response (ECL)				
VB17	0.00 (Baseline)	57	49	132	198	1014	7920
	0.50		56	95	116	377	3801
VB18	1.00	60	55	67	73	208	2088
	1.50		48	64	68	140	1078
VB19	2.00	65	60	68	67	140	837
	3.00		52	61	62	104	435

Analytical Run	EU Enbrel® Concentration (µg/mL)	Screening Cut Point	Anti-SB4 Antibody Concentration (ng/mL)				
			0.00	300.00	500.00	2000.00	10000.00
			Observed Response (ECL)				
VB17	0.00 (Baseline)	57	50	126	203	908	7038
	0.50		53	78	126	390	3973
VB18	1.00	60	53	62	78	193	1679
	1.50		50	60	80	153	1030
VB19	2.00	65	62	63	75	136	821
	3.00		59	61	71	104	431

Reviewer Comment: Although the drug tolerance limits are reported differently for SB4 (2 µg/ml) and EU-approved etanercept (3 µg/ml), which may suggest a slight preferential detection of ADAs to EU-approved etanercept, analysis of the raw data (Table 10) suggests that differences in drug tolerance limits for SB4 and EU-approved etanercept at detecting 500 ng/ml of ADAs may be due to assay variability. For example, the sample with 3 µg/ml of SB4 and 500 ng/ml of ADAs only missed the cut-point by 3 ECL counts, which is within the difference in ECL counts between samples with 3 µg/ml of SB4 and EU-approved etanercept without ADAs present.

PK data from clinical study SB4-G31-RA show that drug levels at the time of immunogenicity testing are on average 2.4 – 2.9 µg/ml and 2.1 – 2.6 µg/ml for SB4 and EU-approved etanercept, respectively (Section 2.7.2). Because the onboard levels of drug coincide with the established drug tolerance of the assay, it was unclear whether the binding antibody assay can perform as intended in the presence of onboard drug and detect a wide range of ADA levels. It was requested that Samsung (i) clarify whether samples that had onboard levels of drug higher than the established drug tolerance of the assay were classified as ADA negative or were excluded from the calculation of the binding ADA incidences, and if applicable, (ii) remove from the calculation of binding ADA incidences those samples that had onboard levels of drug higher than the assay drug tolerance based on detection of ADAs at the level of 500 ng/ml (IR dated November 21, 2017).

In the response to the IR (December 11, 2017, Seq. 0017), Samsung clarified that patient samples with onboard levels of drug above the established drug tolerance of the assay were not excluded from the calculation of ADA incidences partly because only a small subset of patients from the SB4-G31-RA study was monitored for drug levels (PK subset). Samsung provided additional analysis of the PK subset data by removing patient samples that had onboard levels of drug higher than the drug tolerance of the assay, which resulted in removing 28 patient samples (out of 41) from the SB4 group and 10 patient samples (out of 38) from the EU-approved etanercept group. The PK subset samples (without any exclusion) were evaluated by an additional binding antibody assay, which was developed and validated (b) (4) Study Report 8326744, Section 5.3.1.4) specifically to analyze the PK subset samples. Review of the additional binding antibody assay suggests that the assay is suitable for its intended purpose to analyze the PK subset samples and that the assay has a higher drug tolerance limit of 10 µg/ml of drug that can detect a sufficiently low level of ADAs. Analysis of the PK subset with the supportive binding antibody assay did not detect any additional ADA positive SB4 patient samples (1/41), although one additional ADA positive EU-approved etanercept patient sample was identified (8/38; (b) (4) Study Report 8329258, Section 5.3.1.4). Although it's difficult to

compare ADA incidences determined from data generated from different binding antibody assays, these results suggest that drug interference in the original binding antibody assay is minimal, i.e., the lower drug tolerance limit of the original binding antibody assay did not significantly mask the detection of ADAs in the clinical patients that received SB4 or EU-approved etanercept and that the clinical ADA data generated from testing by the original binding antibody assay are meaningful.

Hook Effect: The ability of high concentrations of antibodies to interfere with the screening assay performance to produce false negatives (i.e., hook/prozone effect) was evaluated in analytical run VB26. An ultra-HPC was prepared at a concentration of 50,000 ng/ml and serially diluted 1:20 to produce concentrations of 10,000 to 19.53 ng/ml, which were run in duplicates. The results demonstrate that increasing concentrations of ADAs to the level of the HPC did not impact the ability of the assay to detect a positive response (Table 19). The ADA concentration and ECL counts showed good correlation via linear regression analysis ($r^2=0.989$). Developmental data were provided that demonstrated ADA levels up to 100,000 ng/ml did not impact assay performance (Table 26, (b) (4) Study Report 8295686).

