

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761100Orig1s000

PRODUCT QUALITY REVIEW(S)

BLA STN 761100
Non-proprietary name: Trastuzumab-dttb
Sponsor: Samsung Bioepis

Drug Product Review

Wen Jin Wu, M.D., Ph.D. (Primary Reviewer)
Wendy C. Weinberg, Ph.D. (Secondary Reviewer)

Division of Biotechnology Review and Research I
Office of Biotechnology Products

OBP CMC Review Data Sheet

1. BLA#: 761100
2. Review Date: December 21, 2018
3. Primary Review Team:
 - a. Medical Officer: Tatiana Prowell/ Jennifer Gao (Acting CDTL)
 - b. Pharm/Tox: George Chang/Tiffany Ricks
 - c. Product Quality:
 - OBP ATL: Qing (Joanna) Zhou
 - Drug Substance & Analytical Similarity: Kristen Nickens
 - Drug Product: Wen Jin Wu/Wendy Weinberg
 - Immunogenicity: Milos Dokmanovic/Brian Janelsins
 - DMA/Microbiology Drug Substance: Maria Lopez-Barragan; Drug Product: Lindsey Brown/ Patricia Hughes (QAL)
 - CMC Statistics: Yu-Ting Weng/Meiyu Shen
 - d. Facilities: Wayne Seifert/Peter Qiu
 - e. Clinical Pharmacology: Islam Younis/Lanre Okusanya
 - f. Statistics: Laura Fernandes/Shenghui Tang
 - g. OBP Labeling: Vicky Borders-Hamphill
 - h. OPRO RBPM: Oumou Barry
 - i. Janis Kim/Alice Kacuba
4. Major GRMP Deadlines:
 - a. Filing Meeting: November 16, 2017
 - b. Mid-cycle meeting: March 15, 2018
 - c. Late cycle meeting: July 26, 2018
 - d. Primary review due: December 17, 2018
 - e. Secondary review due: December 21, 2018
 - f. BSUFA action date: January 18, 2018

5. Communications with Sponsor and OND:

Communications with Sponsor (OBP)

Communication/Document	Date
Information Request 1	December 4, 2017
Filing Memo	December 20, 2017
Filing Letter	January 3, 2018
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Information Request 11	December 4, 2018
Information Request 12	December 7, 2018
Teleconference	December 12, 2018
Information Request 13	December 14, 2018
Information Request 14	December 18, 2018
Information Request 15	December 19, 2018
Information Request 16	December 20, 2018

6. Submissions Reviewed for drug product information:

Submission:	Date Received:	Review Completed (yes or no)
761100/0001	October 20, 2017	Yes
761100/0002	November 16, 2018	Yes
761100/0009	February 09, 2018	Yes
761100/0015	June 07, 2018	Yes
761100/0018	June 29, 2018	Yes
761100/0020	July 18, 2018	Yes
761100/0023 (response to IR#1)	July 30, 2018	Yes
761100/0034	November 08, 2018	Yes
761100/0036	November 23, 2018	Yes
761100/0039	December 39, 2018	Yes
761100/0042 (responses to IR#11)	December 11, 2018	Yes
761100/0044 (responses to IR#12)	December 13, 2018	Yes
761100/0047 (response to IR#15)	December 20, 2018	Yes
761100/pending official submission (response to IR#16)	December 21, 2018	Yes

7. Drug Product Name/Code/Type:

- a. Proprietary Name: Ontruzant
- b. Trade Name: Ontruzant
- c. Non-Proprietary Name/USAN: trastuzumab-dttb
- d. CAS Name: 180288-69-1
- e. Common Name: SB3
- f. INN Name: trastuzumab-dttb
- g. Compendial Name: N/A
- h. OBP systematic name: MAB HUMANIZED (IGG1k) ANTI P04626 (HER2_HUMAN) [SB3]
- i. Other names: SAIT103, BIIB604, ED004

8. Pharmacological Category: HER2/neu receptor antagonist

9. Dosage Form: For injection

10. Strength/Potency:

- (i): The concentration/strength of the Drug Product: 150 mg per vial
- (ii): Type of potency assay(s): competitive inhibition binding assay to HER2 by fluorescence resonance energy transfer (FRET), cell-based antiproliferation assay, competitive inhibition binding assay to FcγRIIIa

11. Route of Administration: Intravenous

12. Referenced Drug Master Files (DMF):

DMF #	DMF Type	DMF Holder	Item referenced	Comments
(b) (4)	III	(b) (4)	Glass vial	No review necessary at this time as the relevant information related to compatibility with the product was provided in the BLA
	III		Rubber stopper	

13. Inspectional Activities: The pre-licensure inspection (PLI) of (b) (4) covering the operations for the manufacturing of the SB3 drug product was waived. Refer to Waiver Memorandum uploaded into Panorama by facilities reviewer.

Primary reviewer summary recommendation:

I recommend approval of STN 761100 for Ontruzant (trastuzumab-dttb) manufactured by Samsung Bioepis from drug product (DP) perspective. The CMC information submitted in Section 3.2.P. Drug Product of this BLA application supports the conclusion that the manufacture of DP is well controlled and consistently leads to a product with the appropriate potency, purity, and stability.

Note: Unless otherwise noted, all tables and figures are taken directly from the submission.

3.2.P.1 DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT

1. DESCRIPTION

SB3 Drug product (DP), a proposed trastuzumab biosimilar (trastuzumab-dttb), is a sterile, white to pale yellow, lyophilized powder. It was developed (as per Section P.2) to have a cake-like appearance. The lyophilized product is reconstituted with 7.4 mL of sterile water for injection (SWFI) (not supplied) to yield a single-dose solution, at pH 6.0, containing 21 mg/mL SB3. The container closure system used for SB3 DP consists of (b) (4) 15 ml (b) (4) glass vial, stoppered with a (b) (4) rubber stopper and sealed with an aluminum crimping cap.

2. COMPOSITION

The composition of SB3 DP is shown in Table 1 below:

Table 1: Composition of SB3 DP

Component	Nominal Quantity/Vial	Function	Quality Standard
Trastuzumab	150 mg	Active substance	In-house ^a
L-Histidine hydrochloride monohydrate	3. (b) (4)mg	(b) (4)	Ph. Eur./JP
L-Histidine	2. (b) (4)mg		Ph. Eur./USP/JP
α,α -Trehalose dihydrate ^b	136.2 mg		Ph. Eur./USP-NF
Polysorbate 20	0.6 mg		Ph. Eur./NF/JP
Water for injection ^c	q.s.		Ph. Eur./USP

^a Specification of SB3 DS (trastuzumab) is provided in CTD Section 3.2.S.4.1.

^b Name following the list of excipients in the prescribing information (PI). In the National Formulary (NF) monograph, trehalose is presented as α -D-Glucopyranosyl α -D-glucopyranoside and thus α,α -trehalose dihydrate is the same as trehalose dihydrate. It should be noted that where applicable, “ α,α -Trehalose dihydrate” is also referred as “Trehalose dihydrate” in the relevant CTD Sections.

^c WFI evaporates during DP manufacturing process.

(b) (4)

Reviewer comment:

FDA issued an IR on Dec. 4, 2017 stating that based on information provided in the initial BLA submission, the protein content per vial did not allow for a recoverable protein content of 150mg to support the label claim of 150mg. In response to the IR, the sponsor has made manufacturing changes, (b) (4)

(b) (4) were submitted to FDA on July 30, 2018. Samsung revised the DS (b) (4) to be consistent with current FDA policy regarding the label claim of 150mg recoverable protein content (refer to Section P.3.5, Process Validation of this review for details).

In response to the Agency IR from Dec. 7, 2018, the sponsor submitted an additional table

(b) (4)

3.2.P.2. Pharmaceutical Development

3.2.P.2.1 COMPONENTS OF THE DRUG PRODUCT

1. DRUG SUBSTANCE & EXCIPIENTS

Table 1 below shows each excipient in SB3 DP compared to Herceptin.

Table 1: Excipients in SB3 DP Compared to Herceptin®

Component	SB3 DP	Herceptin®
L-Histidine hydrochloride monohydrate	3. (b) (4) mg/vial	3.36 mg/vial
L-Histidine	2. (b) (4) mg/vial	2.16 mg/vial
Trehalose dihydrate	136.2 mg/vial	136.2 mg/vial
Polysorbate 20	0.6 mg/vial	0.6 mg/vial
Water for Injection	q.s.	q.s.

Reviewer comment:

The following information is directly taken from Herceptin package insert “Highlights of Prescribing Information” for US-licensed Herceptin®: “Each single-dose vial of Herceptin delivers 150 mg trastuzumab, 136.2 mg α,α-trehalose dihydrate, 3.4 mg L-histidine HCl monohydrate, 2.2 mg L-histidine, and 0.6 mg polysorbate 20.”

As presented above and based on publicly available information, the excipients listed in the Table 1 are identical to those used for Herceptin, though it is unclear what the source of the measurements was for the Herceptin levels carried out to 2 significant digits.

3.2.P.2.2 DRUG PRODUCT

1. FORMULATION DEVELOPMENT



(b) (4)

5. PROPOSED SHELF LIFE AND STORAGE CONDITIONS

- The sponsor proposed 36 months for shelf life for the SB3 DP when stored at $5 \pm 3^{\circ}\text{C}$ in the container closure system described in CTD Section 3.2.P.7. This is based on the last acceptable stability data (36 months) available for three clinical DP batches and 24-month data of six PVR batches under long-term conditions.

3.2.P.8.2 POST-APPROVAL STABILITY PROTOCOL AND STABILITY COMMITMENT

The sponsor commits to continue stability testing of the primary stability batches and that for time points beyond the approved shelf-life, stability testing at the ICH-recommended time points will be used to support potential future expiry extension.

The stability of the post-approval DP batches will be monitored under the long-term storage condition ($5 \pm 3^{\circ}\text{C}$). The annual stability plan is included in Table 1. ,

Table 1: Post-approval Stability Plan

Category	Test Item	Shelf Life Acceptance Criteria	Time Points (Month) Shelf Life: 36 Months ^{a,c}	Time Points (Month) Shelf Life: 48 Months ^{b,c}	
General tests	Appearance, pre-reconstitution	White to pale yellow lyophilized powder with a cake-like appearance (b) (4)	0, 3, 6, 9, 12, 24, 36	0, 3, 6, 9, 12, 24, 36, 48	
	Moisture		0, 3, 6, 9, 12, 24, 36	0, 3, 6, 9, 12, 24, 36, 48	
	Reconstitution time		0, 3, 6, 9, 12, 24, 36	0, 3, 6, 9, 12, 24, 36, 48	
	Appearance, post-reconstitution		Clarity	0, 3, 6, 9, 12, 24, 36	0, 3, 6, 9, 12, 24, 36, 48
			Color	0, 3, 6, 9, 12, 24, 36	0, 3, 6, 9, 12, 24, 36, 48
			Visible particles	0, 3, 6, 9, 12, 24, 36	0, 3, 6, 9, 12, 24, 36, 48
	pH, post-reconstitution		0, 3, 6, 9, 12, 24, 36	0, 3, 6, 9, 12, 24, 36, 48	
Quantity	Protein content (A ₂₈₀)	0, 3, 6, 9, 12, 24, 36	0, 3, 6, 9, 12, 24, 36, 48		
Purity and impurities	CE-SDS (non-reducing)	%Total purity	0, 3, 6, 9, 12, 24, 36	0, 3, 6, 9, 12, 24, 36, 48	
		%2H1L	0, 3, 6, 9, 12, 24, 36	0, 3, 6, 9, 12, 24, 36, 48	
	SE-HPLC	%Monomer	0, 3, 6, 9, 12, 24, 36	0, 3, 6, 9, 12, 24, 36, 48	
		%HMW	0, 3, 6, 9, 12, 24, 36	0, 3, 6, 9, 12, 24, 36, 48	
	icIEF	%Acidic	0, 3, 6, 9, 12, 24, 36	0, 3, 6, 9, 12, 24, 36, 48	
		%Main	0, 3, 6, 9, 12, 24, 36	0, 3, 6, 9, 12, 24, 36, 48	
		%Basic	0, 3, 6, 9, 12, 24, 36	0, 3, 6, 9, 12, 24, 36, 48	
Biological activity	Competitive inhibition binding assay to HER2 by FRET	0, 3, 6, 9, 12, 24, 36	0, 3, 6, 9, 12, 24, 36, 48		
	Anti-proliferation assay	0, 3, 6, 9, 12, 24, 36	0, 3, 6, 9, 12, 24, 36, 48		
	Competitive inhibition binding assay to FcγRIIIa	0, 3, 6, 9, 12, 24, 36	0, 3, 6, 9, 12, 24, 36, 48		
Safety	Particulates (HIAC)	0, 3, 6, 9, 12, 24, 36	0, 3, 6, 9, 12, 24, 36, 48		
	Container closure integrity ^d	Pass	12, 24	12, 24, 36	
	Sterility ^e	No microbial growth observed	0, 36	0, 48	

^a Post-approval stability plan if the approved shelf-life is 36 months

Reviewer comment:

The post-approval stability plan presented in Table 1 above incorporated a measure of charge variants in response to an Agency IR. The attributes and acceptance criteria are acceptable. The plan does not include an extension as the 36 month timepoint is stated to define the plan if the approved shelf-life is 36 months.

3.2.P.8.3 STABILITY DATA

1. STABILITY RESULTS OF BATCHES TESTED

Stability studies are currently on-going using three batches of clinical drug product (DP) and six batches of PVR DP, as indicated in Table 1 below.

Table 1: Overview of Stability Studies

Batch Type	Batch Number	Study Purpose	Storage Conditions	Reference Table	Reference Figure
Clinical	P51702A	Shelf life determination	Long-term $5 \pm 3^{\circ}\text{C}$	Table 2	Figure 1
			Accelerated $25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{RH}$	Table 3	
			Stress $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{RH}$	Table 4	
	P51704A	Shelf life determination	Long-term $5 \pm 3^{\circ}\text{C}$	Table 5	Figure 2
	P51705A	Shelf life determination	Long-term $5 \pm 3^{\circ}\text{C}$	Table 6	
PVR	P51708A	Shelf life determination	Long-term $5 \pm 3^{\circ}\text{C}$	Table 7	Figure 3 Figure 4 Figure 5
			Accelerated $25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{RH}$	Table 8	
			Stress $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{RH}$	Table 9	
	P51709A	Shelf life determination	Long-term $5 \pm 3^{\circ}\text{C}$	Table 10	
			Accelerated $25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{RH}$	Table 11	
			Stress $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{RH}$	Table 12	
	P51710A	Shelf life determination	Long-term $5 \pm 3^{\circ}\text{C}$	Table 13	
			Accelerated $25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{RH}$	Table 14	
			Stress $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{RH}$	Table 15	
	P51711A	Shelf life determination	Long-term $5 \pm 3^{\circ}\text{C}$	Table 16	
			Accelerated $25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{RH}$	Table 17	
			Stress $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{RH}$	Table 18	
	P51712A	Shelf life determination	Long-term $5 \pm 3^{\circ}\text{C}$	Table 19	
			Accelerated $25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{RH}$	Table 20	
			Stress $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{RH}$	Table 21	
P51713A	Shelf life determination	Long-term $5 \pm 3^{\circ}\text{C}$	Table 22		
		Accelerated $25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{RH}$	Table 23		
		Stress $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{RH}$	Table 24		
Pilot	(b) (4) 002175	Supportive information	Long-term $5 \pm 3^{\circ}\text{C}$	Table 25	Figure 6
			Accelerated $25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{RH}$	Table 26	
			Stress $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{RH}$	Table 27	
Clinical	P51702A	Temperature cycling study	Short-term temperature cycling $-20^{\circ}\text{C} \pm 5^{\circ}\text{C}$ to $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{RH}$	Table 28	Figure 7
PVR	P51708A		Supply chain cycling (b) (4)	Table 29	Figure 8

Batch Type	Batch Number	Study Purpose	Storage Conditions	Reference Table	Reference Figure
Clinical	P51702A	Photostability study	Photostability 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 in immediate packaging.	CTD Section 3.2.R.4.3.4.	CTD Section 3.2.R.4.3.4.
PVR	P51708A		Photostability 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 in immediate packaging or commercial packaging	Table 30	Figure 9
Clinical	P51702A	In-use stability study	Hold time stability of reconstitution 5 ± 3°C for 48 hours or 25 ± 2°C for 24 hours after reconstitution	Table 31 CTD Section 3.2.R.4.3.5	Figure 10 Figure 11 CTD Section 3.2.R.4.3.5
PVR	P51709A		Infusion bag compatibility and mixture storage stability 25 ± 2°C after dilution for 48 hours in PP, PE, and Glass container containing 250 mL of 0.9% sodium chloride, respectively	Table 32 Table 33 Table 34 Table 35 Table 36 Table 37 CTD Section 3.2.R.4.3.5	Figure 12 Figure 13 Figure 14 CTD Section 3.2.R.4.3.5

Reviewer comment:

Stability data for all lots listed in the above table were reviewed and the review summary of stability data obtained from the clinical and PVR lots can be found in the previous section (3.2.P.8.1).

While all stability results obtained from long-term storage condition, including both clinical and PVR batches, met the acceptance criteria, %Oxidation at Met255 (Report result) for clinical batches at long-term storage condition ranges between 3.7 – 10.4%.

Anti-proliferation assay, SE-HPLC, CE-SDS (non-reducing), icIEF and CEX-HPLC appear to be stability indicating assays.

The sponsor submitted 36-month data from PVR lots during the review cycle.

Data provided support the requested 36 month shelf life for SB3 DP.



Wen
Wu

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Wendy
Weinberg

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Date: 12/22/2018 12:58:11AM
GUID: 508da6d9000264753deac8e517fd0f24

**BLA STN 761100
trastuzumab-dttb
Samsung Bioepis**

Drug Substance and Analytical Similarity

**Kristen Nickens, PhD (Primary Reviewer)
Qing (Joanna) Zhou, PhD (Secondary Reviewer, ATL)**

**Division of Biotechnology Reviewer and Research 1
Office of Biotechnology Products**

OBP CMC Review Data Sheet

1. BLA#: 761100

2. Review Date: December 20, 2018

3. Primary Review Team:

- a. Medical Officer: Tatiana Prowell/ Jennifer Gao (Acting CDTL)
- b. Pharm/Tox: George Chang/Tiffany Ricks
- c. Product Quality:
 - OBP ATL: Qing (Joanna) Zhou
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- h. OPRO RBPM: Oumou Barry
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761100/0014	May 22, 2018	Yes
761100/0017	June 29, 2018	Yes
761100/0019	July 13, 2018	Yes
761100/0020	July 18, 2018	Yes
761100/0021	July 24, 2018	Yes
761100/0023	July 30, 2018	Yes
761100/0026	August 20, 2018	Yes
761100/0037	November 28, 2018	Yes
761100/0044	December 13, 2018	Yes
761100/0045	December 17, 2018	Yes
761100/0046	December 19, 2018	Yes

7. Drug Product Name/Code/Type:

- a. Proprietary Name: Ontruzant
- b. Trade Name: Ontruzant
- c. Non-Proprietary Name/USAN: trastuzumab-dttb
- d. CAS Name: 180288-69-1
- e. Common Name: SB3
- f. INN Name: trastuzumab
- g. Compendial Name: N/A
- h. OBP systematic name: MAB HUMANIZED (IGG1) ANTI P04626 (ERBB2_HUMAN) [SB3]
- i. Other names: SAIT103, BIIB604, ED004

8. Pharmacological Category: HER2/neu receptor antagonist

9. Dosage Form: For injection

10. Strength/Potency:

(i): The concentration/strength of the Drug Product: 150 mg per vial

(ii): Type of potency assay(s): competitive inhibition binding assay to HER2 by fluorescence resonance energy transfer (FRET), cell-based antiproliferation assay, competitive inhibition binding assay to FcγRIIIa

11. Route of Administration: Intravenous

12. Referenced Drug Master Files (DMF):

DMF#	DMF Holder	Item Referenced	Letter of Cross-Reference	Comments (status)
	(b) (4)	Glass vials	Yes	Type III

(b) (4)	Rubber stopper, coatings	Yes	Type III

13. Inspectional Activities: A pre-licensure inspection (PLI) of (b) (4) covering the operations for the manufacturing of the SB3 drug substance was performed from (b) (4) by Zhong Li (lead inspector), Kristen Nickens (OBP), and Ziyang Su (OPF). A 3-item Form FDA 483 was issued to (b) (4) at the end of the inspection which included the following: (b) (4)

Following the response by the applicant, the inspection outcome was “approve.”

14. Consults Requested by OBP: None

15. Quality by Design Elements:

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

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

18. Administrative:

Discipline	Reviewer	Branch/Division	Signature
Drug substance/analytical similarity	Kristen Nickens	Division of Biotechnology Review and Research I	See Panorama
Secondary Reviewer/Application Team Lead	Qing (Joanna) Zhou	Division of Biotechnology Review and Research I	See Panorama

Summary of Quality Assessments

- I. Primary Reviewer Summary Recommendation
I recommend approval of STN 761100 for Ontruzant (trastuzumab-dttb) manufactured by Samsung Bioepis. The data submitted in this application support the conclusion that the manufacture of Ontruzant is well controlled and consistently leads to a product with the appropriate potency and purity.
- II. List of Deficiencies to be Communicated – N/A
- III. List of Post-Marketing Commitments/Requirements
The following are draft post-marketing commitments:

- a. Perform a method validation study to confirm the suitability of the FcγRIIIa AlphaScreen assay for use as a potency assay for drug substance and drug product lot release and stability testing.
- b. Perform a method validation study to confirm the suitability of the Size Exclusion-High Performance Liquid Chromatography assay for use as a purity assay in the detection of high molecular weight species for drug substance and drug product lot release and stability testing.
- c. Perform a qualification study to confirm the suitability of [REDACTED] (b) (4) assay for the detection of product-specific host cell protein impurities.
- d. [REDACTED] (b) (4)
- e. Implement a two-tiered reference standard program that includes the qualification and stability testing of a primary reference standard and a working reference standard to be used for routine drug substance and drug product release and stability testing.

IV. Review of Common Technical Document- Quality Module 1

A. Environmental Assessment of Claim of Categorical Exclusion

Samsung Bioepis Co. Ltd., requested categorical exclusion from the environmental assessment required under 21 CFR 25.31(a) based on the consideration that a series of analytical similarity assessments were performed and support an establishment of “bioequivalence requirements for a human drug or a comparability determination for a biologic product subject to licensing.”

Reviewer comment: *While the Agency does not consider the analytical similarity data as comparability data or demonstrative of bioequivalence, a claim of categorical exclusion is acceptable based on 21 CFR 31(c).*

- V. Primary Container Labeling Review: The OBP review of the drug product label was performed under a separate review covered by Vicky Borders-Hemphill (see review in Panorama).
- VI. Review of Common Technical Document- Quality Module 3.2: The review of Module 3.2.S is provided below. The review of the drug product (Module 3.2.P) was performed under a separate review covered by Wen Jin Wu (see review in Panorama).
- VII. Review of Immunogenicity Assays- Module 5.3.1.4: The review of the immunogenicity assay validation was performed under a separate review covered by Milos Dokmanovic (see review in Panorama).

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Description of Drug Substance

SB3 is a proposed biosimilar to US-licensed Herceptin (trastuzumab) directed against the human epidermal growth factor receptor 2 (HER2). SB3 is a humanized recombinant immunoglobulin G1 (IgG1) monoclonal antibody of the kappa isotype consisting of two identical heavy chains (HCs), which are glycosylated at asparagine (Asn) 300, and two identical light chains (LCs).

Note: Several rounds of information requests (IRs) were communicated between Samsung and FDA regarding the SB3 DS manufacturing process and control strategy, as well as general clarification to enable a comprehensive review of the data. As a result, Samsung was requested to make updates to the BLA. The memo presents the review of the final data and information after the sponsor’s IR responses.

Tables and figures are copied directly from the application, unless otherwise noted.

3.S.2 DRUG SUBSTANCE

3.2.S.1 General Information

3.2.S.1.1 Nomenclature

- International Nonproprietary Name (INN): trastuzumab-dttb
- United States Adopted Name (USAN): trastuzumab-dttb

- Chemical name: IgG1 (human-mouse monoclonal rhuMab HER2 γ_1 -chain anti-human p185^{c-erbB2} receptor), disulfide with human-mouse monoclonal rhuMab HER2 LC, dimer
- Company or laboratory codes: SB3, SAIT103, BIIB604, ED004
- Chemical Abstract Service (CAS) registry number: 180288-69-1
- Chemical formula: C₆₄₆₀H₉₉₇₂N₁₇₂₄O₂₀₁₄S₄₄

3.2.S.1.2 Structure

The molecular weight of SB3 is 148 kDa and consists of 1,328 amino acids; the sequences of the HC (Figure 1) and LC (Figure 2) are shown below (N-linked glycosylation site is indicated by the boxed letter in Figure 1).

1	EVQLVESGGG	LVQPGGSLRL	SCAASGFNIK	DTYIHWVRQA	PGKGLEWVAR
51	IYPTNGYTRY	ADSVKGRFTI	SADTSKNTAY	LQMNSLRAED	TAVYYCSRWG
101	GDGFYAMDYW	GQGTLVTVSS	ASTKGPSVFP	LAPSSKSTSG	GTALGCLVK
151	DYFPEPVTVS	WNSGALTSGV	HTFPAVLQSS	GLYSLSSVVT	VPSSSLGTQT
201	YICNVNHKPS	NTKVDKKEP	KSCDKHTTCP	PCPAPPELLGG	PSVFLFPPKP
251	KDTLMISRTP	EVTCTVVDVDS	HEDPEVKFNW	YVDGVEVHNA	KTKPREEQYN
301	STYRVVSVLT	VLHQDWLNGK	EYKCKVSNKA	LPAPIEKTIS	KAKGQPREPQ
351	VYTLPPSREE	MTKNQVSLTC	LVKGFYPSDI	AVEWESNGQP	ENNYKTTTPV
401	LDSDGSEFLY	SKLTVDKSRW	QQGNVFSCSV	MHEALHNHYT	QKSLSLSPGK
Variable region: Normal letters					
Constant region: Bold underlined letters					
N-linked glycosylation site: Boxed letter					

Figure 1: Amino Acid Sequence of SB3 Heavy Chain(s)

1	DIQMTQSPSS	LSASVGRDVT	ITCRASQDVN	TAVAWYQQKP	GKAPKLLIYS
51	ASFLYSGVPS	RFSGSRSGTD	FLLTISSLQP	EDFATYYCQQ	HYTTPPTFGQ
101	GTKVEIKRTV	AAPSVFIFPP	SDEQLKSGTA	SVVCLLNIFY	PREAKVQWKV
151	DNALQSGNSQ	ESVTEQDSKD	STYLSLSTLT	LSKADYEKHK	VYACEVTHQG
201	LSSPVTKSFN	RGEC			
Variable region: Normal letters					
Constant region: Bold underlined letters					

Figure 2: Amino Acid Sequence of SB3 Light Chains(s)

3.2.S.1.3 General Properties

Additional physical and chemical properties of SB3 drug substance (DS) include an isoelectric point of 8.9, an extinction coefficient of 1.5 mL mg⁻¹ cm⁻¹, pH of 6.0±0.6, with a clear to opalescent and colorless to pale-yellow color. The recognized mechanisms of action of trastuzumab are initiated through the binding of the antibody Fab region to the extracellular domain of the HER2 receptor on the target cell. This selective binding prevents HER2 dimerization, leading to increased endocytic-mediated destruction of the receptor, inhibition of HER2 extracellular domain shedding, activation of immune response (antibody-dependent cellular cytotoxicity), and inhibition of tumor cell growth.

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

The following table summarizes the sites involved in the manufacture, testing, and packaging for SB3.

Table 1: Information of Manufacturing Sites for SB3 DS

Name and Address	Responsibilities
(b) (4)	Manufacturing of the Master Cell Bank (MCB) and Working Cell Bank (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	(b) (4)
(b) (4)	(b) (4)
	(b) (4)
Name and Address	Responsibilities
(b) (4)	(b) (4) appearance, endotoxin, and microbial enumeration) Stability testing of clinical campaign (all tests)
	(b) (4)
	QC release testing (all tests excluding protein concentration, appearance, endotoxin, and microbial enumeration) Stability testing of PVR and commercial campaigns (all tests excluding endotoxin and microbial enumeration)
	Stability testing of PVR and commercial campaigns (endotoxin and microbial enumeration) Storage of the DS
(b) (4)	(b) (4)

Reviewer comment: Inconsistencies in the storage locations of the SB3 Master Cell Bank (MCB) and Working Cell Bank (MCB) were noted between information provided in Section 3.2.S.2.1 and in Section S.2.3, as well as inconsistencies in the location where stability testing is performed (see Established Inspection Report of (b) (4)). In response to IR dated 7/5/2018, Samsung clarified that the SB3 MCB and WCB are currently stored at (b) (4). Additionally, Samsung updated the table to clarify the responsibilities of each manufacturer.

3.2.S.2.2 and 3.2.S.2.4 Description of Manufacturing Process and Process Controls and Process Controls and Control of Critical Steps and Intermediates

(b) (4)



3.2.R.4 Analytical Similarity

Previously, in the United States (US), Herceptin (trastuzumab) was marketed only as a multi-dose vial containing 440 mg of trastuzumab (current label claim revised to 420 mg); however, recently a single-dose vial presentation containing 150 mg of lyophilized trastuzumab was also approved in the US. In the European Union (EU), Herceptin is only marketed as a single-dose vial containing 150 mg of lyophilized trastuzumab. Here, Samsung is seeking licensure for only the 150 mg presentation of SB3 as a proposed biosimilar to US-licensed Herceptin.

To support licensure of SB3 150 mg, a comparative clinical study, SB3-G31-BC, was conducted using EU-approved trastuzumab (instead of US-licensed Herceptin) and SB3 150 mg. To support the use of EU-approved trastuzumab in the pivotal clinical study, a three-way scientific bridging study, including analytical, non-clinical and clinical PK analyses (three-way PK similarity study SB3-G11-NHV), was conducted between SB3 150 mg, US-licensed Herceptin 420 mg and EU-approved trastuzumab.

To support analytical similarity between SB3 and US-licensed Herceptin, Samsung performed a battery of analytical studies including a head-to-head characterization of the physicochemical properties, biological activity, and comparative stability profiles between the products. Because at the time of analysis, the US-licensed Herceptin 150 mg presentation was not yet available on the US market, the entire analytical similarity study was performed comparing SB3 150 mg to US-licensed Herceptin 420 mg. Prior to submission of the 351(k), Samsung held a Type 4 meeting with the FDA (see meeting minutes, pre-IND 123158, September 1, 2017), where the Agency provided advice regarding the amount and types of data needed to support the licensure of SB3 150 mg while leveraging the analytical similarity data generated comparing lots of SB3 150 mg to US-licensed Herceptin 420 mg. In the meeting minutes (i.e., post-meeting addendum), Samsung was advised to submit data directly comparing US-licensed Herceptin 150 mg and SB3 150 mg, based on an analysis of quality attributes that could be impacted by, for example, differential aspects of the US-licensed Herceptin 150 mg and 420 mg manufacturing processes, such as vial filling and lyophilization. The Agency requested that the outcome of the risk assessment and the comparative data be included in the BLA, and clarified that the number of US-licensed Herceptin 150 mg and SB3 150 mg lots included in the evaluation be scientifically justified. During the meeting, Samsung stated that two lots of US-licensed Herceptin 150 mg would be included in the additional similarity study; however, in response to an information request (IR), a total of 8 lots of US-licensed Herceptin 150 mg were included in the analysis (see data discussion below).

***Reviewer comment:** Hereafter, US-licensed Herceptin will be referred to as US-Herceptin 420 mg or US-Herceptin 150 mg; and EU-approved trastuzumab will be referred to as EU-Herceptin. Furthermore, during the review cycle, numerous updates, including reanalysis of data and results from additional studies performed during the review cycle were made to the analytical similarity assessment (including the comparability assessment between US-Herceptin 420 mg and 150 mg) in response to several IRs. The data presented below reflect the final update of the data to support analytical similarity (information and data located in Section 3.2.R.4, document entitled, “Biosimilarity”).*

Comparability assessment between US-Herceptin 150 mg and US-Herceptin 420 mg

To support the use of US-Herceptin 420 mg as the primary comparator to SB3 in the analytical similarity assessment, an analytical study was performed to demonstrate comparability between the two US-Herceptin presentations. Eight lots of US-Herceptin 150 mg with expiry dates from March to July 2021 were analyzed against the quality range (QR) derived from the analysis of up to 65 lots of US-Herceptin 420 mg (the same US-Herceptin 420 lots used in the analytical similarity assessment; see discussion in analytical similarity section below).

***Reviewer comment:** Samsung initially included 3 lots of US-Herceptin 150 mg to support the analytical similarity between US-Herceptin 150 mg and SB3; however, additional information was requested to support the protein concentration similarity data (see IR dated December 4, 2017 and discussion below). In response, Samsung provided analytical data from an additional 5 lots of US-Herceptin 150 mg in the similarity assessment between US-Herceptin 150 mg and SB3, as well as to support comparability between US-Herceptin 150 mg and 420 mg (see SDN 23, Table 3). The expiry dates of the US-Herceptin 150 mg lots suggest that the materials were*

produced using separate runs of the drug product (DP) manufacturing process and could potentially capture some lot-to-lot variability.

The quality attributes evaluated in the comparability study include inhibition of proliferation, ADCC activity, HER2 binding, FcRn binding, FcγRIIIa binding, C1q binding, protein concentration, charge heterogeneity, size variants, and glycosylation profile. Comparability of US-Herceptin 150 mg to 420 mg was evaluated using a QR derived from the mean ± 3 standard deviations (SD) of the 420 mg lots (the US-Herceptin presentation used in the nonclinical, clinical, and analytical similarity studies), data provided in the appendix (Tables 128-131). Scatter plots (Figures 135-156) and tabular data (Tables 106-118) were provided.

Reviewer comment: The list of attributes evaluated are adequate for the assessment of comparability. For attributes evaluated against a research reference standard (RRS), specifically, antiproliferation, ADCC activity, HER2 binding, FcγRIIIa binding, FcRn binding, and C1q binding, only the data generated against RRS2, RRS3, and RRS4, were included in the analysis (see detailed discussion in analytical similarity assessment section regarding implementation of the various RRSs). The following is a discussion of the comparability results for attributes relevant to the potency of the products (i.e., antiproliferation, ADCC activity, HER2 binding, FcγRIIIa binding, and afucosylation plus high mannose (the QRs indicated in the following figures are based on 3SD).

Antiproliferation

The antiproliferation activity values of 8 lots of US-Herceptin 150 mg, 93-111% (Table 106), are around the mean (100%) of the 46 lots of US-Herceptin 420 mg, which range from 81-116% (Table 129). The US-Herceptin 150 mg lots were within the range of the US-Herceptin 420 mg lots (Figure 135).

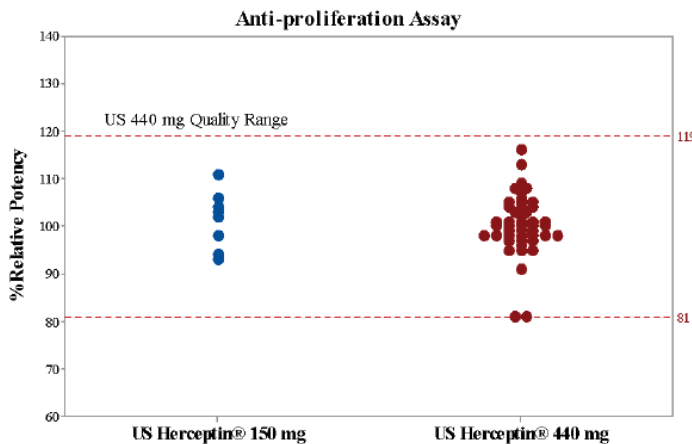


Figure 135: Anti-proliferation Potency of US Herceptin® 150 mg and 440 mg

Reviewer comment: The US-Herceptin 150 mg lots exhibit antiproliferation values across the range the US-Herceptin 420 mg lots and do not appear to be on either the higher and/or lower end of the range. The data show that the antiproliferative activity of the two US-Herceptin presentations are comparable.

HER2

The HER2 binding activity values of 8 lots of US-Herceptin 150 mg, 97-104% (Table 115), are around the mean (99%) of the 46 US-Herceptin 420 mg lots which range from 92-110% (Table 129). The US-Herceptin 150 mg lots were within the range of the US-Herceptin 420 mg lots (Figure 153).

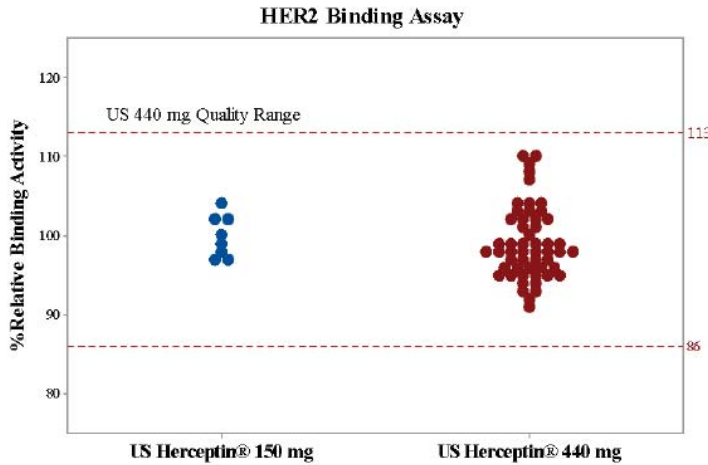


Figure 153: HER2 Binding Activity of US Herceptin® 150 mg and 440 mg

Reviewer comment: The data show consistent values of HER2 binding between the two US-Herceptin presentations and support comparability.

ADCC

The ADCC activity (Figure 136) of 8 lots of US-Herceptin 150 mg, 87-113% (Table 107), are on the upper end (above the mean of 82%) of the ADCC activity data range of the US-Herceptin 420 mg lots which ranged from 44-133% (Table 129).

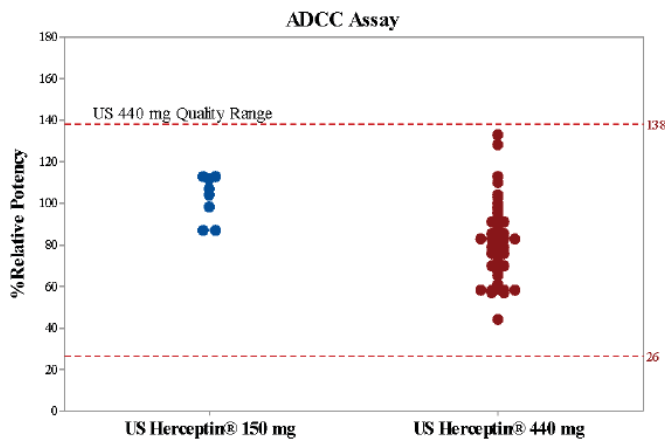


Figure 136: ADCC Potency of US Herceptin® 150 mg and 440 mg

Reviewer comment: The ADCC activity of the US-Herceptin 150 mg are within the US-Herceptin 420 mg QR but are on the upper end of the data spread. The ADCC activity levels appear to also correlate with the FcγRIIIa binding of the US-Herceptin 150 mg lots evaluated (see below). Although the 150 mg lots appear to slightly cluster toward the upper end of the 420 mg QR, the potency values are acceptable considering that the values are consistent with those of several 420 mg lots that have been commercially produced and likely used to treat patients with no impact on safety, efficacy, or immunogenicity. The data support comparability for ADCC activity between US-Herceptin 150 mg and US-Herceptin 420 mg.

FcγRIIIa

The FcγRIIIa binding activity of 8 lots of US-Herceptin 150 mg, 90-104% (Table 117), are on the upper end (above the mean of 83%) of the FcγRIIIa activity data range of the US-Herceptin 420 mg lots of 50-128% (Table 129) but are within the US-Herceptin 420 mg QR (Figure 155).

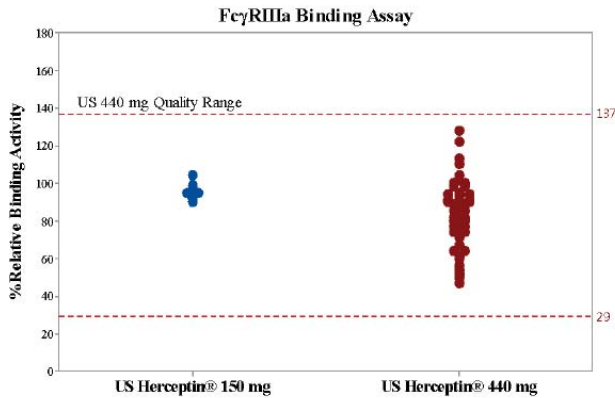


Figure 155: FcγRIIIa (158V/V) Binding Activity of US Herceptin® 150 mg and 440 mg

Reviewer comment: The FcγRIIIa binding activity of the US-Herceptin 150 mg lots appear to be consistent with lots of US-Herceptin 420 mg that are on the higher end of the data spread (slightly above the mean of 83% for the US-Herceptin 420 lots). As discussed above, the levels of FcγRIIIa binding appear to correlate with ADCC activity of the same. The FcγRIIIa values are comparable between the lots of US-Herceptin 150 mg and US-Herceptin 420 mg.

Afucosylation and high mannose (HM)

Afucosylation and HM values were reported together, and the cumulative % for the 8 lots of US-Herceptin 150 mg, 9.4-14.0% (Table 111), are at the midpoint (mean of US-Herceptin 420 mg is 9.5%) of the data range of the US-Herceptin 420 mg lots of 5.9-13.4% (Table 128). One lot of US-Herceptin 150 mg has a value (14.0%) slightly higher than the upper end of the QR (5.2-13.8%); however, the value is only marginally higher and the other 7 lots of 150 mg that are within the 420 mg QR (Figure 142).

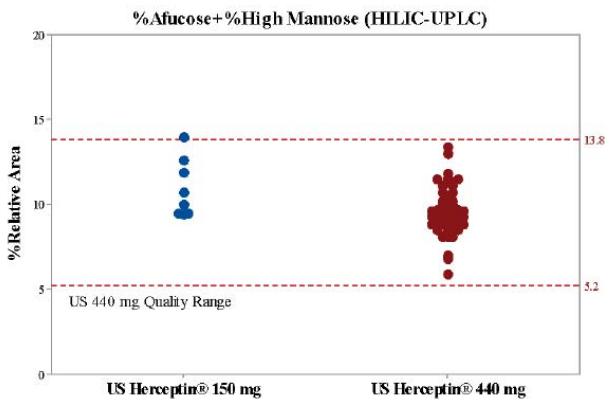


Figure 142: %Afucose + %HM of US Herceptin® 150 mg and 440 mg by HILIC-UPLC

Reviewer comment: Because the % afucosylation and % HM were reported together as a single value, the correlation with ADCC and FcγRIIIa binding with afucosylation is not clearly distinguishable. However, considering additional data requested to separate the two quality attribute assessments, it is likely that the afucosylated species (versus the HM) is the more dominant glycoform of the two detected (see discussion in analytical similarity assessment and IR dated 3/19/18). Additionally, it is not expected that the glycosylation profile of either presentation would be impacted by the DP manufacturing processes. Overall, the cumulative

amount of afucose and HM are comparable between the US-Herceptin 150 mg and 420 mg lots. The amounts of G0F, G1F, and G2F glycoforms were within the US-Herceptin 420 mg QR.

With respect to the additional quality attributes evaluated, minor variability was detected for size and charge species between the two presentations. Aggregates were within the QR (Table 108, Figure 137) but appeared slightly lower in the US-Herceptin 150 mg lots compared to the 420 mg lots, which may be due to differences in the DP manufacturing processes (e.g., fill volume, lyophilization). The impurity assessment supported comparability between the two presentations. The charge variant analysis showed that all US-Herceptin 150 mg lots were within the 420 mg QR, except for one 150 mg lot which had a % basic species marginally above the upper limit of the QR by CEX; however, no major differences were indicated for acidic and main peak, and the charge analysis by icIEF were also supportive of comparability. The protein concentration of the eight lots of US-Herceptin 150 mg are consistent with the US-Herceptin 420 mg lots, which is expected considering the label claim of 21.0 mg/ml for both US-Herceptin presentations, notwithstanding the different reconstitution volumes. Overall, US-Herceptin 150 mg and US-Herceptin 420 mg lots are comparable based on the analytical data generated by Samsung. The data are sufficient to support the use of US-Herceptin 420 mg lots as the primary comparator in the analytical similarity assessment for quality attributes that may not be impacted by, for example, differential aspects of the 150 mg and 420 mg manufacturing processes (e.g., vial filling and lyophilization) and presentations (i.e., reconstituted protein concentration). As such, Samsung performed an additional analytical similarity assessment directly comparing SB3 150 mg and US-Herceptin 150 mg.

Analytical Similarity Assessment

Reviewer comment: The analytical similarity data and the statistical approach applied for data analysis as described below was reviewed and documented prior to the withdrawal of the FDA’s “Draft Guidance for Industry: Statistical Approaches to Evaluate Analytical Similarity”; and therefore, makes reference to statistical tiers. The current FDA thinking on the approach used to statistically evaluate analytical similarity data is still under consideration with respect to the scientific and regulatory issues involved.

Samsung’s Statistical Approach for the Similarity Assessment

The quality attributes assessed as part of analytical similarity were stratified into three statistical tiers (tier 1, 2, and 3) based on a criticality risk assessment that accounted for the potential impact that an attribute may have on safety, efficacy, immunogenicity, and PK/PD. The risk assessment also took into consideration the level of uncertainty of the data and information (i.e., absence or presence of structure-function relationships, toxicology information, clinical experience, non-clinical data, publicly available literature, relevance of data systems and models used in studies) to determine the potential impact of the quality attribute. A risk priority number (RPN) derived by multiplying a numerical impact factor by an uncertainty factor (see Section 3.2.S.6.1), was used, in part, to categorize the quality attributes into one of the three statistical tiers, whereby attributes with an RPN > 59 was classified as tier 1, attributes with an RPN > 24 and ≤ 59 was classified as tier 2, and an RPN ≤ 24 was classified as tier 3. The tiered-based statistical approach corresponding to varying degrees of statistical rigor are summarized as follows:

Tier 1: Equivalence Test – Analytical methods used to assess ADCC activity and the inhibition of proliferation were evaluated by equivalence testing where the equivalence margin was based on 1.5 times the variability of the reference product lots. The quality attribute was defined as equivalent if the (1-2α) 100% two-sided confidence interval of the mean difference between SB3 and the reference product was within the equivalence margin.

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

Tier 2: QR Approach –Analytical methods used to evaluate tier 2 quality attributes were analyzed using QRs expressed as mean ± a SD multiplier (SDM) of 3 for two-sided QR, and either + or – 3SD for one-sided QR evaluations.

Reviewer comment: It was stated that because the distribution and parameters of Herceptin are unknown, that a SDM of 3 was used. The application of a SDM of 3 in a general manner may not be appropriate because the importance of the biological and clinical relevance of each individual attribute, as well as the assay sensitivity, should be taken into consideration. The appropriateness of the evaluation for each attribute will be considered as part of this review and a separate analysis will be performed if necessary.

Tier 3: Visual Displays – Quality attributes assessed using analytical methods not considered amenable to statistical analysis are assigned to Tier 3. Graphical and tabular data were compared in a side-by-side manner.

The quality attributes and the corresponding statistical tier assignments are provided in Table 2 (below). The analytical similarity testing sites (indicated in the table below) were Samsung Bioepis (SB; Incheon, Republic of Korea), (b) (4)

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	Functional activity	Anti-proliferation assay	Method qualified	Samsung Bioepis (SB)
		ADCC assay	Method qualified	SB
Tier 2	Binding properties	HER2 binding assay by FRET	Method qualified	SB
		FcRn binding assay by AlphaScreen®	Method qualified	SB
		FcγRIIIa (158V/V) binding assay by AlphaScreen®	Method qualified	SB
		C1q binding assay by ELISA	Method qualified	SB
	Quantity	Protein concentration determination by UV/VIS at A ₂₈₀	Method qualified	SB
	Purity and impurities	%HMW analysis by SE-HPLC	Method qualified	SB
		%Main (%LC + %HC) analysis by CE-SDS (reducing)	Method qualified	SB
		%NGHC analysis by CE-SDS (reducing)	Method qualified	SB
		%Purity (%IgG) analysis by CE-SDS (non-reducing)	Method qualified	SB
		%2H1L analysis by CE-SDS (non-reducing)	Method qualified	SB
	Glycan profile	%Afucose + %HM, %G0F, %G1F, %G2F analysis by HILIC-UPLC	Method qualified	SB
	Charge variants	%Acidic, %Main, %Basic variants analysis by CEX-HPLC	Method qualified	SB
		%Acidic, %Main, %Basic variants analysis by icIEF	Method qualified	SB

Tier	Category	Test and Analytical Method	Suitability	Testing Site
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 Using Procainamide Labeling	Calibration	SB
	Higher-order structure	Protein secondary structure analysis by CD (Far- and Near-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 SE-HPLC/MALLS	System suitability	
		Aggregates characterization analysis by SV-AUC	System suitability	
		Protein size characterization analysis by DLS	System suitability	
Subvisible particles analysis by MFI		System suitability		
Extinction coefficient determination		System suitability		
Binding properties	FcγRIa binding assay by FRET	Method qualified	SB	
	FcγRIIa binding assay by AlphaScreen [®]	Method qualified	SB	
	FcγRIIb binding assay by AlphaScreen [®]	Method qualified	SB	
	FcγRIIIb binding assay by SPR	Method qualified	SB	
Additional	<i>in vitro</i> angiogenesis assay	Method qualified	SB	

Tier	Category	Test and Analytical Method	Suitability	Testing Site
	functional activity	Surface HER2 expression level measurement	Method qualified	SB
		HER2 ECD shedding	Method qualified	SB
		Inhibition of AKT phosphorylation	Method qualified	SB
		Combination treatment with chemotherapy	Method qualified	SB
		CDC assay	Positive control and no dose response ^c	SB

^a Calibration: Calibration is conducted using the analyte mass to be compensated based on the accurate mass of exact internal calibrant. In addition, 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: ADCC activity and inhibition of proliferation are using equivalence testing, and HER2 binding is evaluated using QR analysis. During the type 4 meeting (see pIND 123158 in DARRTS), Samsung stated that the HER2 FRET assay exhibited poor sensitivity in the structure-function evaluation, which informed their decision to evaluate the assay in Tier 2 rather than Tier 1. FDA conveyed to Samsung that poor assay performance is not an appropriate justification for assay placement in a specific quality tier. The method qualification summary (see discussion in section below) for the HER2 FRET assay support that the method was suitable for its intended use in the analytical similarity assessment. A robust evaluation of sialic acid content was not included; therefore, Samsung was requested to provide the data using a justified number of lots and appropriate statistical analysis (see discussion below).