Selectivity: Ten individual matrix samples were spiked with the LPC and assessed in the screening and confirmatory assays to evaluate the assay selectivity (analytical runs VB13 and VB14). All spiked samples screened positive, and 8 of the 10 screened positive samples were confirmed positive (Table 14). Eight of the 10 unspiked individual samples generated a negative result. The two individual (#1 and #2) unspiked samples that screened positive produced ECL counts (425 and 7,094) similar to the ECL counts (420 and 6,673) from their respective LPC-spiked counterparts. Because of the high ECL counts produced by individual #1 and #2, these samples could not confirm positive.

Table 14: Selectivity (SB4 Assay)

PC level (ng/mL)	Analytical Run	Matrix Identity	Screening-Cut Point	Confirmatory-Cut Point	Observed Response without Drug (ECL)*	Observed Response with Drug (ECL)	%Inhibition	Screening Result	Confirmatory Result
Blank (0.00)	VB13	Ind 1 (IM13/10010718/065 A08)	67	35.1	425	-	-	Positive	-
		Ind 2 (IM13/10010718/065 A09)			7094	-	-	Positive	-
		Ind 3 (IM13/10010718/070 A01)			62	-	-	Negative	-
		Ind 4 (IM13/10010718/070 A02)			57	-	-	Negative	-
		Ind 5 (IM13/10010718/070 A03)			63	-	-	Negative	-
	VB14	Ind 6 (IM13/10010718/070 A04)	73		67	-	-	Negative	-
		Ind 7 (IM13/10010718/070 A05)			65	-	-	Negative	-
		Ind 8 (IM14/10010718/014 A01)			58	-	-	Negative	-
		Ind 9 (IM14/10010718/014 A02)			66	-	-	Negative	-
		Ind 10 (IM14/10010718/014 A03)			71	-	-	Negative	-
LPC (300.00)	VB13	Ind 1 (IM13/10010718/065 A08)	67	35.1	420	347	17.4	Positive	Confirmed Negative
		Ind 2 (IM13/10010718/065 A09)			6673	6706	-0.5	Positive	Confirmed Negative
		Ind 3 (IM13/10010718/070 A01)			142	54	62.0	Positive	Confirmed Positive
		Ind 4 (IM13/10010718/070 A02)			147	63	57.1	Positive	Confirmed Positive
		Ind 5 (IM13/10010718/070 A03)			130	63	51.5	Positive	Confirmed Positive
	VB14	Ind 6 (IM13/10010718/070 A04)	73		136	64	52.9	Positive	Confirmed Positive
		Ind 7 (IM13/10010718/070 A05)			143	70	51.0	Positive	Confirmed Positive
		Ind 8 (IM14/10010718/014 A01)			148	84	43.2	Positive	Confirmed Positive
		Ind 9 (IM14/10010718/014 A02)			138	65	52.9	Positive	Confirmed Positive
		Ind 10 (IM14/10010718/014 A03)			140	63	55.0	Positive	Confirmed Positive

*= Observed response will be used for the screening and confirmatory assessment for selectivity.

Reviewer Comment: Additional studies were performed with the two samples that screened positive without ADAs present (Ind 1 and Ind 2) to determine if it's likely that these patient samples were exposed to EU-approved etanercept or US-licensed Enbrel. Results from these studies suggest that these patients were not exposed to EU-approved etanercept or US-licensed

Enbrel, but instead, the high response is likely due to non-specific binding from an interfering protein. It's unclear what the interfering protein could be. Although RA patients typically have high levels of Rheumatoid Factor (RF), it's unlikely that RF is contributing to the high response in these two samples because the acid dissociation would likely prevent or minimize RF interference in the assay. (b) (4) stated that screened positive samples that do not confirm positive during sample analysis should be treated with caution. Analysis of the SB4-G31-RA clinical immunogenicity data suggests that there were no selectivity issues related to non-specific binding from an interfering protein.

Lipemic and Hemolyzed Matrix: Lipemic and hemolyzed matrix assessments were performed (analytical run VB23) to evaluate the recovery of ADAs (LPC level) in the presence of triglycerides and lysed whole blood, respectively. One individual sample was spiked with triglycerides or lysed whole blood or left untreated; these samples were run in triplicates. The lipemic matrix sample spiked with the LPC was positive for all three triplicates, and the blank matrix generated a negative result (Table 16). However, 2 of the 3 hemolyzed matrix sample triplicates, in addition to the blank matrix triplicates, generated a negative result, indicating that 10% hemolysis interferes with the assay (Table 17). This experiment was repeated with the addition of 2% and 5% hemolysis treatments. All samples at 2%, 5%, and 10% hemolysis when spiked with the LPC produced positive results, although the ECL counts were decreased with increasing hemolysis (Table 18).