Method qualification/validation

Method qualification, calibration, and system suitability summaries were submitted in response to IR dated 3/29/18.

Reviewer comment: Table 2 identified if the methods were qualified, calibrated, or evaluated for system suitability for use in the analytical similarity assessment. During the pre-license inspection of the analytical similarity data in Incheon, Korea, the qualification reports for the following analytical methods used in the similarity assessment were reviewed by Riley Myers: anti-proliferation assay, ADCC assay, HER2 binding assay, FcγRIIIa binding assay, and N-glycan by UPLC. The methods were determined to be suitable for the intended purpose. The method qualification summary data provided for protein concentration by UV/Vis, charge species by icIEF, HMWS by SE-HPLC, and fragments by CE-SDS non-reduced are suitable for use in the similarity assessment. Brief descriptions of the additional methods and qualification/calibration summaries will be discussed below in the section corresponding to the specific attribute; descriptions of methods used in both the analytical similarity assessment and as part of the SB3 DS and DP release and stability testing are summarized in Section S.4.2.

Samples used in the analytical similarity assessment

The analytical similarity assessment included:

- US-Herceptin:
 - Up to 65 lots of US-Herceptin 420 mg with labeled expiration dates ranging from February 2012 through May 2020 (Table 5). Of the 65 lots, 6 lots (all with an expiration date in 2012) were evaluated based on the expiry sourced from the box (based on the bacteriostatic water for injection expiry), not from the DP vial label (which was used for the expiry for all other lots). Of these 6 lots, two (lots 807815 and 822601) were tested about 2 months after the expiration date listed on the box.
 - In addition, a separate analytical similarity assessment was conducted between 8 lots of US-Herceptin 150 mg (Table 7) and 3 lots of SB3 150 mg produced using the most recent (revised)

DP manufacturing process (see Section 3.2.P). The expiration dates of the 8 lots ranged from March to July 2021.

Reviewer comment: Use of the US-Herceptin 420 mg lots as the primary comparator in the analytical similarity assessment has been supported by an analytical comparability analysis between US-Herceptin 150 mg and US-Herceptin 420 mg, and the data support comparability.

The 1998 approval letter (publicly available information) for US-Herceptin indicates that the DP has an expiry of 30 months at 2-8°C and the bacteriostatic water for injection (BWFI) has an expiry of 24 months when stored at 2-8°C. Based on this, the expiration date on the co-packaged box should be 24 months. Taking this information into consideration, and the footnote that lots 807815 and 822601 were tested approximately two months after the box expiration date, it is likely that the testing of the two DP lots was still conducted within the expiry period of the DP (6 months difference between DP and BWFI expiry). While the co-packaged BWFI that may have been used for reconstitution of these DP lots was expired, the shelf-life of BWFI is unlikely to significantly impact the quality attributes for analytical similarity evaluation. Therefore, it is acceptable to include these two lots in the analytical similarity assessment.

- EU-Herceptin: Up to 81 lots of EU-Herceptin with labeled expiration dates ranging from November 2012 through May 2020 (Table 6). Lots were tested within the expiry period.
- SB3: Up to 8 lots of SB3, including 3 DS and 6 DP batches, manufactured from August 2013 through March 2015 (Table 4, below).

Table 4: Information of SB3 Used for the Similarity Assessment

Type	Development Stage	Batch Number	Description	DS Batch Used	Manufacturing Information		Used for Similarity Assessment		
					Date	Site	Tier 1	Tier 2	Tier 3
DS	PVR batch	HP5-14-604-001	Process validation Stability study	N/A ^a	Jan 2015	(b) (4)	-	-	O ^b
		HP5-14-604-003	Process validation Stability study	N/A	Feb 2015	(b) (4)	O	O ^b	O ^b
		HP5-14-604-005	Process validation	N/A	Feb 2015	(b) (4)	O	O ^b	O ^b
DP	Clinical batch	P51702A	Stability study	HP5-13-604-001	Aug 2013	(b) (4)	O	O	O ^b
		P51704A	Stability study Clinical study	HP5-13-604-003	Dec 2013	(b) (4)	O	O	O ^b
		P51705A	Stability study Clinical study	HP5-13-604-004	Jan 2014	(b) (4)	O	O	O ^b
	PVR batch	P51708A	Process validation Stability study	HP5-14-604-001	Feb 2015	(b) (4)	O	O	O ^b
		P51710A	Process validation Stability study	HP5-14-604-002	Feb 2015	(b) (4)	O	O	O ^b
		P51712A	Process validation Stability study	HP5-14-604-004	Mar 2015	(b) (4)	O	O	O ^b

^a Not applicable

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

Reviewer comment: Both SB3 DS and DP lots were included in the analytical similarity assessment. Initially, the lots included were manufactured from various SB3 manufacturing processes including pilot scale (b) (4), clinical process (b) (4), and process validation (PV)/commercial process (b) (4). The material produced from the clinical and commercial processes are comparable, see discussion in Section 3.2.S.2.6. Three of the 5 DS lots (HP5-14-604-001, HP5-14-604-002, HP5-604-003) included in the similarity study were used to make multiple DP lots (the three PV DS lots were used to make the six PV DP lots), which were also included in the similarity assessment. For tier 1 attributes, independent lots of DS and DP were analyzed (see additional discussion regarding lot selection for tier 1 analysis below); however, it appears that DP lots derived from the same DS lots, as well as the originating DS lots, were analyzed for certain tier 2 attributes. An IR was sent to Samsung requesting that only independent lots of SB3 (either DS or DP) be include in the analytical similarity assessment, because the majority of the variability of the critical quality attributes studied is derived from DS manufacturing.

The non-independent lots were removed from the analysis, as well as the SB3 pilot scale DP lot, (b) (4)-002175, which was not representative of the clinical or commercial SB3 lots (based on data provided in Section 3.2.R.4), and therefore, not appropriate for inclusion in the tier 1 analysis to support the analytical similarity assessment (IRs dated 3/29/18 and 4/9/18).

Furthermore, throughout the analytical similarity assessment, various lots and different numbers of SB3, US-Herceptin and EU-Herceptin lots were included for certain attribute analysis. However, no justification was provided for lot selection. In IR response dated 5/29/18, Samsung stated that the number of US-Herceptin and EU-Herceptin lots used to evaluate a specific quality attribute were selected considering the statistical tier, the amount of material available, expiration date, and if the lot was representative of the historical data used for setting the similarity ranges (i.e., the three representative lots of US- and EU-Herceptin used in the side-by-side graphical representations). Scatter plot analysis comparing the historical Herceptin lot data points to the US- and EU-Herceptin lots selected for the side-by-side analysis for anti-proliferation and ADCC activity were provided in the IR response. Although only three lots were included in the side-by-side analysis, a complete set of data for all of the lots analyzed in the similarity assessment were included in the Appendix of Section 3.2.R. The lot selection justification is acceptable.

The following table (prepared by reviewer) summarizes the lots of US-Herceptin (420 mg), EU-Herceptin (150 mg), and SB3 (150 mg) used in the pivotal comparative clinical PK study, SB3-G11-NHV, and the supportive efficacy study, SB3-G31-BC. Lots highlighted in yellow were included in the analytical similarity assessment.

	Clinical Study SB3-G11-NHV (3-way comparative)	SB3-G31-BC (2-way comparative)
US-Herceptin lot (420 mg)	554761	---
EU-Herceptin lot (150 mg)	H4259B01	H4278B02, H4267B06, H4288B02, N1003B01, H4384B01, H4125B02U1, H4384B05, H4385B02, H4424B02, H4373B01, N1017B03, H4440B02, H4518H01, N1030H05, N1029H02, N1034H02, H4561H02, H4577H03, H4586H05, H4560H04, H4561H03, H4544H07, N1037H01, H4595H01, N1041H02
SB3 (150 mg)	P51703A	P51703A, P51704A, P51705A, P51706A, P51707A, P51714A, P51715A

Reviewer comment: One lot each of US-Herceptin, EU-Herceptin and SB3 were administered in the pivotal comparative clinical PK study, of which only EU-Herceptin lot H4259B01 was included in the analytical similarity assessment. It is the Agency’s expectation that lots used in the clinical studies also be included in the similarity assessment to provide a link between the analytical and clinical data, and to facilitate the interpretation of the data. Samsung was requested to provide all available analytical data for lots used in the PK similarity and the comparative clinical study in the analytical similarity assessment (IR dated 3/29/18). In the response, Samsung stated that the lots selected for use in the clinical or similarity assessment were based on the internal purchasing and delivery system and did not submit additional analytical data. Furthermore, of the 11 EU-Herceptin lots included in both the clinical and analytical studies, 7 were identified as having a different quality attribute profile with respect to ADCC activity that correlates with the expiry date of the lot, as compared to other

evaluated batches. Based on the trend analysis information included in the IR response (Figure 1, response to IR dated 3/29/18), it appears that the historical range of potency was captured by the lots of US-Herceptin and EU-Herceptin included in the analytical similarity assessment. Although US-Herceptin lot 554761 was not used in the analytical assessment, the trend analysis report suggests that the lot, and other lots with similar expiry periods, may have similar potency profiles. Several lots with expiry periods close to lot 554761 were included in the analytical similarity assessment; therefore, providing some link between the clinical and analytical similarity assessment data for US-Herceptin. The batch analysis data for SB3 lot P51703A (used in the clinical study but not the analytical similarity assessment) was leveraged to provide an analytical link between the other SB3 lots used in the similarity assessment and clinical data, which were manufactured using the same process (Section 3.2.P.5.4). Overall, the totality of the data submitted in the BLA will be considered in the interpretation of the link between the analytical and clinical similarity study data to support a demonstration of highly similar between SB3 and US-Herceptin.

Sample Formulation

The formulation of SB3 150 mg is the same as US-Herceptin 150 mg and EU-Herceptin. The reconstitution volume of US-Herceptin 150 mg is 7.4 ml to yield a solution containing 21 mg/ml trastuzumab that delivers 7.14 ml of 150 mg trastuzumab. The reconstitution volume of EU-Herceptin (150 mg) is 7.2 ml to yield a 7.4 ml solution containing 21 mg/ml trastuzumab to deliver 150 mg trastuzumab.

Reviewer comment: Samsung stated that SB3 150 mg lots were developed to be consistent with the EU-Herceptin material, without the understanding that the US-Herceptin 150 mg lots (7.4 ml) have a different reconstitution volume compared to the EU-Herceptin lots (7.2 ml). Therefore, the SB3 lots used in the similarity assessment were reconstituted using the same volume as the EU-Herceptin lots (7.2 ml). During the Type 4 meeting the FDA stated that the approach was acceptable for the analysis of quality attributes that may not be impacted by the differential reconstitution volumes; however, the evaluation of protein concentration may be impacted by the different volumes. The additional data for the SB3 PVR lots produced using the revised DP process and the US-Herceptin 150 mg were provided to address these differences.

Results of Analytical Similarity Assessment

Research Reference Standards (RRSs)

Section 3.2.S.5.4 indicates that four RRSs were used across the analytical similarity assessment, all of which were lots of EU-Herceptin (RRS1 – (b) (4); RRS2 - (b) (4); RRS3 - (b) (4); RRS4 – (b) (4)) for assay where values are reported relative to a RRS (antiproliferation, ADCC activity, HER2 binding, FcγRIIIa binding, FcRn binding, C1q binding, FcγRIa binding, FcγRIIa binding, FcγRIIb binding). Physicochemical and biological data were provided as part of the qualification of each RRS (Section 3.2.S.5.4, Tables 43-44). Each RRSs was qualified against the previous RRS and the qualification acceptance criteria were different across each RRS. Additionally, conversion factors were applied to the binding activity values when qualification results were outside of the acceptance ranges. The following table, prepared by the reviewer, summarizes the qualification acceptance criteria and potency values assigned to each RRS.

	RRS1		RRS2		RRS3		RRS4	
	Acceptance Criteria	Result	Acceptance Criteria	Result	Acceptance Criteria	Result	Acceptance Criteria	Result
ADCC	N/A	N/A	(b) (4)	88%	(b) (4)	97%	(b) (4)	107%
Antiproliferation	N/A	N/A		112%		102%		98%
HER2	N/A	N/A		93%		100%		99%

Reviewer comment: Multiple IRs were conveyed to Samsung regarding the use of the four RRSs across the analytical similarity assessment. In response, Samsung provided a detailed list of the RRS lots used in each biological activity assay for each SB3, US-Herceptin and EU-Herceptin lots included in the similarity assessment,

indicating that more than one RRS was used to evaluate a particular attribute. The response also summarized the qualification approach taken for the multiple RRSs and indicated that only RRS3 and RRS4 were qualified using multiple replicates (i.e., at least 15). Insufficient information was provided to support a bridge across all four RRSs, to allow for the data to be pooled (response to IR dated 3/29/18). To determine what data could be pooled the qualification strategy used (i.e., number of replicates) and the resulting data values were considered. Considering the data provided (summarized above) and the qualification program used at the time of the RRS2 implementation (e.g., insufficient replicates and inappropriate acceptance criteria), a bridge was not established between RRS1 and RRS2. RRS3 was qualified against RRS2 using at least 15 replicates, and similarly, RRS4 was qualified against RRS3 (using at least 15 replicates); the results of these qualifications indicate that the potency values were relatively consistent across RRS2, RRS3 and RRS4. Taking each RRS qualification method and the corresponding results into consideration it was determined that a sufficient bridge was established between RRS2, RRS3, and RRS4 and the analytical similarity data generated using these RRSs could be pooled. Because insufficient data and information were provided to support a bridge between RRS2 and RRS1, the data generated using RRS1 could not be pooled with data from the other three RRSs, and Samsung was requested to remove these data from the similarity assessment (i.e., for the product quality attributes where data are evaluated against an RRS). The analytical similarity data evaluated below include lots analyzed against RRS2, RRS3, and RRS4, where applicable (i.e., antiproliferation, ADCC activity, HER2 binding, Fcγ receptor binding, FcRn binding, and C1q binding). IRs related to the RRSs are dated 3/29/18, 6/29/18, and 7/19/18.

Presentation of data

Tier 1: The quality attributes are subjected to equivalence testing. The data are presented in a side-by-side scatter plot comparing all SB3, US-Herceptin, and EU-Herceptin lots evaluated (actual data points included in the appendix to Section R.4). The results of the equivalence testing were provided in graphical and tabular format.

Tier 2 and Tier 3: The quality attributes included in the tier 2 analysis are evaluated using one- or two-sided QR analysis. The graphical analysis presented for each attribute considers 8 lots of SB3 (clinical DP and PVR DS and DP batches) compared to three lots each of US-Herceptin and EU-Herceptin in a side-by-side manner (the selection of the lots included in the side-by-side analysis was discussed above), as well as a summary of the specific data points for the lots included in the graphical analysis. The QRs were established by the entire data set of US-Herceptin and EU-Herceptin lots evaluated (details of the data values for each independent lot contributing to the QR is included in the Appendix to Section 3.2.R.4). The quality attributes included in the tier 3 analysis are compared graphically or in tabular format in a side-by-side manner with no statistical analysis applied.

Reviewer comment: The data presented below are grouped and discussed according to each quality attribute. A separate assessment of the equivalence testing for the tier 1 quality attributes was performed by the CMC-statistical reviewer (see CMC stats memo in Panorama).

Functional Activity

Antiproliferation -Tier 1

The ability of 8 lots of SB3, 46 lots of US-Herceptin, and 61 lots of EU-Herceptin to inhibit the proliferation of HER2 overexpressing human breast cancer cells (BT474 cells) was compared using an in vitro assay, and the data were statistically evaluated by equivalence testing. The relative potency values for SB3 lots (92-103%) are within the ranges of both the US-Herceptin (81-116%) and EU-Herceptin lots (80-114%), as shown in Table 8 and Figure 2 (below). The results from the equivalence test demonstrates that the two-sided confidence intervals of the mean differences of SB3 and US-Herceptin, SB3 and EU-Herceptin, and US-Herceptin and EU-Herceptin were within the equivalence acceptance criteria (EAC, Table 10, Figure 3 below).

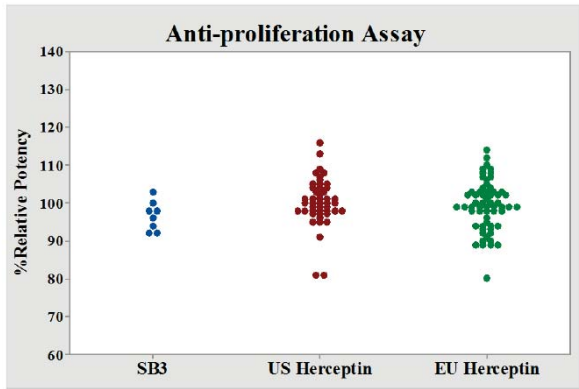


Figure 2: Result of Anti-proliferation Potency of SB3 and Herceptin®

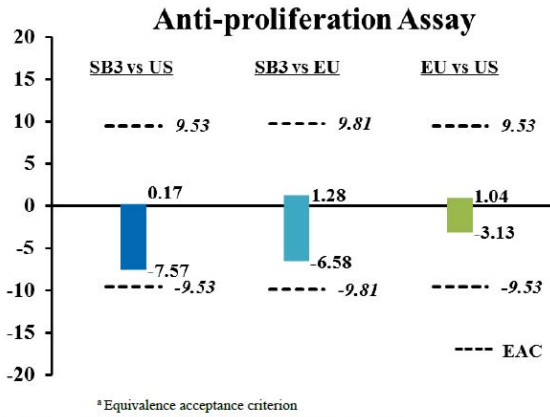


Figure 3: Equivalence Test of Anti-proliferation Potency

Reviewer comment: The evaluation of antiproliferation supports a demonstration of highly similar between SB3 and US-Herceptin, and the establishment of the analytical bridges among SB3, US-Herceptin, and EU-Herceptin.

ADCC – Tier 1

The ability of 8 lots of SB3, 48 lots of US-Herceptin, and 56 lots of EU-Herceptin to elicit ADCC activity in an in vitro assay using SKBR3, HER2 overexpressing breast cancer cells, as target cells, and a human natural killer (NK) cells line expressing CD16 as effector cells, was compared and statistically evaluated by equivalence testing. The relative potency values for the SB3 lots (86-104%) are within the ranges of both the US-Herceptin (44-133%) and EU-Herceptin lots (41-137%), as shown in Table 11 and Figure 4 (below). The results from the equivalence test demonstrates that the two-sided confidence intervals of the mean differences of SB3 and US-Herceptin, SB3 and EU-Herceptin, and US-Herceptin and EU-Herceptin were within the equivalence acceptance criteria (Table 13, Figure 5, below).

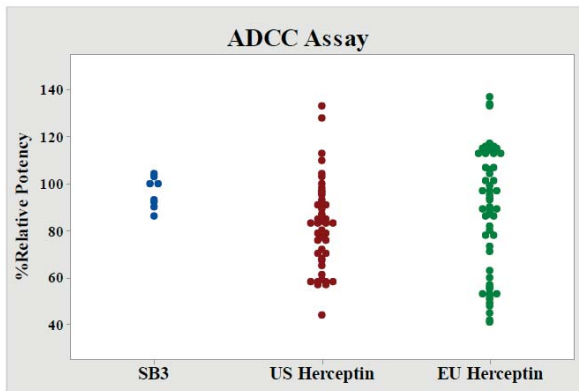


Figure 4: Result of ADCC Potency of SB3 and Herceptin®

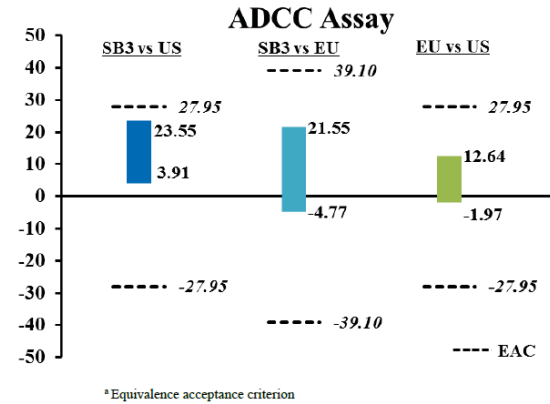


Figure 5: Equivalence Test of ADCC Potency

Reviewer comment: The evaluation of ADCC activity supports a demonstration of highly similar between SB3 and US-Herceptin, and the establishment of the analytical bridges among SB3, US-Herceptin, and EU-Herceptin.

In vitro Angiogenesis – Tier 3

In vitro angiogenesis was assessed by measuring the levels of VEGF present in the growth media 72 hours after BT474 cells were incubated with either SB3, US-Herceptin, and EU-Herceptin by ELISA. The in vitro assay was qualified for specificity, range, linearity, accuracy, and precision. The qualification summary indicates that the assay is qualified for its intended use (intermediate precision: 7-8%).

Two lots of SB3, and one lot each of US-Herceptin and EU-Herceptin were assessed for the ability of the product to reduce the amount of VEGF secreted in the growth media of BT474 cells, as a surrogate indicator of inhibition

of angiogenesis. The untreated control had 426 pg/ml of VEGF, while the assay treated with SB3 resulted in VEGF levels of 270-279 pg/ml, the US-Herceptin treated assay had VEGF detectable at 268 ng/ml, and the EU-Herceptin assay resulted in 283 ng/ml (Table 69, Figure 114). The amount of VEGF detectable in the treated samples were ~1.5 times lower than the amount observed in the untreated control sample.

Reviewer comment: *The lots included in the in vitro angiogenesis assay were very limited, but are generally acceptable for a tier 3 evaluation. The data are similar across all treatment groups, and the in vitro angiogenesis inhibition analysis supports a demonstration of highly similar between SB3 and US-Herceptin, and the establishment of the analytical bridge among SB3, US-Herceptin, and EU-Herceptin.*

Surface HER2 Expression Level – Tier 3

Cell surface HER2 levels were measured by flow cytometry. SKBR3 cells were incubated with either SB3, US-Herceptin or EU-Herceptin and labeled with phycoerythrin (PE)-conjugated IgG or PE anti-human CD340 (erbB2/HER2) antibody. The surface HER2 levels were measured by flow cytometry analysis. The assay was qualified for specificity, range, linearity, accuracy, and precision. The qualification summary indicates that the assay is qualified for its intended use (intermediate precision: 3-4%).

Two lots of SB3, and one lot each of US-Herceptin and EU-Herceptin were assessed for the ability to reduce HER2 cell surface expression on SKBR3 cells. The untreated control had a mean fluorescent intensity (MFI) of 16,282, the cells treated with SB3 had an MFI ranging from 8,585-8,698, the cells treated with US-Herceptin had an MFI of 8,430, and the cells treated with EU-Herceptin had an MFI of 8,755 (Table 70, Figure 115). The amount of cell surface HER2 expressed in the treated samples were ~2 times lower than the amount observed in the untreated control sample.

Reviewer comment: *The data are similar across all treatment groups, and the cell surface HER2 expression analysis supports a demonstration of highly similar between SB3 and US-Herceptin, and the establishment of the analytical bridge among SB3, US-Herceptin, and EU-Herceptin.*

HER2 Extracellular Domain (ECD) – Tier 3

Shedding of HER2 can be induced by treatment with 4-aminophenylmercuric acetate (APMA). The ability of the SB3, US-Herceptin, and EU-Herceptin to block HER2 shedding was measured by treating SKBR3 cells with APMA and drug. Soluble HER2 shed into the growth media was measured by ELISA. The assay was qualified for specificity, linearity, and precision. The qualification summary indicates that the assay has an intermediate precision of up to 21%.

Two lots of SB3, and one lot each of US-Herceptin and EU-Herceptin were assessed for the ability to reduce HER2 ECD shedding. The untreated control had a HER2 ECD shedding level of 24.6 ng/ml, the cells treated with SB3 had levels ranging from 13.5-14.4 ng/ml, the cells treated with US-Herceptin had a level of 14.3 ng/ml, and the cells treated with EU-Herceptin had a level of 14.9 ng/ml (Table 71, Figure 116). The amount of cell surface HER2 expressed in the treated samples were ~2 times lower than the amount observed in the untreated control sample.

Reviewer comment: *The qualification summary indicates that the precision of the assay is poor, 3-21%; however, the levels of HER2 ECD shedding inhibition was similar across the three products tested. The analysis supports a demonstration of highly similar between SB3 and US-Herceptin, and the establishment of the analytical bridge among SB3, US-Herceptin, and EU-Herceptin.*

Inhibition of AKT phosphorylation (pAKT) – Tier 3

The downregulation of pAKT at serine 473 was measured as a surrogate for inhibition of proliferation of SKBR3 cells treated with or without SB3, US-Herceptin or EU-Herceptin. Cells were incubated with drug, lysed with phosphatase inhibitors and harvested, and the levels of pAKT was measured by ELISA. The assay was qualified

for specificity, linearity, and precision. The qualification summary indicates that the assay is qualified for its intended use (intermediate precision: 7-8%).

Two lots of SB3, and one lot each of US-Herceptin and EU-Herceptin were assessed for the ability to downregulate the pAKT expression of SKBR3 cells. The untreated control pAKT level was 100% of the control, the cells treated with SB3 had a pAKT expression of 75%, the cells treated with US-Herceptin had a pAKT expression of 74%, and the cells treated with EU-Herceptin had pAKT expression of 86% (Table 72, Figure 117). The amount of pAKT expressed in the treated samples were ~25% lower than the amount observed in the untreated control sample.

Reviewer comment: *The data are similar across all treatment groups, and the pAKT expression analysis supports a demonstration of highly similar between SB3 and US-Herceptin, and the establishment of the analytical bridge among SB3, US-Herceptin, and EU-Herceptin.*

Combination treatment with chemotherapy – Tier 3

The antiproliferation assay was used to evaluate the synergistic antiproliferative activity of SB3, US-Herceptin, and EU-Herceptin when treated in combination with docetaxel. The data were analyzed using Compusyn software and a combination index (CI) was calculated.

Two lots of SB3, and one lot each of US-Herceptin and EU-Herceptin were assessed for the synergistic inhibition of proliferation of SKBR3 cells. The CI was from 0.56-0.70 0.69 and 0.57 for SB3, US-Herceptin and EU-Herceptin, respectively (Table 73, Figure 118).

Reviewer comment: *The qualification summary indicates that the precision of the assay is poor when evaluating the combination treatment, 24-39%; however, the CI values reported for the three products are similar. The analysis supports a demonstration of highly similar between SB3 and US-Herceptin, and the establishment of the analytical bridge among SB3, US-Herceptin, and EU-Herceptin.*

Complement-dependent cytotoxicity (CDC) – Tier 3

CDC activity was investigated by incubating SKBR3 cells with increasing concentrations (0-25 µg/ml) of SB3, US-Herceptin, or EU-Herceptin in the presence of human serum as the source for complement. A TNF-α expressing Jurkat cell line and adalimumab were included as positive controls. CDC activity was assessed by enzyme-based luminescence detection. Two lots of SB3, and one lot each of US-Herceptin and EU-Herceptin showed no signal at any of the concentrations evaluated for CDC activity, as compared to the positive control samples (Table 74), where dose response curves were shown (Figure 119).

Reviewer comment: *Limited information was provided regarding the suitability of the CDC assay; however, considering the positive controls and various concentrations of drugs evaluated in the assay, as well as the resulting dose-response curves, it appears that the method is suitable for the one-time assessment of CDC activity. The results show no CDC activity among SB3, US-Herceptin, and EU-Herceptin, which is not an expected mechanism of action of trastuzumab.*

Binding Properties

HER2 -Tier 2

Eight lots of SB3, 53 lots of US-Herceptin, and 57 lots of EU-Herceptin were evaluated for HER2 binding activity by FRET assay (Table 38, Figure 64). The HER2 binding activity of the SB3 lots had a range of 93-104% and were within the US-Herceptin QR (86-113%) and the EU-Herceptin QR (87-110%). The binding activity range of the EU-Herceptin lots was 89-108% (Table 131) and were also within the QR of the US-Herceptin lots (Table 129). The binding activity values are consistent among all lots evaluated across all three products.

Reviewer comment: *The evaluation of HER2 binding supports a demonstration of highly similar between SB3 and US-Herceptin, and the establishment of the analytical bridges among SB3, US-Herceptin, and EU-Herceptin.*

FcRn -Tier 2

FcRn binding was performed using a bead-based amplified luminescence proximity homogenous assay screen method (AlphaScreen). Beads (donor or acceptor) were coated with either the drug (i.e., SB3, US-Herceptin, EU-Herceptin) or streptavidin. FcRn was tagged with biotin, and incubated in a mixture with the donor and acceptor beads. Competitive inhibition of the interaction of the donor and acceptor beads by the biotin-labeled FcRn based on interaction of FcRn with the Fc-region of the drug, was measured fluorescently and analyzed using PLA software to calculate binding activity. The qualification summary results indicate that the assay is specific and accurate within a range of 50-150%, with intermediate precision of 5-12% and repeatability of 3%.

Eight lots of SB3, 54 lots of US-Herceptin, and 78 lots of EU-Herceptin were evaluated for FcRn binding activity by AlphaScreen (Table 39, Figure 65). The FcRn binding activity of the SB3 lots had a range of 82-109% and were within the US-Herceptin QR (64-111%) and the EU-Herceptin QR (59-127%). The binding activity range of the EU-Herceptin lots was 69-121% (Table 131) resulting in 6 out of the 78 lots evaluated being outside of the upper US-Herceptin QR limit, which was based on binding activity values of 72-109% (Table 129).

Reviewer comment: *The FcRn binding activity values for the SB3 lots fall within the QR for both US- and EU-Herceptin, while six lots of EU-Herceptin are slightly above the US-Herceptin QR. The difference between the upper limit of the US-Herceptin and EU-Herceptin QRs is only 8%, due to the slight increase in activity detected for the six EU-Herceptin lots. An assessment of the data generated for each product indicates that there is lot-to-lot variability in FcRn binding activity; the variability is greater among the US- and EU-Herceptin lots as compared to the SB3 lots, which is likely due to the larger number of lots assessed for the two products. Overall, the magnitude of the difference between the US- and EU-Herceptin lots, combined with the expected assay variability, is unlikely to result in a potential clinical difference. The evaluation of FcRn binding activity supports a demonstration of highly similar between SB3 and US-Herceptin, and the establishment of the analytical bridge among SB3, US-Herceptin, and EU-Herceptin.*

FcγRIIIa (158V/V) – Tier 2

Eight lots of SB3, 57 lots of US-Herceptin, and 78 lots of EU-Herceptin were evaluated for the binding activity to the high affinity FcγRIIIa isoform V₁₅₈, using the AlphaScreen assay (Table 40, Figure 66). The FcγRIIIa binding activity of the SB3 lots had a range of 86-109% and were within the US-Herceptin QR (29-137%) and the EU-Herceptin QR (31-145%). The binding activity range of the EU-Herceptin lots was 43-127%, and were also within the QR of the US-Herceptin lots, which had a binding activity range of 50-128% (Table 129).

Reviewer comment: *The range of FcγRIIIa binding activity was wide for both the US-Herceptin and EU-Herceptin lots, which resulted in correspondingly wide QRs; however, the results for the SB3 lots are within the ranges of the US-Herceptin and EU-Herceptin lots. The variability observed in ADCC activities of both the US-Herceptin and EU-Herceptin lots was correlated to lower binding activities of a subset of lots with similar expiry periods. While the binding activities of the SB3 lots exhibited only minor variability, likely due to expected inherent assay variability (i.e., assay precision of 6-14%), and appeared to be consistent with most of the US-Herceptin and EU-Herceptin lots evaluated overtime (i.e., not reflective of the variable profile observed in the subset of US- and EU-Herceptin lots). Both the ADCC and the FcγRIIIa binding data demonstrate statistical equivalence and similarity, respectively, among the three products. The observed variability does not preclude a determination of highly similar between US-Herceptin and SB3 or establishment of the analytical bridge among SB3, US-Herceptin, and EU-Herceptin.*

FcγRIa – Tier 3

Eight lots of SB3, three lots of US-Herceptin, and three lots of EU-Herceptin were evaluated for the binding activity to FcγRIa isoform by FRET. The FcγRIa binding activity of the SB3 lots ranged from 92-105%, the US-Herceptin lots ranged from 102-106%, and the EU-Herceptin lots ranged from 97-100% (Table 65, Figure 110).

Reviewer comment: *The minor variability observed across the lots is likely due to inherent assay variability, but the overall data show similar ranges. The evaluation of the FcγRIa binding activity supports a demonstration of highly similar between SB3 and US-Herceptin, and establishment of the analytical portion of the scientific bridges among SB3, US-Herceptin, and EU-Herceptin.*

FcγRIIa – Tier 3

Eight lots of SB3, three lots of US-Herceptin, and three lots of EU-Herceptin were evaluated for the binding activity to FcγRIIa isoform by AlphaScreen. The FcγRIIa binding activity of the SB3 lots ranged from 84-98%, the US-Herceptin lots ranged from 102-107%, and the EU-Herceptin lots ranged from 98-106% (Table 66, Figure 111).

Reviewer comment: *The binding activities of the SB3 lots were slightly lower than the US-Herceptin and EU-Herceptin lots; however, based on the lower criticality of this quality attribute with respect to its potential contribution to the initiation of ADCC activity, the observed differences do not preclude a determination of highly similar between SB3 and US-Herceptin, and establishment of the analytical portion of the scientific bridges among SB3, US-Herceptin, and EU-Herceptin.*

FcγRIIb – Tier 3

Eight lots of SB3, three lots of US-Herceptin, and three lots of EU-Herceptin were evaluated for the binding activity to FcγRIIb isoform by AlphaScreen. The FcγRIIb binding activity of the SB3 lots ranged from 87-104%, the US-Herceptin lots ranged from 103-108%, and the EU-Herceptin lots ranged from 95-105% (Table 67, Figure 112).

Reviewer comment: *The binding activities of most of the SB3 lots were slightly lower than the US-Herceptin lots; however, based on the lower criticality of this quality attributes with respect to its potential contribution to the initiation of ADCC activity, the observed differences do not preclude a demonstration of highly similar between SB3 and US-Herceptin, and support the establishment of the analytical portion of the scientific bridges among SB3, US-Herceptin, and EU-Herceptin.*

FcγRIIIb – Tier 3

Eight lots of SB3, three lots of US-Herceptin, and three lots of EU-Herceptin were evaluated for the binding activity to FcγRIIIb isoform by surface plasmon resonance (SPR). The precision of the SPR assay was qualified to be 8%. The FcγRIIIb binding affinity (equilibrium constant - K_D) of the SB3 lots ranged from 7.79×10^{-6} – 8.96×10^{-6} M, the US-Herceptin lots ranged from 7.70×10^{-6} – 8.93×10^{-6} M, and the EU-Herceptin lots ranged from 8.72×10^{-6} – 8.80×10^{-6} M (Table 68, Figure 113).

Reviewer comment: *The detailed description of the experimental design using the SPR assay was not provided, but SPR is a method commonly implemented for the evaluation of binding kinetics. The FcγRIIIb binding kinetics data show similar ranges in the binding kinetics across all three products. The overall evaluation of FcγRIIIb binding kinetics supports a demonstration of highly similar between SB3 and US-Herceptin, and establishment of the analytical portion of the scientific bridges among SB3, US-Herceptin, and EU-Herceptin.*

C1q -Tier 2

C1q binding was performed using a sandwich ELISA-based assay. The qualification summary results indicate that the assay is specific and accurate, with binding detectable within a range of 50-150%, and an intermediate precision of 1-3%.

Eight lots of SB3, 70 lots of US-Herceptin, and 53 lots of EU-Herceptin were evaluated for C1q binding activity by ELISA (Table 41, Figure 67). The C1q binding activity of the SB3 lots had a range of 88-104% and were within the US-Herceptin QR (74-121%) and the EU-Herceptin QR (78-118%). The binding activity range of the EU-Herceptin lots was 80-109% (Table 131), and were also within the QR of the US-Herceptin lots which was based on binding activity values of 79-109% (Table 128). The binding activity values are consistent among all lots evaluated across all three products.

Reviewer comment: *The evaluation of C1q binding supports a demonstration of highly similar between SB3 and US-Herceptin, and the establishment of the analytical bridge among SB3, US-Herceptin, and EU-Herceptin.*

Quantity

Reconstituted Protein concentration – Tier 2

The protein concentration of 6 lots of SB3 DP 150 mg, 47 lots of US-Herceptin 420 mg, and 52 lots of EU-Herceptin 150 mg, were determined using UV absorbance at 280 nm and the extinction coefficient of 1.50 mg/mg·cm for trastuzumab (see discussion on the adequacy of the extinction coefficient determination below). The lyophilized DP vials were reconstituted with sterile WFI using 7.2 ml for the SB3 and EU-Herceptin lots, and 20 ml for the US-Herceptin lots. The protein concentration ranged from 20.1-21.4 mg/ml for SB3 (Table 37), 20.0-22.3 mg/ml for US-Herceptin (Table 128), and 20.6-22.1 mg/ml for EU-Herceptin (Table 130). The SB3 lots were within the US-Herceptin QR of 19.3-22.8 and the EU-Herceptin QR of 20.1-22.1; the EU-Herceptin lots were also within the US-Herceptin QR (Figure 63).

Reviewer comment: *While the protein concentration of SB3 150 mg lots were within the QRs established from both the US-Herceptin 420 mg and the EU-Herceptin 150 mg, it is not appropriate to use results comparing US-Herceptin 420 mg to SB3 150 mg to support the similarity of protein concentration between US-Herceptin 150 mg and SB3 150 mg, because the filling process, lyophilization process, reconstitution volumes, etc., are specific for each presentation. As such, analytical data between SB3 150 mg and US-Herceptin 150 mg were provided in the BLA providing a comparison of reconstitution volume, reconstituted protein concentration, total protein content per vial, and recoverable protein content for six SB3 PVR DP lots and three US-Herceptin 150 mg lots. The six SB3 DP batches were produced from three SB3 DS batches. Of the duplicate DP batches, each were processed using two separate lyophilizers. Considering that the intent of the comparative assessment of the select quality attributes is to elucidate any potential difference in attributes impacted by the DP manufacturing process, such as lyophilization, the use of the duplicate DP batches in the assessment is acceptable. The data showed that the reconstituted protein concentration from SB3 150 mg lots of 19.6-21.1 mg/ml was lower than the US-Herceptin 150 mg lots of 21.8-21.9 mg/ml. These data do not support that protein concentration is similar between the two products and therefore, Samsung was requested (IR dated 12/4/17) to provide additional protein concentration data to support the similarity of SB3 150 mg to US-Herceptin 150 mg using an appropriately justified number of lots. Furthermore, the recoverable protein content values for five of the six SB3 PVR DP batches ranged from 140-149 mg, which does not support that SB3 can consistently deliver at least 150 mg/vial to meet the label claim expectations (i.e., 150 mg) for licensure in the US as a proposed biosimilar to US-Herceptin 150 mg (recoverable protein content of the three lots, 156-157 mg). Samsung was also requested to modify their DP manufacturing process and control strategy to ensure the appropriate deliverable volume and protein concentration after reconstitution to meet the label claim (IR sent 12/4/17). In response, Samsung committed to (b) (4)*

in order to ensure that the reconstituted DP protein concentration will support the analytical similarity between SB3 150 mg and US-Herceptin 150 mg and recoverable content per vial will meet the expected label claim. Also, Samsung produced 3 lots of SB3 using a revised DP control strategy (see detailed discussion in Section 3.2.P) and evaluated the lots for reconstituted protein concentration in a head to head comparison to 8 US-Herceptin 150 mg lots, as well as reconstituted volume and recoverable protein content per vial. The following data were provided in response to IR dated July 30, 2018. Additional similarity studies were also performed based on a selection of product quality attributes determined by risk assessment between SB3 150 mg and US-Herceptin 150 mg (see discussion in corresponding section below).

Reconstituted Protein concentration (Tier 2) of SB3 150 mg (PVR batches from revised DP process) and US-Herceptin 150 mg

Three lots of SB3 produced from the updated DP manufacturing process (lots P1803011, P1803012, P1803013) and eight lots of US-Herceptin 150 mg were reconstituted with 7.4 ml of SWFI and analyzed for protein concentration (Table 126, Figure 165). Although requested, a Tier 2 analysis was not performed for protein concentration using the QR based on the US-Herceptin 150 mg lot analysis, but the QR was determined by the product quality reviewer based on a 3SD calculation of the US-Herceptin data provided in Table 126. The protein concentration of the SB3 DP lots (ranged from 22.0-22.4 mg/ml) was within the QR (19.7-22.9 mg/ml) for the US-Herceptin 150 mg lots (ranged from 20.3-21.9 mg/ml).

Reviewer comment: The SB3 lots have slightly higher reconstituted protein concentration compared to the US-Herceptin 150 mg lots, but the values for protein concentration fall within the US-Herceptin QR (either 2SD or 3SD). The data confirm that the reconstituted protein concentration in the SB3 vials manufactured using the revised DP manufacturing process are similar to the US-Herceptin 150 mg vials, and the overall protein content evaluation supports the analytical similarity between the two products. Refer to Section 3.2.P for the review of information and IR responses related to recoverable protein content.

Extinction Coefficient -Tier 3

The extinction coefficients of SB3 (PVR DS batch HP5-14-604-001), US-Herceptin (lot 512895), and EU-Herceptin (lot H4196B02) were experimentally determined by amino acid analysis in triplicate (Table63). The absorption at 1 mg/ml for SB3 ranged from 1.42-1.57 mg/ml and an average of 1.49 mg/ml, US-Herceptin from 1.46-1.61 and an average of 1.53 mg/ml, and EU-Herceptin from 1.43-1.50 and an average of 1.48 mg/ml. The extinction coefficient implemented for SB3 and throughout the similarity assessment was 1.50 mg/ml, which is the average absorption of the extinction coefficients experimentally determined for all three products.

Reviewer comment: The value for each product (averaged from the triplicate analyses) were consistent. The extinction coefficient determination and value used is acceptable.

Purity and impurities

Size-exclusion High-performance Liquid Chromatography (SE-HPLC) - Tier 2

Eight lots of SB3, 65 lots of US-Herceptin, and 81 lots of EU-Herceptin were evaluated for HMWS, monomer, and low molecular weight species (LMWS) by SE-HPLC. Representative chromatograms (full and expanded view) were provided for the eight SB3 lots, and each of the three US-Herceptin and EU-Herceptin lots included in the head-to-head analysis (Figure 7). The chromatograms had similar profiles. Tabular data were provided only for % HMWS, and the ranges are as follows: SB3: 0.4-1.1% (Table 15), US-Herceptin: 0.3-0.7% (Table 128), and EU-Herceptin: 0.3-0.7% (Table 130). Three of the SB3 lots were above the upper limit of the US-Herceptin (0.2-0.8%) and EU-Herceptin (0.2-0.8%) QRs (Figure 8).

Reviewer comment: The data show marginally higher HMWS in three SB3 lots compared to the US-Herceptin and EU-Herceptin lots. Additionally, the % monomer and %LMWS were not reported in the size variant analysis. However, considering the chromatograms provided, which show consistent monomer peaks, as well as the orthogonal evaluation of aggregates by SE-HPLC/multi-angle laser light scattering (SE-HPLC/MALLS, see discussion below), which show similar amounts of aggregates and consistent amounts of monomer peak, the evaluation is sufficient. The overall assessment of size variants supports a demonstration of highly similar between SB3 and US-Herceptin, and the establishment of the analytical bridges among SB3, US-Herceptin, and EU-Herceptin.

SE-HPLC/MALLS – Tier 3

The molar mass and % area of monomer and HMWS were evaluated for two lots of SB3, and one lot each of US-Herceptin and EU-Herceptin by SE-HPLC/MALLS. Chromatograms (full and expanded view) were provided for

each lot (Figure 102). The chromatograms had similar profiles. Tabular data were provided and the % area for HMWS and monomer are as follows: SB3: HMWS: 0.534-0.974%, monomer: 99.0-99.5%; US-Herceptin: HMWS: 0.525%, monomer: 99.5%; EU-Herceptin: HMWS: 0.485%, monomer: 99.5% (Table 59).

Reviewer comment: *The molecular mass assessment of size variants supports the overall demonstration of highly similar between SB3 and US-Herceptin, and the establishment of the analytical bridges among SB3, US-Herceptin, and EU-Herceptin.*

Sedimentation Velocity-Analytical Ultracentrifugation (SV-AUC) – Tier 3

HMWS formation was analyzed by SV-AUC as an orthogonal approach to SE-HPLC. The sedimentation coefficient and % areas were provided for monomer and HMWS for two lots of SB3, and one lot each of US-Herceptin and EU-Herceptin. Chromatograms (full and expanded view) were provided for each lot (Figure 103) and tabular data were provided as follows: SB3: HMWS: 1.49-3.47%, monomer: 96.53-98.51%; US-Herceptin: HMWS: 2.44%, monomer: 97.57%; EU-Herceptin: HMWS: 1.52%, monomer: 98.49%. The sedimentation coefficients, frictional ratios, and molecular weights were consistent across all lots for monomer and HMWS (Tables 60 and 61).

Reviewer comment: *The SV-AUC analysis shows similar size variants among the three products and the results are consistent with the SE-HPLC analysis. The SV-AUC data supports the overall demonstration of highly similar between SB3 and US-Herceptin, and the establishment of the analytical bridges among SB3, US-Herceptin, and EU-Herceptin.*

Capillary Electrophoresis-Sodium Dodecyl Sulfate (CE-SDS) reduced – Tier 2

The CE-SDS method involves preparing samples in SDS buffer, alkylated with iodoacetamide, and reducing the protein using 2-mercaptoethanol and analyzed by CE. The method was qualified for specificity, range, linearity, accuracy, precision, quantitation limit, and robustness for the detection of light chain (LC) peak, heavy chain (HC) peak, and non-glycosylated heavy chain (NGHC) peak. The qualification summary indicates that the method is suitable for its intended use.

Eight lots of SB3, 65 lots of US-Herceptin, and 81 lots of EU-Herceptin were evaluated for % main (sum of %HC + %LC) and % NGHC by CE-SDS reduced. Representative chromatograms (full and expanded view) were provided for the eight SB3 lots, and each of the three US-Herceptin and EU-Herceptin lots included in the head-to-head analysis (Figure 10). The chromatograms had similar profiles. The ranges of % main and % NGHC are as follows: SB3, main: 97.5-97.8%, NGHC: 1.0-1.3% (Table 16); US-Herceptin, main 97.4-99.2%, NGHC: 0.4-1.2% (Table 128), and EU-Herceptin: main: 97.4-99.4%, NGHC: 0.4-1.1% (Table 130). For % main (Figure 11), five SB3 lots, two US-Herceptin lots, and two EU-Herceptin lots were below the lower limit of the EU-Herceptin QR (97.7-100.1%), while all lots were within the US-Herceptin QR (97.3-100.0%). For % NGHC (Figure 12), two lots of SB3 were higher than the upper limit of the EU-Herceptin QR (0.2-1.1%), and one lot of SB3 was higher than the upper limit of the US-Herceptin QR (0.2-1.2%).

Reviewer comment: *The SB3 lots with marginally higher NGHC had a correlative slight decrease in the sum of HC and LC. The amount of NGHC has the potential to impact product efficacy through ADCC activity; however, the overall content of NGHC is low among all three products, and the statistical equivalence in ADCC among SB3, US-Herceptin, and EU-Herceptin has been demonstrated (Figure 5). The minor difference in NGHC does not preclude a demonstration of highly similar.*

Overall, the CE-SDS reduced data supports the demonstration of highly similar between SB3 and US-Herceptin, and the establishment of the analytical bridges among SB3, US-Herceptin, and EU-Herceptin.

CE-SDS non-reduced – Tier 2

The CE-SDS method involves preparing samples in SDS buffer, alkylated with iodoacetamide and analyzed by CE. The method was qualified for specificity, range, linearity, accuracy, precision, quantitation limit, and robustness for the detection of main peak. The qualification summary indicates that the method has been suitably qualified for detection of main peak; however, no information was provided to support its use in detecting the 2H1L protein fragment, which is quantitated in the analytical similarity assessment.