TNF- α Interference: Circulating levels of TNF- α in the serum of patients may impact assay performance by binding to the SB4-labeled reagents. The concentration of TNF- α that could impact ADA detection was evaluated in analytical run VB25. TNF- α at 500 pg/ml was spiked into NC, LPC, and HPC samples, which produced positive responses with the exception of the NC samples (Table 22).

Stability: The stability of the HPC and LPC was evaluated by comparing freshly prepared controls to controls subjected to up to 6 freeze thaw cycles at $\leq -50^{\circ}\text{C}$ (-80°C nominal) and 24 hours at room temperature (analytical run VB24).

Freeze-Thaw Stability

The ECL counts of the LPC (99 – 116) and HPC (3,662 – 3,699) samples after 6 freeze-thaw cycles were above the screening cut-point (71 ECL counts) and comparable to baseline LPC (101 – 105) and HPC (3,495 – 3,664) sample ECL counts. The % difference from baseline was calculated as 5.8% and 2.8% for the LPC and HPC samples, respectively. Responses showed acceptable precision (0.5 – 8.0% CV).

Bench Top Stability

The ECL counts of the LPC (109 – 113) and HPC (3,491 – 3,565) samples after 24 hours at room temperature were above the screening cut-point (71 ECL counts) and comparable to baseline LPC (101 – 105) and HPC (3,495 – 3,664) sample ECL counts. The % difference from baseline was calculated as 7.6% and 1.6% for the LPC and HPC samples, respectively. Responses showed acceptable precision (1.1 – 3.3% CV).

Reviewer Comment: The provided data suggest that clinical serum samples are likely stable with minimal deviation in assay responses for up to 6 freeze thaw cycles from -20°C and -80°C storage and 48 hours at room temperature for benchtop use, which cover the working conditions for running the assay. Additional stability data for long-term storage of the positive control were not provided for this assay; however, this is acceptable because antibodies are known to be stable when stored at -80°C for long periods of time, and the positive controls met system suitability during clinical sample analysis.

In conclusion, sufficient information and data are provided to support the suitability of the binding antibody assay to analyze the SB4-G31-RA confirmatory clinical serum samples.

Determination of anti-SB4 and anti-EU-approved etanercept antibodies from clinical study SB4-G31-RA ((b) (4) Study Reports 8276865 and 8309466)

SB4-G31-RA

A randomized, double-blind, parallel group, multi-center study was performed to evaluate the efficacy, safety, PK, and immunogenicity of SB4 compared to EU-approved etanercept in subjects with moderate to severe Rheumatoid Arthritis despite methotrexate therapy. Serum samples were collected for immunogenicity testing at baseline and weeks 2, 4, 8, 12, 16, 24, 52, 76, and 100 weeks. Time-points at 76 and 100 weeks, in addition to a repeat testing at 52 weeks, are part of the open label, extension period of the study (SB4-G31-RA-EXT). The re-calculated incidences of binding ADAs based on the 1% false positive confirmatory study are shown below (Tables 1 and 2, Annex of Section 2.5).

Table 1 Re-calculated Incidence of Anti-drug Antibodies to Etanercept (Safety Set) (Study SB4-G31-RA)

Time point	Parameter	Assessment	SB4			EU Enbrel®			Total		
			N=299			N=297			N=596		
			n'	n	(%)	n'	n	(%)	n'	n	(%)
Week 0	ADA	Positive	299	0	(0.0)	297	0	(0.0)	596	0	(0.0)
		Negative	299	299	(100.0)	297	297	(100.0)	596	596	(100.0)
Week 8 overall ^a	ADA	Positive	299	4	(1.3)	296	68	(23.0)	595	72	(12.1)
		Negative	299	295	(98.7)	296	228	(77.0)	595	523	(87.9)
Week 24 overall ^a	ADA	Positive	299	5	(1.7)	296	69	(23.3)	595	74	(12.4)
		Negative	299	294	(98.3)	296	227	(76.7)	595	521	(87.6)
Week 52 overall ^a	ADA	Positive	299	6	(2.0)	296	69	(23.3)	595	75	(12.6)
		Negative	299	293	(98.0)	296	227	(76.7)	595	520	(87.4)

^a Overall ADA was determined as positive if at least one ADA positive result was obtained up to the time point regardless of the ADA result at Week 0.

ADA: anti-drug antibody

n': number of patients with available ADA results against SB4 at each timepoint

Percentages were based on n'.