Eight lots of SB3, 65 lots of US-Herceptin, and 81 lots of EU-Herceptin were evaluated for % IgG and % 2H1L fragment by CE-SDS non-reduced. Representative chromatograms (full and expanded view) were provided for the eight SB3 lots, and each of the three US-Herceptin and EU-Herceptin lots included in the head-to-head analysis (Figure 14). The representative SB3 chromatogram in Figure 13 indicates the detection of fragments other than 2H1L, including LC, HC, HH, and an unidentified impurity; however, 2H1L was stated to be the most abundant fragment and was the only impurity quantified and assessed using Tier 2 statistical analysis. Overall, the chromatograms have similar profiles, indicating low levels of impurities. The ranges of % IgG and % 2H1L are as follows: SB3, IgG: 97.0-97.6%, 2H1L: 1.5-1.8% (Table 17); US-Herceptin, IgG: 94.3-98.4%, 2H1L: 0.9-4.1% (Table 128), and EU-Herceptin: IgG: 93.8-98.5%, 2H1L: 0.9-4.3% (Table 130). For % 2H1L, all SB3 lots were within the US-Herceptin QR (0.0-3.3%), but 10 lots of EU-Herceptin and 2 lots of US-Herceptin were outside of the upper limit of the QR (Figure 16); all lots were within the EU-Herceptin QR (0.0-4.8%). For % IgG, all SB3 lots were within the US-Herceptin QR (95.4-100.0), but 13 lots of EU-Herceptin and 2 lots of US-Herceptin were outside of the lower limit of the QR (Figure 15); all lots were within the EU-Herceptin QR (93.1-100.7%).

Reviewer comment: *The SB3 lots evaluated were within both the US- and EU-Herceptin QRs, and the overall amount of the main fragment, 2H1L, was low ($\leq 1.8\%$). There were minor differences in the amounts of 2H1L, that corresponded to the differences in amount of IgG, with respect to the EU-Herceptin and US-Herceptin lots, where 84% and 88% of the EU-Herceptin batches were within the US-Herceptin QR for %2H1L and %IgG, respectively. However, the overall range of %IgG and %2H1L detected in the EU-Herceptin and US-Herceptin lots are similar. Chromatograms were provided for each SB3 lot and representative US- and EU-Herceptin lots, which showed similarly low levels of impurities. The overall assessment of fragmentation as determined by CE-SDS non-reduced supports a demonstration of highly similar between SB3 and US-Herceptin, and the establishment of the analytical bridges among the three products.*

Protein size characterization by Dynamic Light Scattering (DLS) – Tier 3

Two lots of SB3, and one lot each of US-Herceptin and EU-Herceptin were evaluated for subvisible particles in the nanometer size range and poly dispersity values by DLS. The average hydrodynamic diameter of the SB3 lots ranged from 7.5-7.8 nm, which were similar to the diameters of US-Herceptin (7.1 nm) and EU-Herceptin (7.8 nm). The polydispersity values for SB3 were 0.205-0.271, and were greater than the values reported for US-Herceptin of 0.183 and 0.174 for EU-Herceptin, indicating that the size distribution of the particles present in the SB3 lots is greater than that of the US-Herceptin and EU-Herceptin lots (Table 62).

Reviewer comment: *The variability observed in the polydispersity values among the three products may indicate differences in the distribution of subvisible particles, and will be discussed further in the micro-flow imaging (MFI) section below. However, considering that the variability is not substantial as well as the SD of each measurement (Table 62), the differences among the three products in polydispersity are not likely to be meaningful.*

Subvisible particle analysis by MFI – Tier 3

Subvisible particles in the size of ≥ 1 -25 μm were detected by MFI for two lots of SB3 and one lot each of US-Herceptin and EU-Herceptin. Distinction was made between round and not round particles and the overall particle sizes were reported and are summarized in the following table prepared by the reviewer. SB3 lots have higher amounts of subvisible particles in the range of ≥ 1 , 2, 5, and 10 μm compared to US-Herceptin and EU-Herceptin (Table 64, Figures 105-109).

	≥ 1 μm	≥ 2 μm	≥ 5 μm	≥ 10 μm	≥ 25 μm
SB3	143,886-200,218	63,641-98,236	12,861-21,089	1,080-1,342	23-29
US-Herceptin	110,888	42,477	6,517	470	24
EU-Herceptin	68,322	26,178	3,515	243	28

Reviewer comment: The limited number of SB3 lots evaluated may impact the assessment. Also, the differences in DP presentation (150 mg vs. 420 mg), reconstitution volume and sample processing may impact the formation and amount of subvisible particles. Control over subvisible particles are addressed as part of the SB3 DP manufacturing control strategy (see review memo for 3.2.P).

Glycan profile

N-Glycan analysis using 2-aminobenzamide (AB) labeling and hydrophilic interaction ultra-performance liquid chromatography (HILIC-UPLC) -Tier 2

The glycans of 8 lots of SB3, 65 lots of US-Herceptin, and 81 lots of EU-Herceptin were released by PNGase F treatment, labeled with 2-AB, separated and resolved using HILIC-UPLC. A representative chromatogram of the glycosylation profile of SB3 (Figure 17, below) shows nine peak groups identified: M3F, G0, G0F, M5, G1/G1', G1F/G1F', M6, G2, and G2F. Representative chromatograms were also provided for each of the SB3 lots, and the three representative US-Herceptin and EU-Herceptin lots selected for the head-to-head analysis (Figure 18).

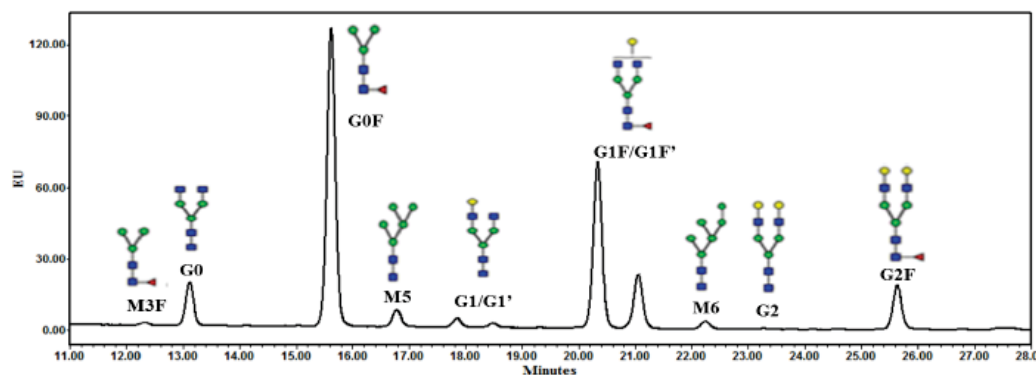


Figure 17: Representative N-Glycan Profile of SB3

Quantitative analysis was provided for % afucosylated + % high mannose (HM), % G0F, %G1F, and %G2F; however, the other glycoforms, detected in small abundance, were not included in the analysis (Table 18). Additionally, afucosylated glycans and HM species were reported as a single entity for the evaluation, however, because the isoforms have differential impacts on ADCC activity, as well as PK, they should be analyzed separately as two individual quality attributes. Samsung was requested to provide a separate analysis of the afucosylated and HM data (IR dated 5/29/18). The data are discussed below.

The QRs applied using 3SD resulted in a very wide QR, therefore, the data were independently reanalyzed using the US-QR based on 2SD. The majority of the glycoforms observed are G0F and G1F. The G0F (Figure 22) and G1F (Figure 23) content present in each of the SB3 lots are within the US-Herceptin QRs, while one lot each of US-Herceptin and EU-Herceptin were slightly above the upper limit of the US QR. All lots were within the US-Herceptin QR for G2F (Figure 24).

The total afucosylated glycans consist of G0, G1/G1', and G2. The range of % total afucose in the SB3 lots are 6.7-8.5%, for US-Herceptin are 4.5-8.8%, and for EU-Herceptin are 4.4-10.8%. When evaluating the data using the US-Herceptin QR based on 2SD of 4.7-9.1%, all lots of SB3 fall within the QR, but 2 EU lots are outside of

the lower limit and 4 are outside the upper limit of the QR; all SB3 and US-Herceptin lots are within the EU-Herceptin QR (Figure 19).

Reviewer comment: *Afucosylated glycans play a role in Fc-receptor binding and ADCC activity. The total afucosylated species of SB3 are within the US- and EU-Herceptin QRs, and several EU lots were slightly outside of the US-Herceptin QR. The range of % afucose of the SB3 lots is less variable than the US- and EU-lot ranges; however, the difference in the ranges are minor considering the ADCC data and the FcγRIIIa binding data that demonstrate statistical equivalence or similarity, respectively, among the three products. Overall the afucosylation data support a demonstration of highly similar between SB3 and US-Herceptin, and the establishment of the analytical portion of the scientific bridges among SB3, US-Herceptin and EU-Herceptin.*

The total HM species of SB3 lots ranged 3.7-5.4%, for US-Herceptin lots from 1.0-6.8%, and for EU-Herceptin from 0.9-3.1%. All SB3 and EU-Herceptin lots were within the US-Herceptin QR (0.0-5.4%). However, considering the EU-Herceptin QR based on 2SD (0.8-2.8%), all eight SB3 lots and 21 out of the 65 US-Herceptin lots were outside of the upper limit of the QR. The graph presented below include the QRs based on 3SD (Figure 20).

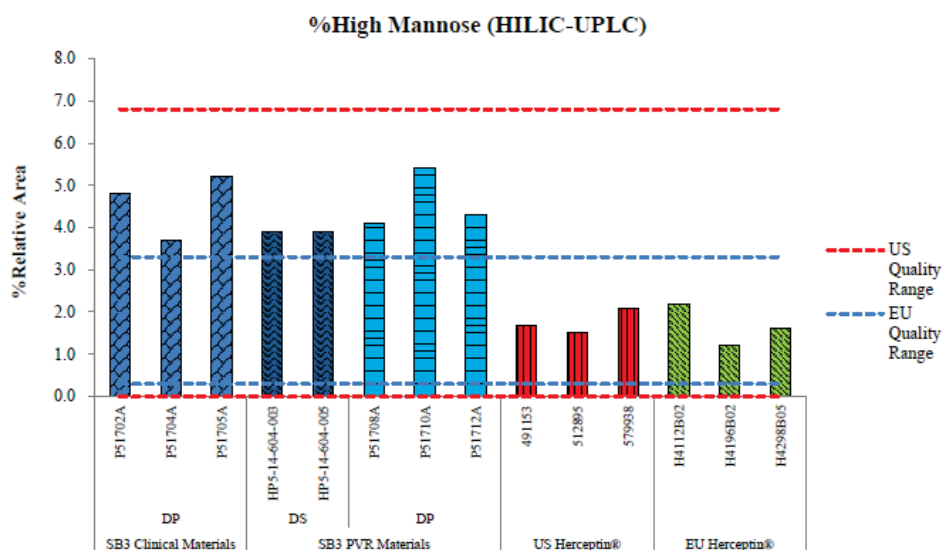


Figure 20: Similarity of %High Mannose between SB3 and Herceptin® by HILIC-UPLC

Reviewer comment: *Antibodies with high levels of HM content have been associated with increased antibody clearance and decreased efficacy. The HM content is higher in all SB3 lots compared to the EU-Herceptin lots and outside of the EU-QR, but within the QR of the US-Herceptin lots. Given minor differences observed between SB3 and the overall US-Herceptin lots, and the magnitude of the difference between the SB3 and EU-Herceptin lots (not only the three lots selected in Figure 20), clinical impact is not expected. The minor differences observed between SB3, US-Herceptin and EU-Herceptin do not preclude a demonstration of highly similar.*

Identification of N-linked Glycosylation Site – Tier 3

Two lots of SB3, one lot of US-Herceptin, and one lot of EU-Herceptin were deglycosylated with PNGase F and evaluated for the N-linked glycosylation site using UPLC-ESI-MS/MS (the mass spectrometer was calibrated for accuracy using an internal standard prior to use). The detected masses of the deglycosylated peptides were compared to the theoretical masses. The detected masses were identical for each lot evaluated (Table 50); representative MS/MS spectra were provided for each product lot evaluated (Figures 85 and 86).

Reviewer comment: *The overall assessment of the N-linked glycosylation sites as determined by UPLC-ESI-MS/MS supports a demonstration of highly similar between SB3 and US-Herceptin, and the establishment of the analytical bridges among the three products.*

N-Glycan Identification using Procainamide Labeling – Tier 3

The N-glycans for two lots of SB3, one lot of US-Herceptin, and one lot of EU-Herceptin were characterized by labeling the glycans with procainamide and separating the labeled glycans using UPLC-ESI-MS/MS. The identified glycans were identical across all three products (Table 51); representative glycan profiles were provided for each product lot evaluated (Figures 87).

Reviewer comment: *The overall assessment of the glycoforms identified by UPLC-ESI-MS/MS supports a demonstration of highly similar between SB3 and US-Herceptin, and the establishment of the analytical bridges among the three products.*

Charge Variants

Charged glycans (sialic acid) by HILIC-UPLC – Tier 2

Terminal sialic acid was assessed by quantitating the sum of charged glycan species by HILIC-UPLC for 8 lots of SB3, 65 lots of US-Herceptin, and 81 lots of EU-Herceptin (Table 22). The quantitative range for SB3 is 1.2-1.4%, for US-Herceptin is 0.1-2.1%, and for EU-Herceptin is 0.3-2.9% (Figure 41). All lots were within the US-Herceptin (QR: 0.0-2.8) and EU-Herceptin (QR: 0.1-3.0) QR.

Reviewer comment: *The qualification of this method was determined to be acceptable during the pre-license inspection of the analytical similarity data at Samsung Bioepis (Korea). The total amount of N-acetyl neuraminic acid (NANA) and N-glycolylneuraminic acid (NGNA) were assessed together by measuring charged glycan content, with the justification that all charged glycan species contain at least one terminal sialic acid. Considering the assessment, it is not clear if there are differences in the amount of NANA versus NGNA. However, the overall amounts of sialic acid are consistent across the three products, and are detected at low levels (no more than 2.9%). The assessment of charged glycans as an indicator of sialic acid levels by HILIC-UPLC supports a demonstration of highly similar between SB3 and US-Herceptin, and the establishment of the analytical bridges among the three products.*

Cation Exchange-High Performance Liquid Chromatography (CEX-HPLC) and Imaged Capillary Isoelectric Focusing (icIEF) – Tier 2

CEX-HPLC separates protein variants based on charge. The method was qualified for specificity, range, linearity, accuracy, precision, detection limit, quantitation limit, and robustness for the detection of acidic, main, and basic peaks. The qualification summary indicates that the method was suitably qualified for the intended use.

Eight SB3 lots, 65 US-Herceptin lots, and 80 EU-Herceptin lots were assessed for charge variants (acidic, main, and basic species) using CEX-HPLC (Table 19). Representative chromatograms show similar peaks among the three products (Figure 26). The following are the quantitative ranges for the identified variants:

- SB3: acidic – 32.5-37.6%; main – 49.1-53.5%; basic – 13.3-14.4%
- US-Herceptin: acidic – 24.6-37.4%, main – 55.2-63.0%, basic – 7.4-13.2%
- EU-Herceptin: acidic – 23.3-35.9%, main – 56.1-67.4%, basic – 6.7-11.0%

SB3 lots have marginally higher acidic species (mean – 34.5%), lower main peak (mean – 51.6%), and higher basic species (13.9%) compared to US-Herceptin and EU-Herceptin lots. For acidic species, all of the SB3 lots are within the US-Herceptin QR (22.1-38.6%) and the EU-Herceptin QR (19.1-38.1%); all EU-Herceptin lots are also within the US QR (Figure 27). In contrast, all SB3 lots were outside of both the US-Herceptin (54.0-65.5%) and EU-Herceptin (54.2-70.3%) QRs for main peak, and 9 out of 80 (~11%) EU-Herceptin lots were outside of the upper end of the US-Herceptin QR (Figure 28). For basic species, two SB3 lots were marginally higher than

the upper limit of the US QR (5.8-14.0%), and all were outside of the upper limit of the EU QR (6.3-12.0%); the EU-Herceptin lots were within the US QR with respect to basic species (Figure 29).

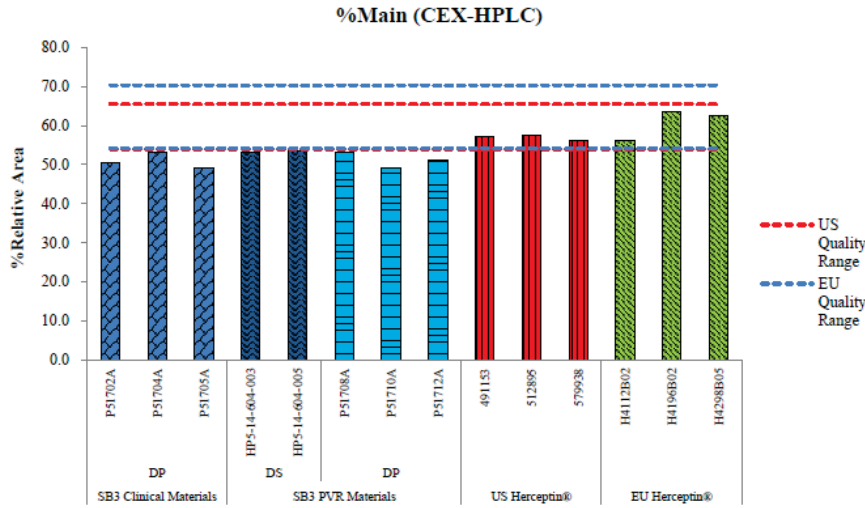


Figure 28: Similarity of %Main between SB3 and Herceptin® by CEX-HPLC

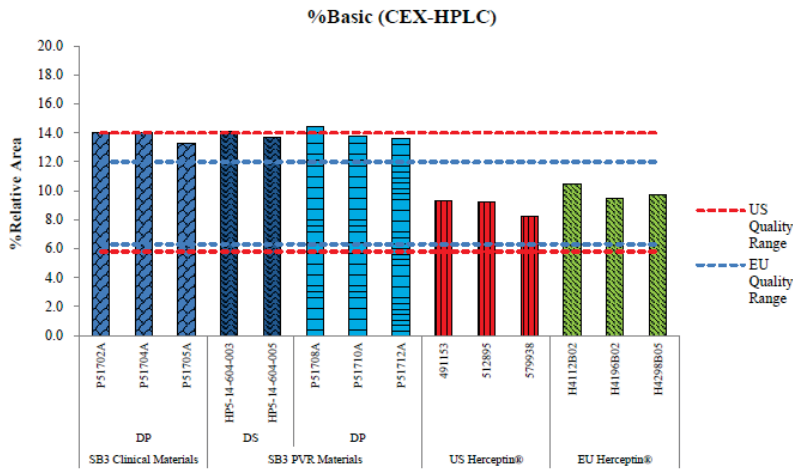


Figure 29: Similarity of %Basic between SB3 and Herceptin® by CEX-HPLC

An additional assessment of charge variants (acidic, main, and basic species) based on the isoelectric point (pI) was conducted for 8 lots of SB3, 56 lots of US-Herceptin, and 71 lots of EU-Herceptin using icIEF (Table 20). The method was qualified for specificity, range, linearity, accuracy, precision, quantitation limit, and robustness for the detection of acidic, main, and basic peaks. The qualification summary indicates that the method was suitably qualified for the intended use; this method has been validated for use as part of the SB3 DS and DP release and stability specifications.

Representative chromatograms show similar peaks among the three products (Figure 31). The following are the quantitative ranges for the identified variants:

- SB3: acidic – 39.7-45.5%; main – 46.4-51.8%; basic – 8.0-8.8%
- US-Herceptin: acidic – 34.2-43.4%, main – 52.2-59.4%, basic – 3.6-6.9%
- EU-Herceptin: acidic – 30.3-43.8%, main – 52.1-65.0%, basic – 2.5-6.5%

Consistent with the CEX-HPLC data, SB3 lots show a marginal increase in acidic species, lower main peak (mean – 51.6%), and higher basic species compared to US-Herceptin and EU-Herceptin lots. For acidic species, all of the SB3 lots are within the US-Herceptin QR (31.8-46.5%) and the EU-Herceptin QR (27.4-46.7%); all EU-Herceptin lots are also within the US QR (Figure 32). For main peak, four of the SB3 lots were outside of the lower end of the US-Herceptin (49.7-62.2%) and three SB3 lots were outside of the lower end of the EU-Herceptin (49.3-66.9%) QRs; and 5 out of 80 EU-Herceptin lots were outside of the upper end of the US-Herceptin QR (Figure 33). For basic species, all of the SB3 lots were outside of the upper limit of the US (2.3-7.5%) and EU (2.7-7.1%) QRs; all EU-Herceptin lots were within the US QR (Figure 34).

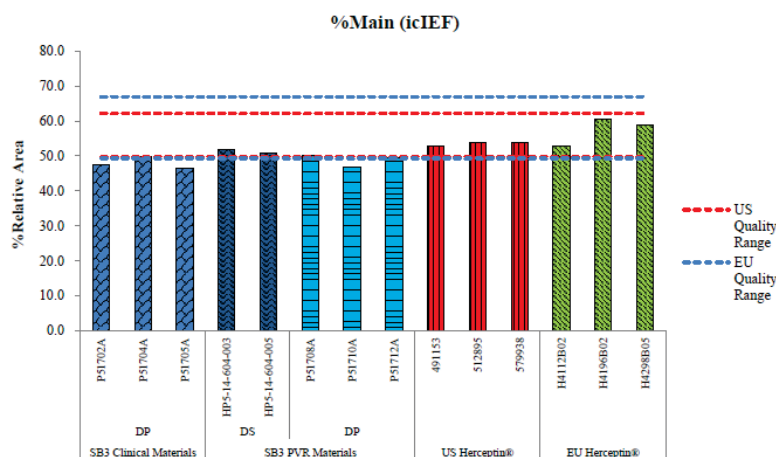


Figure 33: Similarity of %Main between SB3 and Herceptin® by icIEF

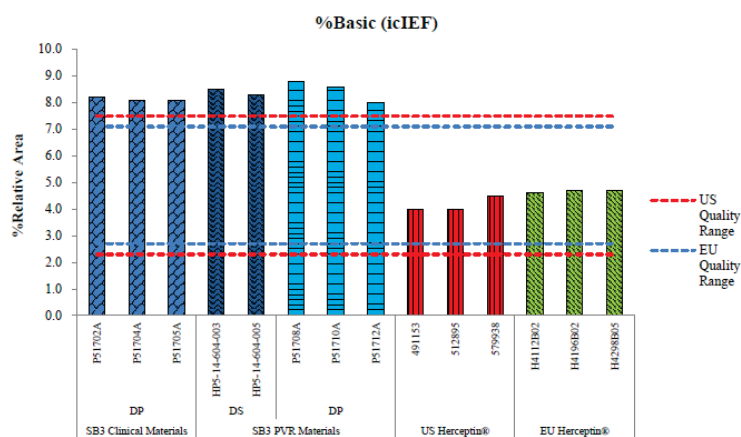


Figure 34: Similarity of %Basic between SB3 and Herceptin® by icIEF

The results for charge variants by CEX-HPLC and icIEF show that SB3 has higher amounts of basic species compared to US-Herceptin and EU-Herceptin. Structure-activity-relationship (SAR) characterization studies were performed where a single lot of SB3 and EU-Herceptin (no US-Herceptin lot included in the assessment) were fractionated by CEX-HPLC, and four acidic, two basic, and the main species were isolated (Figures 35-39). Peptide mapping using LC-ESI-MS/MS of the fractions showed that acidic fractions contained deamidated Asn 55 on the HC, Asn 30 on the LC, isomerized (iso) Asp102 of the HC in the CDR, sialic acid, and deamidation of the Fc. Basic fractions contained isoAsp 102, and c-terminal lysine (Figure 35). Deamidation of proteins, for example at Asn 55 and Asn 30, as well as isoAsp102 have the potential to impact potency (i.e., increase %isoAsp102 has been shown to correlate with a decrease in trastuzumab potency).

Reviewer comment: Samsung was requested to provide a head-to-head assessment of the SAR of SB3, US-Herceptin, and EU-Herceptin with respect to charge, potential modifications (e.g., isoAsp102, Asn 30, Asn 55),

and biological activity. It was also requested that the evaluation of the isoAsp102 data be statistically analyzed using methods applicable to tier 2 analysis. In response to IRs dated 3/29/18 and 5/15/18, Samsung provided data using QR analysis of the fractionated charge species and indicated that additional SAR studies would be submitted to the BLA with additional US-Herceptin lots. The additional SAR data were provided in IR response dated 6/29/18, and all related data are reflected in the following discussion.

SAR studies

The basic 1 and acidic 2 charged species isolated from the fractionation of 8 lots of SB3, 65 lots of US-Herceptin, and 80 lots of EU-Herceptin were analyzed using QR as a surrogate measurement for the quantitation of isoAsp102 and deamidated Asn 30, respectively (Table 21). The quantitative ranges and QRs for % basic 1, representative of % isoAsp102, and %acidic 2, representative of Asn 30 deamidation, are as follows:

- SB3 – basic 1: 4.7-5.1%; acidic 2: 9.5-10.7%
- US-Herceptin – basic 1: 5.0-7.4%; acidic 2: 10.8-14.1%
- EU-Herceptin – basic 1: 4.4-7.1%; acidic 2: 9.3-14.3%

The SB3 lots have slightly lower amounts of % basic 1 compared to US- and EU-Herceptin lots, but all SB3 and EU-Herceptin lots were within the US (4.6-7.4%) and EU (4.3-7.1%) QRs (Figure 40, below). The % acidic 2 fraction was lower in SB3 lots compared to US-Herceptin, where two SB3 lots were outside of the lower limit of the US-Herceptin QR (9.9-15.7%); all EU-lots were within the US QR (Figure 42, below). SB3 lots were slightly lower in acidic 2 levels compared to EU-Herceptin lots, but all lots were within the EU QR (7.7-15.7%).