Table 2 Re-calculated Incidence of Anti-drug Antibodies to Etanercept (Extended Population) (Study SB4-G31-RA)

Time point	Parameter	Assessment	SB4/SB4			EU Enbrel®/SB4			Total		
			n'	n	(%)	n'	n	(%)	n'	n	(%)
Week 52 Overall ^a	ADA	Positive	126	3	(2.4)	119	31	(26.1)	245	34	(13.9)
		Negative	126	123	(97.6)	119	88	(73.9)	245	211	(86.1)
Week 100 Overall ^a	ADA	Positive	126	4	(3.2)	119	32	(26.9)	245	36	(14.7)
		Negative	126	122	(96.8)	119	87	(73.1)	245	209	(85.3)
Week 100 Overall ^b	ADA	Positive	126	2	(0.8)	117	1	(0.9)	243	3	(1.2)
		Negative	126	124	(98.4)	117	116	(99.1)	243	240	(98.8)

^a Overall ADA results at Week 52 and Week 100 were determined as “positive” if at least one ADA positive until the timepoint regardless the ADA result at Week 0, otherwise was determined as “negative” if no ADA positive until the timepoint regardless the ADA result at Week 0.

^b Overall ADA results at Week 100 were determined as “positive” if at least one ADA positive until the timepoint after Week 52, otherwise was determined as “negative” if no ADA positive until the timepoint after Week 52.

Reviewer Comment: Review of the clinical ADA data and assessment of similarity related to immunogenicity is deferred to the clinical and clinical pharmacology teams.



Rachel
Novak

Digitally signed by Rachel Novak

Date: 3/11/2018 09:16:07AM

GUID: 52e163f70002ba9e745b4e39384c76d7



Marjorie
Shapiro

Digitally signed by Marjorie Shapiro

Date: 3/12/2018 10:48:28AM

GUID: 508da6d700026360986b5a21cc1642e3

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment
WO Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

To: Administrative File, **STN 761066**
From: Maxwell Van Tassell, Ph.D., DMA Branch IV
Through: Reyes Candau-Chacon, Ph.D., Acting Quality Assessment Lead, DMA Branch IV
Subject: New 351(k) Biologics License Application (BLA)
US License: 2046
Applicant: Samsung Bioepis Co., Ltd.
Product: SB4 (Proposed biosimilar to etanercept)
Indication: Rheumatoid Arthritis (RA), Polyarticular Juvenile Idiopathic Arthritis, Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Plaque Psoriasis (PsO).
Dosage: Single-dose pre-filled syringe for SC injection; 25 mg, 50 mg
Facilities:  (b) (4)

Receipt Date: 05/25/2017

Action Date: 03/23/2018

Recommendation for Approvability: The drug substance part of this BLA was reviewed from a product quality microbiology perspective and is recommended for approval.

Review Addendum

In an information request issued on February 12, 2018, the agency requested that the applicant remove bioburden and endotoxin testing from the drug substance stability program because the drug substance is stored frozen.

In Section 1.11.1 *Response to the Quality Information Request Issued Feb 12*, dated 02-15-2018 (eCTD 0031), the applicant indicated in response to Question 1 that they would eliminate the bioburden and endotoxin testing from the post-approval stability program of the drug substance, but would continue to monitor these attributes for the ongoing 48 month stability study described in Section 3.2.S.7.1. Section 3.2.S.7.2 of the BLA was updated accordingly.

SATISFACTORY

Conclusion

- I. The drug substance section of this BLA, as amended, was reviewed from a product quality microbiology perspective and is recommended for approval.
- II. Information and data in this submission not related to microbial control of the drug substance should be reviewed by the appropriate division.
- III. A pre-license inspection was conducted at [REDACTED] (b) (4) [REDACTED] from [REDACTED] (b) (4) [REDACTED] by OPF/DIA (Michael Shanks) and OBP (Ralph Bernstein and Brian Janelins). A six-item Form FDA 483 was issued. Refer to Panorama for compliance status of the facilities.



Maxwell
Van Tassell

Digitally signed by Maxwell Van Tassell
Date: 3/06/2018 10:28:03AM
GUID: 588f9a18000bb6ac3ec7300751755758



Reyes
Candau-Chacon

Digitally signed by Reyes Candau-Chacon
Date: 3/06/2018 11:16:32AM
GUID: 508da7160002977f7ca389c8f849b707

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: Reyes Candau-Chacon, Ph.D.

BLA: 761066
Applicant: Samsung Bioepis Co, Ltd.
US License Number: 2046
Submission Reviewed: 351(k) BLA
Product: SB4 (Proposed biosimilar to etanercept)
Indication: Rheumatoid Arthritis (RA), Polyarticular Juvenile Idiopathic Arthritis, Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Plaque Psoriasis (PsO)
Dosage Form: Single dose pre-filled syringe for subcutaneous injection (25 mg and 50 mg)
Manufacturing Sites: Drug product: (b) (4)
(b) (4)
FDA Receipt Date: 05 March 2017
Action Date: 25 March 2018

Conclusion and Approvability Recommendation

The drug product portion of this BLA, as amended, was reviewed from a product quality microbiology and sterility assurance perspective and is not recommended for approval.

The following deficiencies should be communicated to the sponsor:

1. The sterilization validation data provided to support the (b) (4) sterilization of sterile product-contact items used to manufacture SB4 at (b) (4) is deficient, as it does not

include information for the minimum (b) (4). Provide (b) (4) sterilization validation information for the minimum (b) (4)

2. The BLA does not include (b) (4) as a critical process parameter for sterile filtration. Performing sterile filtration outside of the parameters validated by the microbial retention study may result in a non-sterile product. Include the sterile filtration (b) (4) as a critical process parameter and provide the respective acceptance criteria in section 3.2.P.3.4 of the BLA.

Additional Comments

1. The preliminary action limit of total number of rejected units for filling at (b) (4) is not acceptable. Lower the preliminary action limit of the total number of rejected units for filling at (b) (4) and update section 3.2.P.3.4 of the BLA accordingly.
2. The Agency's expectation for the container closure integrity testing acceptance criterion is 100% integral units during shipping validation. Revise the acceptance criterion for the shipping validation study to be (b) (4) samples be integral.

3. (b) (4)

Product Quality Microbiology Assessment: Drug Product

Drug Product Quality Microbiology Information Reviewed

Sequence number	Date	Description
0031	02/15/2018	Response to Information Request
0032	02/21/2018	Response to Information Request

Module 3.2

P.3 Manufacture

P.3.3 Description of the Manufacturing Process and Process Controls

(b) (4) **50 mg**

Description of PFS Manufacturing Process

Step (b) (4) Sterile Filtration

2 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this
pagee

Conclusion

I. The BLA, as amended, is not recommended for approval from a sterility assurance and

product quality perspective.

II. Product quality aspects other than microbiology should be reviewed by OBP or CDRH.

III. Inspection follow-up items were not identified.

Quality Microbiology Information Requests Sent

IR Submitted: February 12, 2018

1. Section 3.2.P.3.5 – (b) (4) indicates that the operational qualification container closure integrity test (CCIT) acceptance criterion is (b) (4) samples should be integral. Provide a justification for the CCIT acceptance criterion used for shipping qualification.
2. The SB4 PFS Assembly Validation Report (refer to Section 3.2.P.3.5 – (b) (4) indicates that the CCIT acceptance criterion is (b) (4) samples must be integral. Provide a justification for the CCIT acceptance criterion used for PFS assembly validation.

IR Submitted: February 15, 2018

1. Provide the following information regarding the placement of (b) (4) validation at each manufacturing site:
 - a. Clarify whether (b) (4) were placed in the filling needles for the (b) (4)
 - b. Clarify whether (b) (4) were placed in the filling needles for the (b) (4)

Provide a justification if the validation was performed without (b) (4) in the filling needles at either manufacturing site.



Reyes
Candau-Chacon

Digitally signed by Reyes Candau-Chacon
Date: 2/22/2018 03:39:30PM
GUID: 508da7160002977f7ca389c8f849b707



Jessica
Hankins

Digitally signed by Jessica Hankins
Date: 2/22/2018 03:46:13PM
GUID: 57640ae700ea29dfdaa5ef6b52b35c55

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: Reyes Candau-Chacon, Ph.D.

BLA: 761066
Applicant: Samsung Bioepis Co, Ltd.
US License Number: 2046
Submission Reviewed: 351(k) BLA
Product: SB4 (Proposed biosimilar to etanercept)
Indication: Rheumatoid Arthritis (RA), Polyarticular Juvenile Idiopathic Arthritis, Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Plaque Psoriasis (PsO)
Dosage Form: Single dose pre-filled syringe for subcutaneous injection (25 mg and 50 mg)
Manufacturing Sites: Drug product: (b) (4)
(b) (4)
FDA Receipt Date: 05 March 2017
Action Date: 25 March 2018

Conclusion and Approvability Recommendation

The drug product portion of this BLA, as amended, was reviewed from a product quality microbiology and sterility assurance perspective and it is recommended for approval pending the verification of (b) (4) during sterile filtration at (b) (4) and (b) (4) addition of the (b) (4) sterilization minimum (b) (4) to the (b) (4) requalification program at (b) (4) Justification of the acceptance criterion for CCIT for the shipping qualification and PFS assembly process, and the action limit for the number of rejected units during filling at (b) (4)

Product Quality Microbiology Assessment: Drug Product

Drug Product Quality Microbiology Information Reviewed

Sequence number	Date	Description
0000	05/25/2017	Original BLA
0003	06/30/2017	Response to Information Request
0014	11/13/2017	Response to Information Request
0015	11/21/2017	Response to Information Request
0022	01/17/2018	Response to Information Request
0027	02/06/2018	Response to Information Request

Reviewer comment: The following information will be reviewed in a review addendum. Outstanding review issues are listed below.