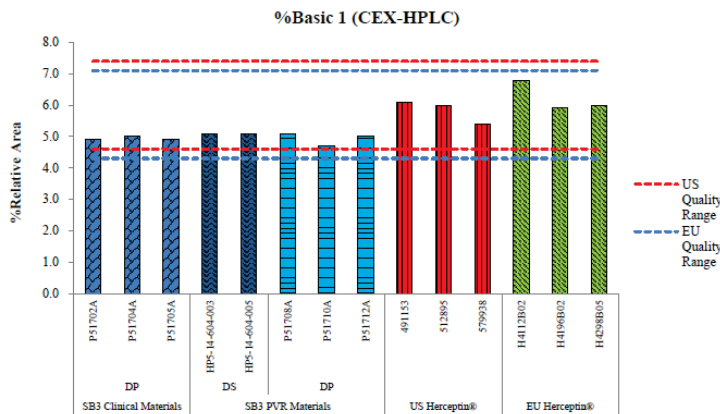


Figure 40: Similarity of %Basic 1 between SB3 and Herceptin® by CEX-HPLC

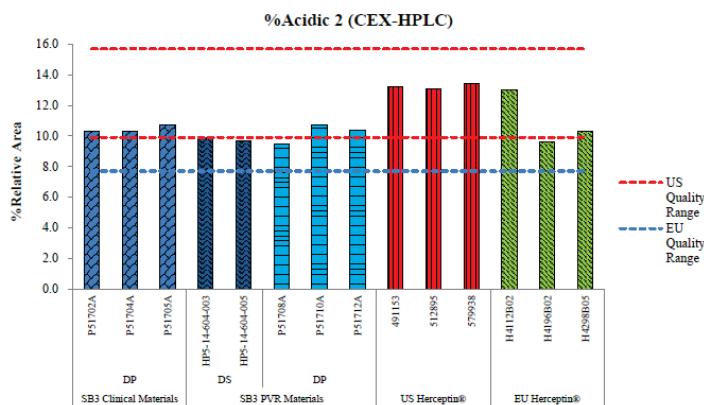


Figure 42: Similarity of %Acidic 2 between SB3 and Herceptin® by CEX-HPLC

Reviewer comment: *Samsung did not specifically quantify the overall amount of isoAsp102 or Asn 30 present in a sufficient number of SB3, US-Herceptin and EU-Herceptin lots to allow for a robust statistical analysis as requested. However, the additional SAR study data provided below will be considered in the overall evaluation of the potential impact of these modifications on biological activity.*

An additional SAR study was performed using two lots each of SB3 (PVR DP lots P51710A and P51712A), US-Herceptin 150 mg (expiry dates March 2021 and April 2021), and EU-Herceptin 150 mg (expiry March 2020 and February 2020). The fractionation was performed, as described above, and verified by CEX-HPLC (Figures 44-49). Degradation of the acidic 1 and basic 2 fractions was detected (indicated in Figures 44-49 by red arrows) and confirmed by SE-HPLC. However, these two fractions were in the least abundance compared to the other seven fractions (including the main peak fraction). It appears that the basic 2 fraction was not detected/isolated, or was in very low abundance, for US-Herceptin lot 3179410 (Figure 46).

Degradation-related modifications present in charge peak fractionated groups

Deamidation of the LC at Asn 30 was detected primarily in the acidic groups (most abundant in acidic groups 1 and 2). There were significantly higher levels of deamidated Asn 30 (Table 25, Figure 50, below), most abundantly present in the acidic 2 fraction, in the US-Herceptin (up to 30.4%) and EU-Herceptin (up to 28.1%) lots compared to SB3 (up to 15.3%). The amount of deamidated Asn 55 was detected in most abundance in acidic group 1, and was slightly lower in the SB3 lots (up to 5.9%) compared to the US-Herceptin (up to 11.8%) and EU-Herceptin (up to 11.0%) lots, while consistently low levels (up to 1.5%) were detected in the other fractionated groups across the three products (Table 26, Figure 51).

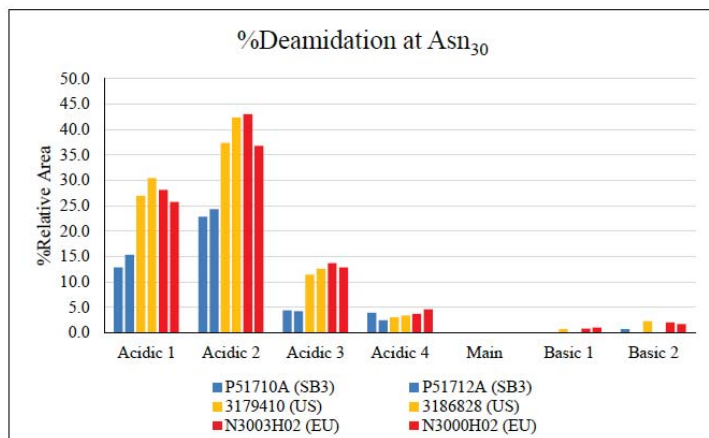


Figure 50: %Deamidation of Light Chain Asn₃₀ by Fraction

Reviewer comment: *Asn 30 is located in the CDR and is likely the most critical deamidation site with respect to efficacy; SB3 lots have less deamidated Asn 30 compared to US- and EU-Herceptin. The fractions in which the highest amount of deamidated Asn 30 (acidic fraction 2 and to a lesser extent acidic fraction 1) were detected shows slightly lower amounts of HER2 binding compared to all other fractions. Also, the US- and EU-Herceptin lots show slightly lower amounts of HER2 binding in those acidic fractions compared to SB3, but no significant difference in ADCC activity or antiproliferation in the same fraction. Moreover, the analytical similarity assessment binding data and potency assays indicate that the differences seen here in deamidated Asn 30 and Asn 55 do not significantly impact in vitro potency.*

The amount of isoAsp102 was measured by endoproteinase treatment followed by peptide mapping. The majority of isoAsp102 was detectable in the basic 1 fraction with SB3 lots having slightly lower amounts of isoAsp102 in the fraction (up to 26.1%) compared to the US-Herceptin (up to 39.2%) and EU-Herceptin (up to 34.7%) lots; a similar trend, although to a much lesser extent, was detected in the basic 2 fraction (Table 27, Figure 52, below). The isoAsp102 detectable in the acidic fractions were low and relatively consistent across all three products.

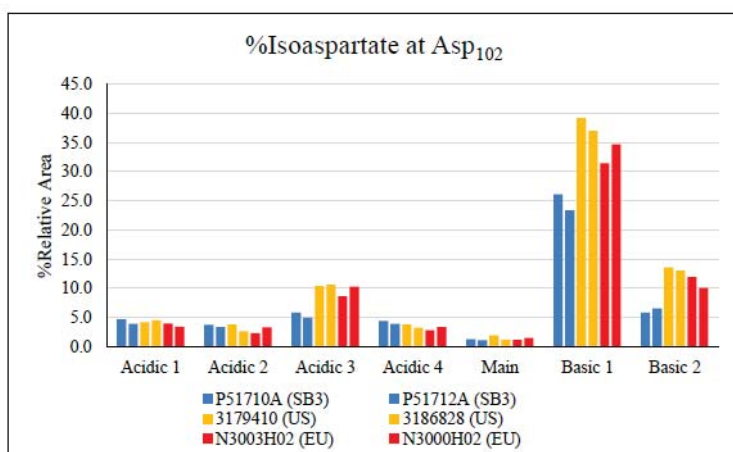


Figure 52: %Isoaspartate of Heavy Chain Asp102 by Fraction

Reviewer comment: The cumulative amount of isoAsp102 was greater in the US-Herceptin and EU-Herceptin lots compared to SB3, which correlates with the higher amount of basic 1 fraction in the US- and EU-Herceptin lots compared to SB3 (Figure 41). IsoAsp102 has been reported in the literature to significantly reduce the potency of trastuzumab, and typically, isoAsp modifications of monoclonal antibodies result in an increase in basic species. The data in Figure 60 (below) show a correlative decrease in antiproliferation in the basic 1 fraction for all three products, with the EU-Herceptin lots showing a slightly greater reduction in potency. These data support the capability of the antiproliferation assay to detect a decrease in potency related to degradation products. Overall, it does not appear that the amount of isoAsp 102 in the three products is at level that would lead to a decrease in overall potency, considering the analytical similarity data demonstrating equivalence in potency across the three products. Additionally, while the SB3 lots appear to have higher amount of overall basic species, these data indicate that isoAsp 102 is not the primary contributor to the higher levels but may be due to increased levels of c-terminal lysine residues and/or % methionine 255 oxidation in SB3 lots compared to the US-Herceptin and EU-Herceptin lots (see additional discussion below).

Glycan analysis of charge peak fraction groups

The amount of combined % afucose and % HM were assessed in each fraction by HILIC-UPLC (Table 28, Figure 53). The amounts were marginally higher in one of the two SB3 lots in all acidic fractions compared to the US- and EU-Herceptin lots. The most abundant amount of % afucose and % HM was detected in the basic 2 fraction and the data show higher amounts in the US- (up to 23.3%) and EU- (up to 27.2%) Herceptin lots compared to SB3 (up to 15.4%).

The assessment of % charged glycans, as a measurement of sialic acid, showed that the majority of charged glycans were present in the acidic fractions (to a greater extent in acidic fractions 3 and 4), with minor amounts of less than 1% detectable in the main and basic fractions. There were slightly lower amounts of charged glycans in the acidic 3 and 4 fractions of SB3 (up to 4.3%) compared to the US- (up to 7.5%) and EU- (up to 7.7%) Herceptin lots (Table 29, Figure 54). The overall differences across the three products with respect to charged glycans in the various fractions was variable.

Reviewer comment: The analysis for fractionated lots of the three products are consistent with the analytical similarity assessment of the glycosylation profiles, indicating combined levels of % afucose plus % HM detected are slightly higher in SB3 lots compared to US-Herceptin and EU-Herceptin lots. The SAR analysis showed higher %afucose + %HM in the basic 2 fraction for all three products compared to the other fractions, which appeared to correlate with a slightly higher amount of ADCC activity in the basic 2 fraction (Table 34, Figure

61). However, the overall amount of combined %afucose and HM do not appear to impact overall ADCC activity, considering the equivalence demonstrated between the three products in the analytical similarity assessment.

The charged glycan analysis (surrogate analysis of sialic acid) indicates a slightly higher amount in the US-Herceptin and EU-Herceptin lots compared to SB3 mainly in acidic fractions 3 and 4; however, the analytical similarity analysis of a larger number of lots indicates that the overall amount of charged glycans are similar among the three products.

Size analysis of charge peak fraction groups

The fractions were evaluated for HMWS by SE-HPLC for the two SB3, US-Herceptin, and EU-Herceptin lots. Overall the amount of HMWS was consistent and low across all fractions and all three products, with the highest amount of HMWS detected in US-Herceptin lot 3179410, at 3.1%, of which was attributed to degradation of the fractionated basic 2 peak group. The greatest amount of HMWS detected in SB3 was 0.5%, which was also present in the basic 2 peak group. To determine the amount of degradation, the monomer content was detected in each fractionated group, which showed that the highest amount of degradation was present in the acidic 1 and basic 2 groups. The overall impact of degradation was factored into the assessment of functional activity with respect to the fractionated groups.

Functional activity of charged peak fraction groups

HER2 binding of each charge group showed lower amounts of binding activity in the acidic fractions (to a greater extent in acidic group 1), compared to the basic and main fractions across all lots evaluated (Table 32, Figure 59, below). A large decrease in binding activity was observed in the basic 2 fraction of one US- and one EU-Herceptin lot, which correlated with degradation of the fraction. With the exception of the degraded basic group fractions in the US- and EU-Herceptin lots, the overall amount of binding activity detected in each fraction group was similar across the three products.

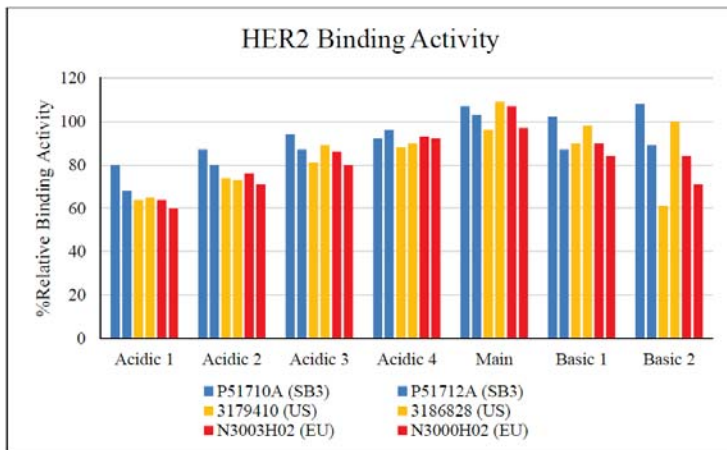


Figure 59: The Results of HER2 Binding Assay

Antiproliferation was assessed for each fraction across the three products (Table 33, Figure 60, below). The acidic peak groups showed higher antiproliferation activity compared to the basic peak groups, with a clear decrease in activity in the basic 1 peak group, across all three products. The lower amount of antiproliferation in the basic 1 group correlates with the high amounts of isoAsp102 present in the same basic fraction. ADCC activity was evaluated, and there was no major difference (only minor variability) across all fractions for the three products, with the exception of the basic 2 peak for US-Herceptin lot 3179410, which was associated with degradation of the fraction (Table 34, Figure 61). The assessment of FcRn binding indicated similar amounts of activity across all fractions, with the exception of acidic 1 and basic 2 peaks, in which a slight increase in activity

was detected in the US- and EU-Herceptin lots compared to SB3 in the acidic 1 peak, and variability was detected within the US- and EU-Herceptin lots for basic peak 2.

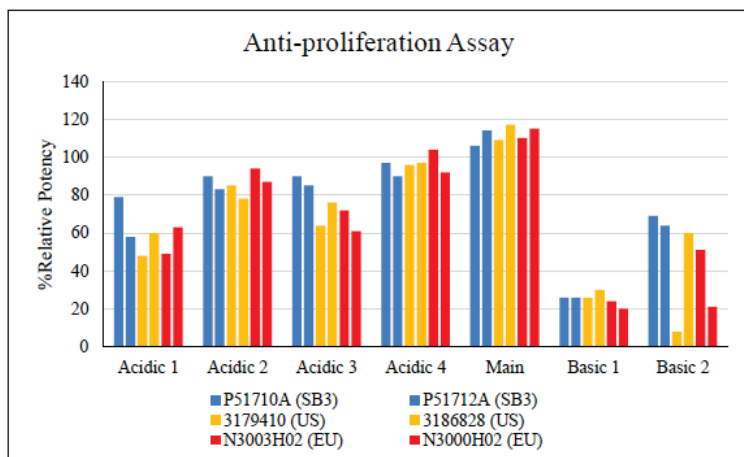


Figure 60: The Results of Anti-proliferation Assay

Reviewer comment: The analytical similarity data for charge heterogeneity show higher levels of basic, and to a lesser extent, acidic variants in the SB3 lots compared to the US-Herceptin and EU-Herceptin lots. However, the difference in overall charge variants (i.e., increase in basic species) do not appear to correlate with Asn 30, Asn 55, or isoAsp102, as the amounts of these modifications were consistent or slightly higher in the US- and EU-Herceptin lots compared to the SB3 lots in the related charge fractions. The SAR data of the fractionated charge peaks with respect to HER2 binding, antiproliferation, and ADCC activity also indicate that the minor variability detected in these modifications is not significant enough to impact potency, or PK considering the analytical data. Additional analytical similarity analysis of attributes such as c-terminal variants and methionine (Met) oxidation, indicate that these attributes may contribute to the higher amount of basic charge species in the SB3 batches (see discussion below). The comparative stability study data also indicate an increasing trend in basic species under stressed conditions after 6 months, which correlate with an increase in Met 255 oxidation (see comparative stability section below). Taking these data into consideration, the formation of basic species of SB3 will be part of the overall control strategy for SB3.

Methionine Oxidation by UPLC-ESI-MS/MS – Tier 3

Tabular data were provided for the amount of oxidation at Met 83, 107, 255, 431 on the HC, and at Met 4 on the LC for 8 lots of SB3, and three lots each of US-Herceptin and EU-Herceptin (Table 48). The quantitative ranges at each site of Met oxidation for the three product is summarized in the following table (prepared by reviewer). The data show that the amount of Met 255 oxidation is slightly higher in the SB3 lots compared to both the US-Herceptin and EU-Herceptin lots, while the levels of oxidation for the other methionine residues evaluated were similar across the three products.

	Met 83	Met 107	Met 255	Met 431	Met 4
SB3	0.4-0.6%	0.4-1.1%	4.5-5.8%	0.1-0.2%	0.3-0.5%
US-Herceptin	0.4-0.6%	0.8-1.1%	3.4-3.8%	0.2-0.3%	0.4-0.8%
EU-Herceptin	0.4-0.7%	0.7-1.0%	3.3-3.8%	0.1%	0.4-0.6%

Reviewer comment: There is ~1.0-2.0% higher amounts of Met 255 oxidation in the SB3 lots compared to the US- and EU-Herceptin lots evaluated. The difference may contribute to the higher amount of basic charge species present in the SB3 lots. This is consistent with the comparative heat stressed stability study data that show after six months storage, an increase in basic species that correlates with an increase in Met 255 oxidation. The same trends in the product quality attributes are detected among all three products, however, the baseline amount of

basic species and Met 255 oxidation are greater in the SB3 lots compared to the US- and EU-Herceptin lots, and there is a slightly greater increase in Met 255 oxidation over time (SB3 - ~5%; US-Herceptin - ~3%; EU-Herceptin ~2%). Typically, oxidation of Met 255 which is located in the Fc region of a monoclonal antibody may impact binding to the FcRn. This is confirmed from the comparative stability data. After exposure to oxidative conditions for 6 hours, an increase in Met 255 oxidation was observed among the three products which is correlated with a decrease in FcRn binding. The amount of increase in Met 255 oxidation and decrease in FcRn binding were similar between SB3 and US-Herceptin (see additional discussion in comparative stability study). However, the analytical similarity data with respect to FcRn binding, ADCC, and antiproliferation, as well as the SAR study data, show that there are no major differences in potency, or in PK as indicated by the analytical data. The amount of Met 255 oxidation detected in lots of SB3 of up to 2.0%, is not expected to have a clinical impact. The minor differences do not preclude a conclusion of high similarity between SB3 and US-Herceptin and support the establishment of the analytical bridge among the products.

Deamidation by UPLC-ESI-MS/MS – Tier 3

Tabular data were provided for deamidation at Asn 28, 55, 77/84, 387/392/393 on the HC, and at Asn 30 on the LC for 8 lots of SB3, and three lots each of US-Herceptin and EU-Herceptin (Table 49). The quantitative ranges at each site of Asn deamidation for the three product is summarized in the following table (prepared by reviewer). The data show that the amount of deamidation at all sites were similar among the three products, except for deamidation at Asn 387/392/393 and Asn 30. The amount of deamidated Asn 387/392/393 and EU-Herceptin were similar yet slightly lower than the US-Herceptin lots. The amount of Asn 30 deamidation in SB3 (5.5-7.4%) is lower than the amount in US-Herceptin lots (9.3-10.1%), and slightly lower than the EU-Herceptin lots (6.5-10.2%).

	Asn 28	Asn 55	Asn 77/84	Asn 387/392/393	Asn 30
SB3	0.1-0.3%	0.9-1.2%	0.1%	0.2-0.3%	5.5-7.4%
US-Herceptin	0.2-0.4%	1.0-1.1%	0.1%	0.5-0.8%	9.3-10.1%
EU-Herceptin	0.2-0.3%	0.9-1.2%	0.1%	0.3-0.4%	6.5-10.2%

Reviewer comment: The SB3 lots have lower amounts of Asn 30 deamidation compared to US- and EU-Herceptin lots evaluated. Asn 30 is located in the CDR and is likely the most critical deamidation site with respect to efficacy, as such, Samsung was requested to provide additional data to analyze the quality attribute in SB3, US-Herceptin and EU-Herceptin lots (IR dated 3/29/18). The additional SAR study data provided in response shows that the acidic charged fractions with the highest amount of Asn 30 deamidation correlate with a decrease in HER2 binding among all three products, with US-Herceptin and EU-Herceptin lots having greater amounts of Asn 30 deamidation and lower amounts of HER2 binding compared to SB3 (see SAR discussion above). The overall analytical similarity assessment binding data and potency assays indicate that the differences seen here in Asn 30 deamidation do not significantly impact in vitro potency. The differences do not preclude a conclusion of high similarity between SB3 and US-Herceptin, and support the establishment of the analytical bridge among the products.

Assessment of primary, secondary, and higher order structure

Molecular weight by UPLC-ESI-MS – Tier 3

Intact and deglycosylated molecular mass analysis under reduced and non-reduced conditions were evaluated for eight lots of SB3, and three lots each of US-Herceptin and EU-Herceptin by UPLC-ESI-MS (Table 42). Representative electropherograms provided for each product show consistent peak areas across the three products under each condition evaluated (Figures 69-71), except for the HC under deglycosylated and reduced conditions in which the SB3 lots have higher amounts of c-terminal lysine detected compared to the US- and EU-Herceptin lots in which the corresponding peak was not detectable (Table 42 and Figure 71). The remainder of the quantitative molecular weight analysis was similar among the three products.

Reviewer comment: *The higher amount of c-terminal lysine detected by the mass analysis likely contribute to the higher amount of basic species detected in the SB3 lots compared to the US- and EU-Herceptin lots (see additional discussions below). Overall, the data support a demonstration of highly similar between SB3 and US-Herceptin, and the establishment of the analytical portion of the scientific bridges among SB3, US-Herceptin, and EU-Herceptin.*

Amino acid sequencing by UPLC-ESI-MS – Tier 3

The amino acid sequence of two lots of SB3 and one lot each of US-Herceptin and EU-Herceptin by UPLC-ESI-MS showed the same peptide fragments (figures 73-75) were identified in among the three products, and the mass analysis showed similar masses (Table 43).

Reviewer comment: *The amino acid sequence of the three products are identical.*

N-terminal sequencing by UPLC-ESI-MS – Tier 3

The N-terminal sequences were evaluated for eight lots of SB3 and three lots each of US-Herceptin and EU-Herceptin after trypsin digestion, peptide separation, sequencing and quantitation by UPLC-ESI-MS/MS. Representative spectra were provided for the HC and LC N-terminal sequences for the three products (Figures 76-77), and the masses for the HC (intact and pyro-E variant) and the LC were identical among the three products, although the calculated relative contents of the pyro-E variant was slightly lower in the SB3 lots (2.0-2.9%) compared to the US-Herceptin (3.2-3.4%) and EU-Herceptin (2.9-3.5%) lots; however, the amount of the pyro-E variant was relatively low among all three products (Table 44).

Reviewer comment: *The data support a demonstration of highly similar between SB3 and US-Herceptin, and the establishment of the analytical portion of the scientific bridges among SB3, US-Herceptin, and EU-Herceptin.*

C-terminal sequencing by UPLC-ESI-MS – Tier 3

The C-terminal sequences were evaluated for eight lots of SB3 and three lots each of US-Herceptin and EU-Herceptin with or without digestion with Lys-C followed by peptide separation, sequencing and quantitation by UPLC-ESI-MS/MS. Representative spectra were provided for the intact, lysine deleted, and α -amidated pro form of the HC, as well as the C-terminal sequence of the LC for the three products (Figures 78-79). The detected masses were identical for each HC and LC sequence; however, the relative content of intact and α -amidated pro form of the HC of the SB3 lots were higher, and the lysine deleted form was lower, than the relative content detected in the US-Herceptin and EU-Herceptin lots (Table 45). The data are summarized in the following table prepared by the reviewer.

	Intact HC	Lys-deleted HC	α -amidated pro HC
SB3	2.6-4.0%	95.2-96.5%	0.6-0.9%
US-Herceptin	0.4-0.5%	99.3-99.4%	0.2%
EU-Herceptin	0.4-0.5%	99.1-99.4%	0.2-0.4%

Reviewer comment: *SB3 lots have higher amounts of intact c-terminal variants, which corresponds to greater amounts of c-terminal lysine content, as indicated by the lower amount of relative content of the lysine deleted form, compared to the US-Herceptin and EU-Herceptin lots. C-terminal lysine variants are quite basic, and therefore, the difference detected here may contribute to the higher amount of basic charged species present in SB3 compared to US-Herceptin and EU-Herceptin lots. C-terminal lysine are typically cleaved for therapeutic products delivered intravenously, such as SB3, US-Herceptin and EU-Herceptin, therefore the variable amounts are not expected to impact safety, potency, or PK of the products, and the differences do not preclude a demonstration of analytical similarity between SB3 and US-Herceptin, and the establishment of the analytical portion of the scientific bridges among the three products.*

Peptide mapping by UPLC-ESI-MS – Tier 3

Peptide mapping was performed for two lots of SB3, and one lot each of US-Herceptin and EU-Herceptin by digesting the samples with trypsin, lys-C and Asp-N followed by analysis by UPLC-ESI-MS/MS. Representative chromatograms were provided for the three products digested under the three different conditions which showed identical peak identification and consistent retention times across the three products (Figures 80-82).