1. Verification of (b) (4) during sterile filtration at (b) (4) and (b) (4)
2. Addition of the (b) (4) sterilization minimum (b) (4) to the (b) (4) requalification program at (b) (4)
3. Action limit for the number of rejected units during filling at (b) (4)
4. Justification of the acceptance criterion for CCIT for the shipping qualification and PFS assembly process.

Module 3.2

P.1 Description and Composition of the Drug Product

The drug product (DP) has the same composition as the drug substance (DS). The DP manufacturing process involves (b) (4) filling of a clear glass (b) (4) PFS with a stainless steel needle, rubber needle shield and rubber plunger. For the 25 mg product, the PFS nominally contains (b) (4) mL and for the 50 mg product, the PFS contains (b) (4) mL of the DP solution.

The composition for the 25 mg DP solution for injection is shown below.

Table 1: Composition of SB4 Solution for Injection

Component	Nominal Quantity/Unit	Function	Quality Standard
Etanercept	25 mg	Active substance	In-house
Sucrose	5.0 mg	(b) (4)	Ph.Eur./NF
Sodium chloride	4.09 mg		Ph.Eur./USP/JP
Sodium phosphate monobasic monohydrate	0.519 mg		USP
Sodium phosphate dibasic heptahydrate	0.333 mg		USP
Water for injection	q.s.		Ph.Eur./USP

The composition for the 50 mg DP solution for injection is shown below.

Table 1: Composition of SB4 Solution for Injection

Component	Nominal Quantity/mL	Function	Quality Standard
Etanercept	50 mg	Active substance	In-house
Sucrose	10.0 mg	(b) (4)	Ph.Eur./NF
Sodium chloride	8.18 mg		Ph.Eur./USP/JP
Sodium phosphate monobasic monohydrate	1.038 mg		USP
Sodium phosphate dibasic heptahydrate	0.665 mg		USP
Water for injection	q.s.		Ph.Eur./USP

Reviewer comment: There are two 3.2.P.1 sections listed in the eCTD. The information from each 3.2.P.1 section was combined in the review memo.

DESCRIPTION IS SATISFACTORY

P.2 Pharmaceutical Development

Microbiological Attributes

The 50 and 25 mg drug product solutions are manufactured as sterile, single-dose products, without preservatives. Sterility and endotoxin are performed on release and are monitored during the stability program.

Reviewer comment: The applicant provided the CCIT method development in section P.8.3 since CCIT is used only for stability testing (sequence 0014). The new method validation report for CCIT was provided in sequence 0014 (refer to section 3.2.R.3, Attachment 36-1 and 36-2).

SATISFACTORY

P.3 Manufacture

P.3.1 Manufacturers

The table below, provided in section P.3.1, describes the sites involved in DP manufacturing, testing, and labeling.

Table 1 Manufacturing Sites involved in the Manufacture of SB4 Pre-filled Syringe

Name and Address of Manufacturing Site	Activity / Responsibility
(b) (4)	Manufacture of pre-filled syringe
	QC release testing (sterility test)
	In-process test (IPT) testing (all tests)
	Manufacture of pre-filled syringe
	QC release testing (sterility test)
	In-process test (IPT) testing (all tests)
	Secondary packaging
	QC release testing (all tests excluding endotoxin and sterility)
	Stability testing (all tests excluding endotoxin and sterility)
	Stability testing (TNF- α neutralisation assay by NF- κ B reporter gene)
(b) (4)	QC release testing (alternative site, used as back-up)
	QC release testing (endotoxin)
	Stability testing (endotoxin, sterility test)

Reviewer comment: The applicant provided an updated Table 1 in sequence 0014 to specify that the (b) (4) facility is an alternative site all endotoxin release testing (and other release tests). Sterility testing is only performed at (b) (4) and (b) (4)

SATISFACTORY

P.3.2 Batch Formula

(b) (4)



Reyes
Candau-Chacon

Digitally signed by Reyes Candau-Chacon
Date: 2/12/2018 04:17:32PM
GUID: 508da7160002977f7ca389c8f849b707



Jessica
Hankins

Digitally signed by Jessica Hankins
Date: 2/13/2018 03:52:19PM
GUID: 57640ae700ea29dfdaa5ef6b52b35c55

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment
WO Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

To: Administrative File, **STN 761066**
From: Maxwell Van Tassell, Ph.D., DMA Branch IV
Through: Reyes Candau-Chacon, Ph.D., Acting Quality Assessment Lead, DMA Branch IV
Subject: New 351(k) Biologics License Application (BLA)
US License: 2046
Applicant: Samsung Bioepis Co., Ltd.
Product: SB4 (Proposed biosimilar to etanercept)
Indication: Rheumatoid Arthritis (RA), Polyarticular Juvenile Idiopathic Arthritis, Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Plaque Psoriasis (PsO).
Dosage: Single-dose pre-filled syringe for SC injection; 25 mg, 50 mg
Facilities:  (b) (4)

Receipt Date: 05/25/2017

Action Date: 03/23/2018

Recommendation for Approvability: STN 761066 was reviewed from a product quality microbiology perspective and is recommended for approval. Response to an information request regarding drug substance stability testing will be submitted to the BLA in February 2018 and reviewed in an addendum to this review memo.

Review Summary

Samsung Bioepis Co. Ltd. submitted 351(k) BLA 761066 in eCTD on May 25, 2017 to obtain approval of SB4, a proposed biosimilar to the US-licensed reference product Enbrel®. SB4 is a recombinant chimeric monoclonal antibody that inhibits TNF- α binding for treating autoimmune disease.

This review contains the assessment of the microbial quality attributes of the SB4 drug substance (DS) from a microbiological quality perspective. For review of drug product aspects of the application, please see review by Jessica Hankins, Ph.D.

Drug Substance Quality Microbiology Information Reviewed

Sequence number	Date	Description
eCTD 0001	05/25/2017	Original 351(k) BLA submission
eCTD 0018	12/15/2017	Response to Information Request
eCTD 0023	01/19/2018	Response to Information Request
eCTD 0027	02/06/2018	Response to Information Request

Review Assessment
3.2.S DRUG SUBSTANCE
3.2.S.1 GENERAL INFORMATION

SB4 is a chimeric protein that includes the ligand-binding domain of human tumor necrosis factor receptor fused to the Fc domain of human IgG1. Biological activity is derived from its competitive inhibition of TNF- α binding to cell surfaces. SB4 is a homodimeric glycoprotein (467 amino acids each monomer) with a molecular weight of approximately 130 kDa. There are twenty-nine Cys residues, predominantly in the TNF- α receptor domain, that facilitate inter- and intra-chain disulfide bridging and 16 potential glycosylation sites in each chain.

Reviewer Comment

SB4 is expressed in the Chinese Hamster Ovary (CHO) (b) (4) cell line, as described in Section 3.2.S.2.3.3 of the submission.

SATISFACTORY

3.2.S.2 MANUFACTURE
3.2.S.2.1 Manufacturer(s)

The following facilities are used for the manufacture and testing of the SB4 drug substance (DS):

Table 1: SB4 Drug Substance Manufacturing Sites

Name and Address of Manufacturing Site	Responsibilities
(b) (4)	Manufacturing of the MCB and WCB Storage of the MCB and WCB
	Storage of the MCB and WCB
	Storage of the MCB and WCB ^a
	Storage of the MCB and WCB ^a

Samsung Bioepis Co., Ltd. 107, Cheomdan-daero, Yeonsu-gu, Incheon, Republic of Korea	In-process test (IPT) testing (b) (4)
	(b) (4) IPT testing (b) (4)
	Manufacturing and packaging Batch release QC release testing (protein concentration, appearance, endotoxin, microbial enumeration) Back-up site for QC release testing (all tests) Stability testing (all tests) In-process Control (IPC) testing (all tests) In-process Test (IPT) testing (all tests excluding (b) (4)
	QC release testing (all tests excluding protein concentration, appearance, endotoxin, microbial enumeration) Stability testing (all tests excluding endotoxin and microbial enumeration)
	Stability testing (TNF- α neutralisation assay by NF- κ B reporter gene)
	Stability testing (endotoxin, microbial enumeration)
	Storage of drug substance

^a MCB and WCB were transferred from (b) (4)

3.2.S.2.2 Description of Manufacturing Process and Process Controls

The overall process for DS manufacturing is summarized in Figure 1 of Section 3.2.S.2.2, reproduced below from the submission:

26 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

SATISFACTORY

3.2.S.6 CONTAINER CLOSURE SYSTEM

The SB4 BDS container closure system is a (b) (4)

(b) (4)

Reviewer Note:

The extractables and leachables study should be reviewed by OBP.

SATISFACTORY

3.2.S.7 STABILITY

3.2.S.7.1 Stability Summary and Conclusions

The proposed shelf life for SB4 DS is (b) (4). Stability studies are ongoing for three process validation batches made using the commercial manufacturing process (Process B). Stability studies are planned for up to 48 months involving long-term, intermediate, and accelerated conditions of $-70\pm 10^{\circ}\text{C}$, $-20\pm 5^{\circ}\text{C}$, and $5\pm 3^{\circ}\text{C}$, respectively. At the $-70\pm 10^{\circ}\text{C}$ and $-20\pm 5^{\circ}\text{C}$ conditions, stability samples are tested for endotoxin and bioburden at time points for months 0, 12, 24, 36, and 48. Endotoxin and bioburden are not assayed for samples held under accelerated conditions. Samples are held in (b) (4) composed of the same material as is used for the commercial product. 12 months of data are available for long-term and intermediate conditions with no observed changes in product quality attributes. One additional lot of the DS will be added to the post-approval stability program annually if SB4 DS is manufactured.