Reviewer comment: The peptide mapping sequences for SB3, US-Herceptin, and EU-Herceptin are highly similar.

Disulfide bond analysis by UPLC-ESI-MS – Tier 3

Trastuzumab has 16 disulfide bonds, including 12 intra-chain and 4 inter-chain linkages. The disulfide linkages of two SB3 lots and one lot each of US-Herceptin and EU-Herceptin were assessed by UPLC-ESI-MS/MS under non-reduced and reduced conditions after trypsin digestion (Table 46). The expected disulfide linkages were detected for each product as shown by the identical representative chromatograms (Table 84).

Reviewer comment: The disulfide bond analysis supports a demonstration of highly similar between SB3 and US-Herceptin, and the establishment of the analytical portion of the scientific bridges among the three products.

Free sulfhydryl group quantification by fluorescence – Tier 3

The free thiol content of eight SB3 lots, and three lots each of US-Herceptin and EU-Herceptin was determined by measuring the molar concentration of free thiols as determined by the fluorescent measurement of the thiol quantitation reagent solution used in the assay. The molar concentration of SB3 lots was slightly higher (3.3-4.1 μM) compared to the US-Herceptin (2.3-2.5 μM) and EU-Herceptin (2.2 μM) lots (Table 47).

Reviewer comment: The data show slightly higher amounts of free thiol content in the SB3 lots, suggesting that there may be differences in the disulfide bond formation compared to the US-Herceptin and EU-Herceptin lots. The improper formation of disulfide bonds may impact the secondary structure of the antibodies, however, the higher order structure analysis (see discussion below) indicates that the products are consistently and properly formed and support the structural analysis of the three products. Moreover, the overall concentration of free thiol content is low ($\leq 4.1 \mu\text{M}$). The data supports a demonstration of highly similar between SB3 and US-Herceptin, and the establishment of the analytical portion of the scientific bridges among the three products.

Protein secondary structure by Far UV- and Near UV-Circular Dichroism (CD) – Tier 3

Two lots of SB3, and one lot each of US-Herceptin and EU-Herceptin were assessed for beta-sheet structure by Far-UV CD (Table 52, Figure 88) and the spectral regions that the maximum wavelength of the products were detected by Near-UV CD (Table 53, Figure 89). The Far-UV CD data showed that the α -helix, anti-parallel, parallel, beta-turn, and random coil levels and spectral overlays (included spectra for four SB3 lots, and one lot each of US- and EU-Herceptin) were similar among the three products (variability within 0.1-0.4%). The maximum wavelengths determined by Near-UV-CD were also similar and the values were within 0.5 nm of the wavelengths for each lot, the representative overlay (included the same lots used in the Far-UV CD analysis) were similar.

Reviewer comment: The Far- and Near-UV CD spectral analysis show similarity among the secondary structures of SB3, US-Herceptin and EU-Herceptin lots.

Protein folding analysis by extrinsic fluorescence spectroscopy (EF) – Tier 3

EF spectroscopy was used to assess protein folding by measuring the hydrophobic interaction between the 1-anilino-naphthalene-8-sulfonate (ANS) fluorescent dye and the protein. The maximum wavelength and maximum intensity of the fluorescence were similar for two lots of SB3, one lot each of US-Herceptin and EU-Herceptin, and the SB3 DP formulation buffer alone (Table 55). Representative spectral overlays for four lots of SB3 and the US- and EU-Herceptin lots, as well as the formulation buffer, show similar spectra (Figure 92).

Reviewer comment: The formulation buffer maximum wavelength and intensity was slightly lower than the SB3 DP lots evaluated, indicating potential background in the dye-protein interaction. Overall, the wavelengths and spectral overlays were similar across the three products.

Protein secondary structure by Fourier transform infrared (FTIR) spectroscopy – Tier 3

Secondary structure was also assessed using FTIR for two lots of SB3, and one lot each of US-Herceptin and EU-Herceptin. The contents of the amide I region for each product lot including the beta-sheets, random coil, alpha-helix, and beta-turn, and the amounts were similar among the three products (Tables 56-57). The spectral overlays were similar for the amide I region by FTIR and second derivative FTIR among four SB3 lots and the single US- and EU-Herceptin lots (Figures 93-94).

Reviewer comment: The overall assessment of secondary structure supports a demonstration of highly similar between SB3 and US-Herceptin and the establishment of the analytical portion of the scientific bridges among the three products.

Protein tertiary structure by intrinsic fluorescence spectroscopy (ITF) – Tier 3

Two lots of SB3, and one lot each of US-Herceptin and EU-Herceptin were assessed for tertiary structure by ITF. Representative emission spectral overlays under native and denaturing conditions (included four SB3 lots and one lot each of US- and EU-Herceptin) showed similarity among the three products (Figures 90-91). The maximum wavelengths under both conditions were within 0.5 nm among the three products (Table 54).

Reviewer comment: The ITF analysis shows similarity among the tertiary structures of SB3, US-Herceptin and EU-Herceptin lots.

Protein tertiary structure by Hydrogen/Deuterium Exchange (H/DX-MS) – Tier 3

The conformational structure of two lots of SB3, and one lot each of US-Herceptin and EU-Herceptin were assessed by H/DX followed by peptide analysis by MS. A representative coverage map of the MS results was provided (Figure 95). The kinetic curves of the deuterium uptake were plotted and the overlays showed similar kinetics among the three products (Figure 96-97), butterfly plots of the deuterium uptake also showed similar uptake between the SB3 and US-Herceptin lots (Figure 98), the SB3 and EU-Herceptin lots (Figure 99), and the US-Herceptin and EU-Herceptin lots (Figure 100).

Reviewer comment: The overall assessment of tertiary structure supports a demonstration of highly similar between SB3 and US-Herceptin and the establishment of the analytical portion of the scientific bridges among the three products.

Thermal stability by Differential Scanning Calorimeter (DSC) – Tier 3

DSC was used to determine the thermodynamic differences for two lots of SB3, and one lot each of US-Herceptin and EU-Herceptin. A representative overlay of the resulting thermograms show similar profiles among the three products (Figure 101) and consistent with the overlays, the quantitative data show similarity among the melting temperatures (Table 58).

Reviewer comment: The DSC analysis demonstrates structural similarity among the three products.

Additional Similarity Studies with SB3 and US-Herceptin 150 mg

An additional comparative analytical similarity assessment was performed between three lots of SB3 150 mg and eight lots of US-Herceptin 150 for a selection of quality attributes, that were determined to be potentially impacted by differences in the manufacturing processes of the US-Herceptin 150 mg and 420 mg presentations. These data were used to further support the analytical similarity assessment performed between SB3 150 mg and US-Herceptin 420 mg. The quality attributes (HMWS, charge variants, Met oxidation, HER2 binding, and

antiproliferation), selected based on a risk assessment (Table 119), and the resulting data analysis for the SB3 and US-Herceptin 150 mg lots are summarized in the following table, prepared by the reviewer (Tables 120-124, Figure 157-163). The protein concentration, reconstituted volume, and recoverable protein content analysis between SB3 and US-Herceptin 150 mg lots were discussed in the quantity section (above).

	SE-HPLC	icIEF			Met oxidation	HER2	Antiproliferation
	%HMWS	% acidic	% main	% basic	%relative oxidation	%relative binding	%relative potency
SB3	0.6-0.7	39.0-39.4	52.1-52.4	8.5-8.6	3.1-3.3	97-101	93-103
US-Herceptin 150 mg	0.3-0.4	35.2-40.0	54.9-58.7	4.9-6.9	2.6-2.8	97-104	93-111

Reviewer comment: The risk assessment performed to identify quality attributes that may be impacted by differences in the manufacturing processes between a 150 mg and 420 mg presentation is acceptable. The data from the analytical similarity data generated between SB3 150 mg and US-Herceptin 150 mg show higher amounts of HMWS, higher amounts of basic charge species that correlates with lower amounts of main peak, higher amounts of Met oxidation, and similar amounts of acidic species, HER2 binding and antiproliferation activity. These differences are consistent with the difference indicated in the analytical similarity assessment between SB3 and US-Herceptin 420 mg. These data are acceptable and support that SB3 150 mg is highly similar to US-Herceptin 150 mg.

Comparative Stability

To support a demonstration of highly similar, the degradation profiles of SB3 DP (pilot, clinical, and PVR batches), US-Herceptin 150 mg and 420 mg, and EU-Herceptin lots were assessed in a comparative forced degradation and in-use stability studies. The degradation conditions studied include heat stress, oxidative stress, base stress, and light exposure.

Reviewer comment: Samsung was requested (through multiple IRs) to provide additional comparative forced degradation data, because the data included in the original assessment did not include US-Herceptin lots, and the data would not support the analytical similarity between SB3 and US-Herceptin or the analytical portion of the scientific bridge between among the three products. In response Samsung submitted forced degradation data from both US-Herceptin 150 mg and 420 mg lots and compared the data to SB3 and EU-Herceptin. The additional data submitted are included in the discussion below.

Temperature Stress:

Two lots of SB3 (one clinical and one PVR), two lots of US-Herceptin 420 mg, and one lot of EU-Herceptin were stored at 40±2°C, 75±5%RH, for up to 6 or 12 months. No significant differences or trending were detected in appearance (pre- or post-reconstitution), pH, osmolality (where evaluated), protein concentration (or total content per vial, where evaluated), particulate matter, and HER2 binding. The following changes were detected after 6 to 12 months (Tables 77-85, Figure 120-121):

- An increase in moisture levels of ~1.0-1.4% for SB3, and ~1.3% for EU-Herceptin; moisture levels were not evaluated for US-Herceptin lots. There was no apparent correlation between the increase in moisture content and reconstitution time across the three products.
- A significant decrease in potency by antiproliferation for SB3 lots after 6 months (20-30%) and 12 months (undetectable to 44%), after 6 months for US-Herceptin (~10%), and after 12 months (undetectable to 30%).
- An increase in HMWS in SB3 lots of ~7% and 4% (after 12 and 6 months, respectively), in US-Herceptin lots of ~4% (after 6 months), and in EU-Herceptin lots of ~5.5% (after 12 months).

- An increase in 2H1L impurity corresponding to a decrease in main peak in SB3 lots (impurity - ~1%, main peak - ~3%), in EU-Herceptin lots (impurity - ~1%, main peak - ~4%), there was not significant trending in US-Herceptin lots.
- An increase in basic charge species that corresponds with a decrease in main peak in SB3 lots after 6 months (basic - ~7%, main - ~10%) and after 12 months (basic - ~12%; main - 13%). US-Herceptin lots also had an increase in basic species of ~10% and a decrease in main of ~7 after 6 months, and EU-Herceptin had an increase in basic of ~15% and a decrease in main peak of ~15% after 12 months. There was no major trending in acidic species. The charge data were generated from both icIEF and CEX methods, and similar trends were indicated for both methods.
- An increase in Met oxidation in SB3 lots after 6 months of ~4.5% that decreases slightly by ~3% after 12 months, a similar trend is detected in the EU-Herceptin lot and the US-Herceptin lot.

Oxidative Stress:

Two lots of SB3, two lots of US-Herceptin 150 mg and two lots of EU-Herceptin were reconstituted and treated with hydrogen peroxide (0.01% or 0.05%), stored at 5±3°C and evaluated after 3 or 6 hours for oxidation at Met-83, 107, 255, 361, 431, 4, and/or HMWS, size impurities, charge variants, HER2 binding, antiproliferation, and FcRn binding. Tabular data, trending charts, and representative chromatograms were provided (Tables 87-89, Figure 122-126). The following is a summary of the changes and trending over the evaluated time period.

- No major increase or trending was detected for Met 83, 107, 361, 431 or 4 among the three products. A significant increase was detected in Met 255 in SB3 lots of ~9%, in US-Herceptin lots of ~9%, and in EU-Herceptin lots of ~6%.
- No major increase or trending was detected in size variants.
- There was a slight increase in acidic species among all three products of ~1-2%, a corresponding decrease in main species, and a slight decrease in basic species of ~1% among the three products.
- No major decrease or trending was detected in potency by HER2 binding or antiproliferation. However, a decrease in FcRn binding was detected of ~9-20% for SB3 lots, ~2-10% for US-Herceptin lots, and ~3-9% for EU-Herceptin lots, which appears to correlate with the increase in Met oxidation.

Base Stress:

Two lots each of SB3, US-Herceptin 150 mg, EU-Herceptin were reconstituted and treated with 0.5 N NaOH to pH 8.0. The samples were stored at 5±3°C, neutralized with 0.5 N HCl, and evaluated for deamidation, size variants, charge variants, and biological activity. Tabular data, trending charts, and representative chromatograms were provided (Tables 91-93, Figures 127-133).

- No major increase or trending was detected in deamidated Asn 28, 77/84, 162/210/212, 318, or 138. A slight increase was detected in Asn 55 deamidation after 7 days of ~0.5% for SB3, ~1% for US-Herceptin and EU-Herceptin lots. A similar trend was detected for Asn 387/391/393 deamidation among the three products. A significant increase in deamidation at Asn 30 was detected in all three products, with a ~12% increase in SB3 lots, ~17% increase in US-Herceptin lots, and ~13% increase in EU-Herceptin lots.
- No major trending was detected in HMWS, however, a minor increase in 2H1L levels corresponding to a decrease in main species was detected among all three products.
- An increase in acidic species was detected of ~15% for SB3 lots, ~20% in US-Herceptin lots, and ~17% in EU-lots, as well as a decrease in basic species of ~2.5% for SB3 lots, ~2% for US-Herceptin, and ~2% for EU-Herceptin, which corresponded to a decrease in main peak.
- A decrease was detected in antiproliferation (SB3 - ~7%, US-Herceptin - ~10%, EU-Herceptin ~10%) and HER2 binding (SB3 - ~10%, US-Herceptin - ~8%, EU-Herceptin - ~14%).

Photostability:

Two lots of SB3, and one lot each of US-Herceptin 420 mg and EU-Herceptin were exposed to either no light (dark control) or at least 1.2 Mlux·h of light for the duration required to reach the illumination exposure (monitored by a calibrated radiometer). No significant differences or trending were detected in appearance (pre- or post-reconstitution), pH, reconstitution time, moisture content, particulates, protein concentration, HER2 binding, antiproliferation, and Met 255 oxidation. The following changes were detected after exposure (Tables 96-98, Figure 134):

- A slight increase in acidic species, a minor decrease in basic species, correlating to a minor decrease in main peak was detected for all three products.
- A minor increase in HMWS, an increase in 2H1L, and a decrease in total purity were similarly detected among the three products.

Reviewer comment: *The forced degradation assessment indicates that there are numerous degradation pathways identified for SB3, US-Herceptin and EU-Herceptin, such as Met oxidation which correlates with increased basic charge species and a decrease in FcRn binding; and degradation through Asn deamidation which correlated with a decrease in potency. An assessment of ADCC activity and isoAsp 102 formation were not included in the forced degradation studies. However, the SAR study evaluated the potential correlation between isoAsp 102, charge, and potency and the data suggest no major correlation and indicate that the difference in basic species detected among the three products is not likely contributed to isoAsp 102 levels. ADCC activity was not monitored in the forced degradation studies, however, considering that HER2 binding must first occur for ADCC activity to be elicited, it is likely that the impact of associated degradation pathways (i.e., deamidation) on ADCC would be similar to the impact of the degradation on HER2 binding. Although some attributes for SB3 are higher at baseline compared to the US-Herceptin and EU-Herceptin lots, the same degradation pathways and similar degradation rates were detected in the forced degradation studies among the three products. The data collected in these studies support a conclusion of highly similar between SB3 and US-Herceptin, and support the establishment of the analytical portion of the scientific bridges among the products.*

In-use stability

Two comparative in-use stability studies were performed using one lot of SB3 and two lots of EU-Herceptin, a hold time stability study after reconstitution, and an infusion bag compatibility study. For the hold time stability study, two vials of each product were reconstituted with WFI and analyzed at 0 or 48 h after storage at 5±3°C. The samples were evaluated for appearance, pH, protein content, size variants, charge variants, HER2 binding, antiproliferation, and subvisible particles (Table 100). There was no major trending in any of the attributes evaluated across the time points for both products.

Infusion bag compatibility was assessed by reconstituting 20 vials of SB3 and EU-Herceptin lots in WFI, followed by storage at 5±3°C for 48 hours. The vials were injected into in four different infusion bags to a concentration of 640 mg in 250 ml in either a polyethylene (PE), polypropylene (PP), polyvinylchloride (PVC) bag containing 0.9% NaCl solution, or a PE bag containing 5% dextrose solution. The infusions bags were then inverted 10 times for mixing. Samples of the infusion bag content were either pulled immediately after mixing or after 24 or 48 h additional storage at 25±2°C. The samples were assessed for protein concentration, size variants, charge variants, HER2 binding, antiproliferation, and subvisible particles (Tables 101-104). The results show no major changes among the SB3 and EU-Herceptin in the product quality attributes evaluated after 48 h storage in the PP, PE infusion bag (not containing dextrose solution), or the PVC bag containing 0.9% NaCl solution. The samples stored in the PE bag containing 5% dextrose solution showed an increase in acidic species, a decrease in main peak, and a decrease in basic peak which were similar between SB3 and EU-Herceptin. The values for HER2 binding and antiproliferation values at each time point (including initial) for the SB3 batches were below the lower limit of the acceptance range, 76% and 66%, respectively; the potency values for EU-Herceptin, while on the lower end, were not outside of the acceptance range. All other attributes were within the acceptance ranges and were consistent between the two products. It is indicated that trastuzumab products should not be diluted in dextrose solutions. The data presented here support the preparation instructions.

Reviewer comment: As a general matter, in-use stability data are not needed to support analytical similarity; however, these data were provided and reviewed within the purview of the totality of data and information provided as part of the BLA. These data indicate that SB3 is stable upon reconstitution for up to 48 h at 5±3°C, and that the product is compatible with PP, PE, and PVC infusion bags not containing 5% dextrose solution. The data also demonstrate consistent stability profiles between SB3 and EU-Herceptin lots under in-use preparation and storage conditions.

Overall summary and conclusions of the analytical similarity assessment

Reviewer comment: The analytical similarity assessment presented by Samsung included the pairwise evaluation of SB3 150 mg and US-Herceptin 420 mg, as well as a side-by-side assessment of SB3 to a select number of US-Herceptin 150 mg lots. An analytical bridge was also established between SB3, US-Herceptin, and EU-Herceptin, thereby supporting the use of the EU-Herceptin in the comparative clinical studies. In addition, an analytical comparability study was conducted between US-Herceptin 150 mg and 420 mg lots to further support the use of US-Herceptin 420 mg lots as the primary comparator in the analytical similarity assessment.

The analytical similarity assessment included orthogonal physicochemical, biochemical, and functional assays. Differences between US-Herceptin and SB3 were shown in charge variants and glycosylation. Specifically, SB3 has higher levels of basic variants and HM compared to US- and EU-Herceptin. The differences seen in basic species correlates with higher amounts of c-terminal lysine and may potentially be associated with the higher baseline levels of methionine 255 oxidation in SB3 lots. The cumulative amounts of isoAsp 102 were greater in the US-Herceptin and EU-Herceptin lots compared to the SB3 lots as shown in the SAR study, indicating that the higher levels of basic charge species are not associated with increased isoAsp102, and not likely to impact in vitro potency. Overall, the differences in charge variants do not preclude a determination of highly similar between SB3 and US-Herceptin or the establishment of the analytical portion of the scientific bridges among SB3, US-Herceptin, and EU-Herceptin.

The difference in HM among the three products was minor, as the levels detected in SB3 were within the US-Herceptin range, but not within that of the EU-Herceptin lots. Given the magnitude of the differences observed, clinical impact is not expected. Therefore, the differences in HM do not preclude a determination of highly similar between SB3 and US-Herceptin or the establishment of the analytical portion of the scientific bridges among the three products.

In conclusion, the totality of the analytical similarity data supports a conclusion that SB3 is highly similar to US-Herceptin and the establishment of the analytical portion of the scientific bridges among SB3, US-Herceptin, and EU-Herceptin.



Kristen
Nickens

Digitally signed by Kristen Nickens

Date: 12/21/2018 08:41:09AM

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Qing
Zhou

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Date: 12/21/2018 09:41:44AM

GUID: 508da7430002bbad737ae8d4b9c59845

Recommendation: Approval

BLA/NDA Number: 761100
Review Number: First Round
Review Date: December 21, 2018

Drug Name/Dosage Form	Ontruzant (trastuzumab-dttb) Biosimilar to Herceptin
Strength/Potency	150 mg/vial
Route of Administration	Intravenous
Rx/OTC dispensed	Rx
Indication	Treatment of HER-2 overexpressing breast cancer, gastric cancer
Applicant/Sponsor	Samsung Bioepis Co., Ltd.

Product Overview

Ontruzant (trastuzumab-dttb) is a proposed biosimilar to US-Herceptin (trastuzumab). It is a humanized IgG1k monoclonal antibody produced in CHO cells. Trastuzumab targets and binds human epidermal growth factor receptor 2 (HER2) to inhibit HER2 receptor dimerization and subsequent downstream signaling and to activate antibody-dependent cellular cytotoxicity (ADCC) activity through concomitant binding to Fcγ receptors on immune effector cells.

Trastuzumab-dttb drug substance (DS) is produced in genetically engineered CHO cells. Trastuzumab-dttb drug product (DP) is manufactured to the same strength and presentation as US-Herceptin at 150 mg/vial. Trastuzumab-dttb DP is supplied at 150 mg/vial as a sterile, lyophilized powder for intravenous infusion. Ontruzant is proposed as a treatment for HER2-overexpressing breast cancer and gastric cancer.

Quality Review Team

Discipline	Reviewer	Branch/Division
Drug Substance/Analytical Similarity	Kristen Nickens	OPQ/OBP/DBRR1
Drug Product	Wen Jin Wu/Wendy Weinberg	OPQ/OBP/DBRR1
Immunogenicity	Milos Dokmanovic/Brian Janelsins	OPQ/OBP/DBRR1
OBP Labeling	Vicky Borders Hemphill	OPQ/OBP
Facility	Wayne Seifert/ Zhihao (Peter) Qiu	OPQ/OPF/DIA
Microbiology	Maria Jose Lopez-Barragan (DS) Lindsey Brown (DP)	OPQ/OPF/DMA
Microbiology Team Lead	Reyes Candau-Chacon	OPQ/OPF/DMA
CMC statistics	Yu-Ting Weng/Meiyu Shen	OTS/OB/DBV
CMC RBPM	Oumou Barry	OPQ/OPRO
Application Team Lead	Qing (Joanna) Zhou	OPQ/OBP/DBRR1
OBP Tertiary Reviewer	Kathleen Clouse	OPQ/OBP/DBRR1

Multidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Fatima Rizvi	OND/OHOP/DOP-1

Cross-disciplinary Team Lead	Jennifer Gao	OND/OHOP/DOP-1
Medical Officer	Jennifer Gao	OND/OHOP/DOP-1
Pharm/Tox	George Chang/Tiffany Ricks	OND/OHOP/DOP-1
Clinical Pharmacology	Islam Younis/Lanre Okusanya	OTS/OCP/DCPV
Clinical Statistics	Laura Fernandes/Shenghui Tang	OTS/OB/DBIV

1. Names:

- a. Proprietary Name: Ontruzant
- b. Trade Name: Ontruzant
- c. Non-Proprietary Name: trastuzumab-dttb
- d. CAS name: 180288-69-1
- e. INN Name: trastuzumab
- f. OBP systematic name: MAB HUMANIZED (IGGI) ANTI P04626 (ERBB2_HUMAN) [SB3]

Communications with Sponsor (OBP)

Communication/Document	Date
Information Request 1	December 4, 2017
Filing Memo	December 20, 2017
Filing Letter	January 3, 2018
Information Request 2	March 29, 2018
Information Request 3	April 9, 2018
Mid-cycle Communication	May 11, 2018
Information Request 4	May 15, 2018
Information Request 5	June 25, 2018
Information Request 6	June 29, 2018
Information Request 7	July 5, 2018
Information Request 8	July 19, 2018
Late-Cycle Meeting Background Package	August 7, 2018
Review Extension – Major Amendment	August 31, 2018
Late-Cycle Meeting Minutes	September 14, 2018
Information Request 9	November 19, 2018
Information Request 10	November 21, 2018
Information Request 11	December 4, 2018
Information Request 12	December 7, 2018
Teleconference	December 12, 2018
Information Request 13	December 14, 2018
Information Request 14	December 18, 2018
Information Request 15	December 19, 2018
Information Request 16	December 20, 2018

Submissions reviewed (OBP):

Submission	Date Received	Review Completed (Yes/No)
761100/0001	October 20, 2017	Yes
761100/0012	April 12, 2018	Yes
761100/0013	April 19, 2018	Yes
761100/0014	May 22, 2018	Yes
761100/0017	June 29, 2018	Yes
761100/0019	July 13, 2018	Yes
761100/0020	July 18, 2018	Yes
761100/0021	July 24, 2018	Yes
761100/0023	July 30, 2018	Yes
761100/0026	August 20, 2018	Yes
761100/0037	November 28, 2018	Yes
761100/0042	December 11, 2018	Yes
761100/0044	December 13, 2018	Yes
761100/0045	December 17, 2018	Yes
761100/0046	December 19, 2018	Yes
761100/0047	December 20, 2018	Yes
Information request 16 response By email	December 21, 2018	Yes

Submissions Reviewed (DMA):

Submission(s) Reviewed	Document Date
761100/0001	October 20, 2017
761100/0013	April 19, 2018
761100/0015	June 07, 2018
761100/0016	June 21, 2018
761100/0017	June 26, 2018
761100/0020	July 18, 2018
761100/0022	July 27, 2018
761100/0023	July 30, 2018
761100/0036	November 23, 2018
761100/0039	December 06, 2018
761100/0042	December 11, 2018
761100/0044	December 13, 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	Code ¹	Status ²	Date Review Completed	Comments
(b) (4)	III	(b) (4)	Glass vial	3	N/A		
	III		Rubber stopper	3	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 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. **None**

3. Consults: **None**

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

a. Recommendation:

The Office of Pharmaceutical Quality, CDER, recommends approval of STN 761100 for trastuzumab-dttb, manufactured by Samsung Bioepis, Co. The data submitted in this application are adequate to support the conclusion that the manufacture of trastuzumab-dttb is well controlled and leads to a product that is pure and potent. We recommend that trastuzumab-dttb be approved for human use under the conditions specified in the package insert.

b. Action letter Language:

- Manufacturing location:
 - Drug Substance: (b) (4)
 - Drug Product: (b) (4)
- Fill size and dosage form: 150 mg single-dose vial for injection
- Dating period:
 - Drug Product: 36 months when stored at 2 to 8°C
 - Drug Substance: (b) (4) when stored at (b) (4)
- Exempt from lot release
 - Yes
 - Rationale: Specified product in accordance with 21 CFR 601.2a.