Reviewer's Comments:

Endotoxin and bioburden testing are not required for stability testing of drug substance. The stability program and data provided should be further assessed by OBP.

Information Request submitted 2/12/2018, Item #1

Please eliminate bioburden and endotoxin testing from the drug substance stability program

(b) (4) Update the BLA accordingly.

Environmental Assessment

cGMP Status

Refer to Panorama for cGMP status of the relevant facilities.

Conclusion

- I. The drug substance section of this BLA, as amended, was reviewed from a product quality microbiology perspective and is recommended for approval. Additional information

regarding drug substance stability testing will be reviewed in an addendum to this review memo.

- II. Information and data in this submission not related to microbial control of the drug substance should be reviewed by the appropriate division.
- III. A pre-license inspection was conducted at (b) (4) by OPF/DIA (Michael Shanks) and OBP (Ralph Bernstein and Brian Janelins). A six-item Form FDA 483 was issued. Refer to Panorama for compliance status of the facilities.



Maxwell
Van Tassell

Digitally signed by Maxwell Van Tassell
Date: 2/12/2018 02:48:18PM
GUID: 588f9a18000bb6ac3ec7300751755758



Reyes
Candau-Chacon

Digitally signed by Reyes Candau-Chacon
Date: 2/12/2018 03:15:32PM
GUID: 508da7160002977f7ca389c8f849b707



Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg. 51, 10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: 2/5/2018
To: Administrative File, STN 761066
From: Michael Shanks, Biologist, CDER/OPQ/OPF/DIA
Endorsement: Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA
Subject: Biologic License Application for SB4 (etanercept-xxxx) that is a biosimilar* to Enbrel (etanercept)
US License: | 2046
Applicant: Samsung Bioepis Co., Ltd
Mfg Facility: Drug Substance:

(b) (4)

Drug Product:

(b) (4)

Proposed Trade Name: To be determined
Nonproprietary Name: To be determined. Referred to as "Enbrel (etanercept)" by the applicant*)
Dosage: SB4 is presented in single-dose pre-filled syringes of 25 mg/ (b) (4) and 50 mg/ (b) (4) to be administered via subcutaneous (SC) injection.
Indication: SB4 (etanercept-xxxx) is indicated for the treatment of Rheumatoid Arthritis(RA), Polyarticular Juvenile Idiopathic Arthritis, Psoriatic Arthritis(PsA), Ankylosing Spondylitis(AS), Plaque Psoriasis(PsO)..
Due Date: 03/23/2018

RECOMMENDATION: This application is recommended as APPROVE from a facility review perspective.

SUMMARY

The subject BLA proposes the manufacture of SB4 (etanercept-xxxx), that is a biosimilar to Enbrel (etanercept). Samsung Bioepis Co., Ltd's SB4 Drug Substance (DS) and Drug Product (DP) is a homodimer of a chimeric protein genetically engineered by fusing the extracellular ligand binding domain of human TNFR2/p75 to the Fc domain of human IgG1. SB4 DS is produced by Chinese hamster ovary (CHO) cell expression system as a dimeric, secreted, soluble protein. The starting material, is a CHO cell culture harvest using a (b) (4)

ASSESSMENT

DRUG SUBSTANCE FACILITIES

3.2.S Drug Substance [Substance – Manufacturer]

3.2.S.2. Manufacture

3.2.S.2.1 DS Manufacturers.

The sites proposed for SB4 Drug Substance manufacture and testing is presented below in Table 1.

Table 1. Proposed Sites for SB4 DS Manufacture, Cell Banking and Testing Operations

Site Name	Address	FEI Number	Responsibilities
		(b) (4)	Drug Substance manufacturing, packaging, and testing.
			Manufacturing and storage of the MCB and WCB.
			Storage of the MCB and WCB.
			Storage of the MCB and WCB.
			Storage of the MCB and WCB.
			Drug Substance In-process testing .
			Drug Substance In-process testing .
			Drug Substance release and stability testing.
			Drug Substance stability testing.
			Drug Substance stability testing.
			Drug Substance storage.

Reviewer Comment 1: The facilities for manufacture of SB4 DS are adequately described.

—Satisfactory—

• Prior Inspection History for DS Manufacturing and Testing Sites

--



Michael
Shanks

Digitally signed by Michael Shanks

Date: 2/05/2018 06:52:39PM

GUID: 530ccee5000e6dd4f24ae71fb1d5aaa5



Zhihao Peter
Qiu

Digitally signed by Zhihao Peter Qiu

Date: 2/06/2018 07:14:21AM

GUID: 508da7480002bfb5825e149b2b4eb91d