B. Benefit/Risk Considerations:

Ontruzant (trastuzumab-dttb) is proposed as a biosimilar to US-Herceptin (trastuzumab) for treatment of HER2 overexpressing breast cancer and gastric cancer. By targeting human epidermal growth factor receptor 2 (HER2), the proposed mechanisms of action for trastuzumab include inhibition of HER2 signaling through the receptor and subsequent cell proliferation,

adhesion, and differentiation through inhibition of HER2 receptor dimerization, increased destruction of the endocytic portion of the HER2 receptor, and inhibition of extracellular domain shedding. Activation of cell-mediated immune defenses, such as ADCC activity, has also been identified as a potential mechanism of action of trastuzumab.

With respect to analytical similarity, Ontruzant was evaluated and compared to US-Herceptin and EU-Herceptin using a battery of biochemical, biophysical, and functional assays, including assays that addressed each major potential mechanism of action (see Section II A, Table 1, Analytical Similarity, below). Based on the extensive comparison of the functional, physicochemical, protein and higher order structure attributes, Ontruzant is highly similar to US-Herceptin, notwithstanding minor differences in clinically inactive components.

With respect to manufacturing process, the overall control strategy for Ontruzant manufacture incorporates control over raw materials, facilities and equipment, the manufacturing process, adventitious agents, release of Drug Substance (DS) and Drug Product (DP), and stability of these materials.

The technical assessments for OBP (including analytical similarity, drug substance, drug product quality and immunogenicity assays), DMA (including drug substance and drug product quality microbiology), and DIA facility are located as separate documents in Panorama.

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

1. Draft PMCs:

- a. Perform a method validation study to confirm the suitability of the FcγRIIIa AlphaScreen assay for use as a potency assay for drug substance and drug product lot release and stability testing.
- b. Perform a method validation study to confirm the suitability of the Size Exclusion-High Performance Liquid Chromatography assay for use as a purity assay in the detection of high molecular weight species for drug substance and drug product lot release and stability testing.
- c. Perform a qualification study to confirm the suitability of [REDACTED] (b) (4) assay for the detection of product-specific host cell protein impurities.
- d. Establish a two-tiered system for trastuzumab-dttb reference standard and provide qualification data for the working reference standard to be implemented.
- e. [REDACTED] (b) (4)
- f. Conduct a study to determine [REDACTED] (b) (4) at the pump speed setting used for the PPQ batches. The study should be conducted using trastuzumab-dttb drug product.

- g. Monitor [REDACTED] (b) (4) and provide [REDACTED] (b) (4)
- h. Update the dye-ingress container closure integrity test to include vial reconstitution prior to visual inspection.

II. Summary of Quality Assessments:

A. Analytical Similarity Assessment

Table 1. Summary of Quality Attributes Evaluated, Analytical Methods and Statistical Analysis Used for Analytical Similarity Assessment

Quality Attribute	Analytical Procedure	Statistical Testing
Potency	- Anti-proliferation assay - ADCC assay	1 1
Additional Functional Activity	Binding to HER2 target antigen by FRET	2
	In vitro angiogenesis assay	3
	Surface HER2 expression	3
	HER2 ECD shedding	3
	Inhibition of AKT phosphorylation	3
	Combination treatment with chemotherapy	3
	CDC assay	3
N-linked glycan Profile	% afucose, high mannose, G0F, G1F, G2F by HILIC-UPLC	2
	N-linked glycosylation site by UPLC-ESI-MS/MS	3
	N-glycan Identification Using Procainamide Labeling	3
Charge heterogeneity	% acidic, main and basic variants by CEX-HPLC	2
	% acidic, main and basic variants by icIEF	2
Size Variants/Aggregates	% HMW by SE-HPLC	2
	% NGHC, HC+LC, IgG, 2H1L by CE-SDS (reducing and non-reducing)	2
	Aggregates characterization analysis by SE-HPLC/MALLS	3
	Aggregates characterization analysis by SV-AUC	3
Protein Concentration (after reconstitution)	UV/VIS spectroscopy at A280 nm	2
Primary Structure	Amino acid sequence by UPLC-ESI-MS/MS	3
	Molecular mass by UPLC-ESI-MS	3
	N-terminal sequencing by UPLC-ESI-MS/MS	3
	C-terminal sequencing by UPLC-ESI-MS/MS	3
	Peptide mapping by UPLC-ESI-MS/MS	3
	Disulfide bond analysis by UPLC-ESI-MS/MS	3
	Free sulfhydryl group quantification by FLR	3
	Methionine oxidation by UPLC-ESI-MS/MS	3
	Deamidation by UPLC-ESI-MS/MS	3
Higher Order Structure	Protein secondary structure analysis by CD (Far- and Near-UV)	3
	Protein tertiary structure analysis by intrinsic fluorescence spectroscopy	3

	- Protein folding analysis by extrinsic fluorescence spectroscopy - Protein secondary structure analysis by FTIR spectroscopy - Protein tertiary structure analysis by H/DX-MS - Thermal stability analysis by DSC - Protein size characterization analysis by DLS - Subvisible particles analysis by MFI - Extinction coefficient determination	3 3 3 3 3 3 3
Fc and complement receptor binding	- FcγRIIIa binding assay by AlphaScreen® - FcRn binding by AlphaScreen® - C1q binding assay (ELISA) - FcγRIa binding assay by FRET - FcγRIIa binding assay by AlphaScreen® - FcγRIIb binding assay by AlphaScreen® - FcγRIIIb binding assay by SPR	2 2 2 3 3 3 3

1. Equivalence testing
2. Quality range testing
3. Visual comparison

Trastuzumab-dttb was found to have the same primary, secondary and tertiary structure as US-Herceptin and EU-Herceptin by the methods listed in Table 1, above. All spectrometry-based methods yielded overlapping spectra among trastuzumab-dttb, US-Herceptin and EU-Herceptin. DSC was used to measure the melting temperatures of the protein subunits. Quantitative analysis and representative thermograms also indicate structural similarity among the three products (i.e., trastuzumab-dttb, US-Herceptin and EU-Herceptin).

ADCC activity and inhibition of proliferation of HER2 expressing cells, which reflect the presumed primary mechanisms of action of US-Herceptin, were determined to be equivalent among the three products. HER2, FcγRIa, FcγRIIIa, FcγRIIIb, C1q and FcRn binding was found to be similar between Ontruzant and US-Herceptin. The binding activities to FcγRIIa and FcγRIIb were slightly lower in Ontruzant as compared to those of US-Herceptin; however, binding to FcγRII in general is not expected to impact product safety, quality, potency, PK and immunogenicity. Therefore, the slight differences observed do not preclude the demonstration of highly similar between Ontruzant and US-Herceptin.

The glycan distribution, including the levels of afucosylated species, sialic acid and high mannose, which can impact product potency and PK, is similar among Ontruzant, US-Herceptin and EU-Herceptin. A slight increase in the levels of non-glycosylated heavy chain (NGHC) was observed in Ontruzant as compared to those of US-Herceptin, which may have the potential to impact product potency through ADCC; however, ADCC activity was demonstrated to be equivalent among Ontruzant, US-Herceptin and EU-Herceptin. Other size variants, including high and low molecular species, are similar among the three products. Higher amounts of basic variants were observed in Ontruzant as compared to those of US-Herceptin and EU-Herceptin. Results from additional characterization studies indicate the differences observed in basic variants are attributed to differences in the amount of deamidated Asn30 and Asn55, isoAsp102, and oxidated Met255, which may have the potential to impact HER2 binding, anti-proliferative activities and PK (through binding to FcRn), respectively. However, results from structure function studies show the level of differences observed in each of these variants does not significantly impact product potency (HER2 binding and anti-proliferation) and FcRn binding activity. This is further supported by data from analytical similarity assessment. Therefore, the observed

differences in product associated variants do not preclude the demonstration of highly similar between Ontruzant and US-Herceptin.

Trastuzumab-dttb meets the statutory “same strength” requirement under section 351(k)(2)(A)(i)(IV) of the PHS Act.

Based on the extensive comparison of the functional, physicochemical, protein and higher order structure attributes, Ontruzant is highly similar to US-Herceptin, notwithstanding minor differences in clinically inactive components. In addition, the analytical component of the three-way scientific bridge has been adequately established.

B. CQA Identification, Risk and Lifecycle Knowledge Management

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

CQA	Risk	Origin	Control Strategy	Other notes
HER2 binding (potency)	Efficacy	Intrinsic to the molecule. Impacted by aggregation, fragmentation, and potentially deamidation. Minimal change is expected during storage through expiry.	(b) (4)	N/A
Inhibition of proliferation (potency)	Efficacy	Intrinsic to the molecule. Impacted by aggregation, fragmentation, isomerization and deamidation. Minimal change is expected during storage through expiry.		N/A
ADCC activity (potency)	Efficacy	Intrinsic to the molecule. Impacted by glycosylation, aggregation and fragmentation and deamidation Minimal change is expected during		Fc γ RIIIa binding assay was qualified for use in the analytical similarity assessment and validated for use as a lot release test. The sponsor is asked to provide

		storage through expiry.		data to support method validation to demonstrate suitability of the method as a stability test in a PMC.
Identity	Safety and Efficacy	Intrinsic to the molecule	(b) (4)	N/A
High Molecular Weight (HMW) species/Aggregates (product-related impurities)	Efficacy (HER2 binding and ADCC), Safety/Immunogenicity and potentially PK	Manufacturing process and exposure to heat. Minimal change is expected during storage under recommended conditions through expiry.		The SE-HPLC assay was validated for the detection of monomer content as a lot release and stability test, but not appropriately validated for the evaluation of HMW species. The sponsor is asked to provide data to support method validation for the assessment of HMW species as a PMC.
Fragments (LMW species)	Efficacy and PK	Manufacturing process and exposure to heat and light stress. Minimal increase in fragments is expected during storage under recommended conditions.		N/A
Glycosylation (afucosylated species)	Efficacy (ADCC activity/FcγRIIIa binding)	Cell culture process No change is expected during downstream manufacturing and storage.		N/A

Glycosylation (high mannose)	PK and efficacy (afucosylated)	Cell culture process No change is expected during downstream manufacturing and storage.	(b) (4)	N/A
Deamidation (Asn 30)	Efficacy	Manufacturing process including hold, storage, exposure to heat.		N/A
Heavy Chain Asp102 isomerization	Efficacy	Manufacturing process including hold, storage, exposure to heat.		N/A
Methionine (Met 255) oxidation	PK	Manufacturing process including hold, storage, exposure to heat, oxidative stress.		N/A
Osmolality	Safety, Efficacy (control of degradation through formulation)	Formulation		N/A
pH	Safety and Efficacy	Formulation		N/A

Protein Content	Efficacy	Manufacturing process	(b) (4)	N/A
Polysorbate 20	Safety and efficacy (control of degradation)	Formulation		N/A

C. Drug Substance [Ontruzant] Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

Table 2: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management.

CQA	Risk	Origin	Control Strategy	Other notes
Appearance	Safety	Controlled by the manufacturing process	(b) (4)	N/A
Host Cell Proteins (Process-related impurity)	Safety and Immunogenicity	Production cell line		The current HCP assay has low coverage (b) (4) and was evaluated against HCP (b) (4). The sponsor will be asked to provide additional data to support the use of this assay in a PMC.
Host Cell DNA (Process-related impurity)	Safety	Production cell line		N/A

			(b) (4)	
(b) (4) (Process-related impurity)	Safety and Immunogenicity	Process related impurity (b) (4)		N/A
(b) (4) (Process-related impurity)	Safety, immunogenicity	Cell bank (b) (4)		N/A
Viruses (Contaminant)	Safety	Contamination during manufacture, most likely during cell culture operations		N/A

			(b) (4)	
Mycoplasma (Contaminant)	Safety	Mycoplasma would most likely be introduced during cell culture operations.		N/A
Leachables (Process-related impurity)	Safety	Manufacturing components and the DS container closure system		N/A
Bioburden	Safety, purity, and efficacy (degradation or modification of the product by contaminating microorganisms)	Bioburden can be introduced by raw materials and throughout the manufacturing process		N/A
Endotoxin	Safety and purity	Endotoxin can be introduced by raw materials and throughout the manufacturing process		N/A

- **Description:** Trastuzumab-dttb is an IgG1 kappa monoclonal antibody with two identical HCs and two identical LCs, covalently linked with four inter-chain disulfide

bonds. It contains one N-linked glycosylation site located at Asn300 on each heavy chain. The theoretical molecular mass is 148kDa. The theoretical isoelectric point (pI) is 8.9. The experimental extinction coefficient at 280 nm is 1.5 (mg/mL)⁻¹ cm⁻¹ (b) (4)

- **Mechanism of Action (MoA):** Multiple mechanisms of action have been proposed for trastuzumab. These include inhibition of HER2 signaling through the receptor and subsequent cell proliferation, adhesion, and differentiation through inhibition of HER2 receptor dimerization, increased destruction of the endocytic portion of the HER2 receptor, and inhibition of extracellular domain shedding. Activation of cell-mediated immune defenses, such as ADCC activity, through concomitant binding to HER2 and to Fcγ receptors on immune effector cells has also been identified as a potential mechanism of action of trastuzumab. It appears that NK cells are important mediators of ADCC activity in the context of trastuzumab-treated breast cancer. Complement-dependent cytotoxicity (CDC) is not considered to be a major mechanism of action for trastuzumab.
- **Potency Assay:** Three assays are used to control the biological activity of trastuzumab-dttb. A cell-based bioassay which measures the level of growth inhibition of HER2 expressing cancer cells (BT474) induced by trastuzumab-dttb is used to control anti-proliferative activity of trastuzumab-dttb.

A binding assay which measures the inhibition of the binding of trastuzumab to Human Epidermal growth factor Receptor 2 (HER2) by trastuzumab-dttb is used to control the relative binding activity of trastuzumab-dttb to HER2 ligand.

A binding assay which measures the inhibition of the binding of IgG to FcγRIIIa by trastuzumab-dttb is used to control the relative binding activity of trastuzumab-dttb to FcγRIIIa, as a surrogate for ADCC activity. This assay is currently validated for use as a lot release test and qualified for use in the similarity assessment. A PMC will be communicated to the sponsor to provide method validation for the Competitive inhibition binding assay to FcγRIIIa for use as a stability test method.

- **Reference Materials:** (b) (4)
PMC will be communicated to the sponsor to establish a two-tier system for the reference standard.

- **Critical starting materials or intermediates:** (b) (4)

- **Manufacturing process summary:**



(b) (4)

(U) (4)

- **Container closure:** The DS is (b) (4) The container closure system is suitable for trastuzumab-dttb, based on stability data and maintenance of closure integrity.
- **Dating period and storage conditions:** The DS can be stored (b) (4) for up to (b) (4)

D. Drug Product [Ontruzant] Quality Summary:

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
Color and clarity of solution (general)	Safety and Efficacy	Formulation, contamination, or degradation	(b) (4)	N/A
Lyophilizate appearance	Safety and Efficacy (stability)	Manufacturing process	(b) (4)	N/A
Moisture content	Efficacy (stability)	Manufacturing Process	(b) (4)	N/A

			(b) (4)	
Particulate Matter (visible and subvisible) (Product or Process Related Impurities)	Safety/ Immunogenicity	Manufacturing process and container closure system		N/A
Deliverable Content (general)	Efficacy/Dosing	Manufacturing process		N/A
Leachables (process-related impurities)	Safety	Manufacturing equipment and container closure		N/A
Sterility (Contaminant)	Safety risk to patients (infection) Efficacy (degradation or modification of the product by microorganisms or their byproducts)	Contaminants could be introduced throughout DP manufacturing of by container closure integrity failure		PMC to monitor (b) (4)
Endotoxin (Contaminant)	Safety, purity, and immunogenicity	Contaminants could be introduced throughout DP manufacturing process and through raw materials		N/A
Container Closure Integrity (Sterility Assurance)	Safety (Failure in closure integrity may lead to contamination through a loss of sterility) or evaporation/leakage (impacting concentration or content)	May be impacted by storage conditions		PMC to update the CCIT

- **Potency and Strength:** Ontruzant is supplied at 150 mg/vial. Potency is defined as the percent activity relative to the current trastuzumab-dttb reference standard. The potency assays are the same as described for the DS.
- **Summary of Product Design:** Ontruzant is supplied as a sterile, single-dose, preservative-free lyophilized powder for IV infusion in a 15-mL vial. Ontruzant is formulated in 5.0 mM L-histidine, 60 mM trehalose dihydrate, 0.01% polysorbate 20 at pH 6.0. Reconstitution with 7.4 mL sterile water for injection (WFI) yields a solution containing approximately 21 mg/mL Ontruzant. The deliverable amount is 150 mg.
- **List of Excipients:** L-Histidine, L-Histidine hydrochloride monohydrate, trehalose dihydrate, and polysorbate 20. All excipients are compendial.
- **Reference Materials:** See DS section above.
- **Manufacturing process summary:** (b) (4)
- **Container closure:** Trastuzumab-dttb is packaged in 15 mL (b) (4) clear glass vials with (b) (4) rubber and crimp seals with flip-off caps.
- **Dating period and storage conditions:** The sponsor proposed 36 months of shelf life when stored at 5 ± 3 °C, protected from light. The drug product reconstituted in sterile WFI can be stored at 2-8°C for no more than 24 hours. The reconstituted drug product diluted in sterile 0.9% sodium chloride solution can be stored at 2-8°C for no more than 24 hours.
- **List of co-package components, if applicable:** N/A

E. Establishment Information:

Overall Recommendation: Approve
DRUG SUBSTANCE

Function	Site Information	FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Manufacture of the MCB and WCB and Storage.	(b) (4)	(b) (4)	No further evaluation. MCB and WCB manufacture and storage only.	Not Applicable	No further evaluation required, MCB and WCB manufacture and storage only.
Storage of the MCB and WCB.			No further evaluation. MCB and WCB storage only.	Not Applicable	No further evaluation required, MCB and WCB storage only.
Storage of the MCB and WCB.			No further evaluation. MCB and WCB storage only.	Not Applicable	No further evaluation required, MCB and WCB storage only.
Storage of the MCB and WCB.			No further evaluation. MCB and WCB storage only.	Not Applicable	No further evaluation required, MCB and WCB storage only.
(b) (4)	(b) (4)	(b) (4)	Approve facility based on profile.	Not Applicable	Approval
			Approve facility based on profile.	Not Applicable	Approval
			Approve facility based on profile.	Not Applicable	Approval
DS storage	(b) (4)	(b) (4)	Approve facility based on profile.	Not Applicable	Approval
DS manufacture and packaging, QC release testing (protein concentration, appearance, endotoxin, and microbial enumeration). Stability testing (all			Approve facility based on inspectional assessment.	3-Item Form FDA 483	Approval. Firm's response to the objectionable conditions were adequate.

tests). IPT testing (b) (4)					
QC release testing (all tests excluding protein concentration, appearance, endotoxin, and microbial enumeration). Stability testing (all tests excluding endotoxin and microbial enumeration).	(b) (4)		Approve facility based on profile.	Not Applicable	Approval
Stability testing (endotoxin and microbial enumeration).			Approve facility based on profile.	Not Applicable	Approval
DRUG PRODUCT					
DP manufacture, QC release testing (Sterility), Stability testing (CCIT), and in-process test (IPT) all tests.	(b) (4)		Approve facility based on district office recommendation and drug product waiver memo.	Not Applicable	Approval
Stability testing (all tests excluding CCIT).			Approve facility based on inspectional assessment.	3-Item Form FDA 483.	Approval. Firm's response to the objectionable conditions were adequate.
QC release testing (all tests excluding endotoxin and sterility). Stability testing (all tests excluding endotoxin and sterility).			Approve facility based on profile.	Not Applicable	Approval

Stability testing (anti-proliferation assay).	(b) (4)	Approve facility based on profile.	Not Applicable	Approval
QC release and stability testing (endotoxin and microbial enumeration).		Approve facility based on profile.	Not Applicable	Approval
Secondary packaging		No further evaluation. Secondary packaging facility.	Not Applicable	No further evaluation, secondary packaging facility only.
Secondary packaging		No further evaluation. Secondary packaging facility.	Not Applicable	No further evaluation, secondary packaging facility only.

F. Facilities: This application is recommended as approve from a facility review perspective.

G. Lifecycle Knowledge Management:

a. Drug Substance:

- i. **Protocols approved:** (b) (4)
(b) (4) DS annual stability protocol
- ii. **Outstanding review issues/residual risk:** None
- iii. **Future inspection points to consider:** None

b. Drug Product

- i. **Protocols approved:** DP annual stability protocol
- ii. **Outstanding review issues/residual risk:** None
- iii. **Future inspection points to consider:** None

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]			x
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		x	
18.	SPOTS (special products on-line tracking system)		x	
19.	USAN assigned name	x		
20.	Other [fill in]			x
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}			x



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**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

Primary Reviewer: Lindsey Brown, Ph.D.

Secondary Reviewer: Reyes Candau-Chacon, Ph.D.

Date: 5/15/2018

To: Administrative File

STN: 761100

Subject: 351(k) Biosimilar BLA

Applicant: Samsung Bioepis Co., Ltd

US License Number: 2046

Facility: [REDACTED] (b) (4)

Product: Proposed biosimilar to US referenced Herceptin (SB3)

Indication: Adjuvant Breast Cancer (ABC), Metastatic Breast Cancer (MBC), Metastatic Gastric Cancer (MGC)

Dosage Form: Single-dose vial, 150 mg lyophilized powder for intravenous infusion

PDUFA Date: 01/20/2019

Recommendation for Approvability: BLA 761100 is recommended for approval from a sterility assurance and microbiology product quality perspective.

The following will be submitted as post-marketing commitments:

1. Conduct a study to determine [REDACTED] (b) (4) at the pump speed setting used for the PPQ batches. The study should be conducted using SB3 drug product.

2. Monitor [REDACTED] (b) (4) and provide [REDACTED] (b) (4)

STN 761100/SB3 (Samsung Bioepis Co., Ltd)

3. Update the dye-ingress container closure integrity test to include vial reconstitution prior to visual inspection.

Review Summary

Samsung Bioepis Co., Ltd has submitted BLA 761100 for approval to manufacture SB3, a biosimilar biological product to US referenced Herceptin using the contact manufacturer

(b) (4)

The following amendments have been reviewed in support of 761100.

eCTD Sequence	Date	
0000	10/20/2017	Original Submission
0013	04/19/2018	Response to Information Request (IR)
0015	06/07/2018	Response to IR
0017	06/29/2018	Response to IR
0020	07/18/2018	Response to IR
0023	07/30/2018	Response to IR
0036	11/23/2018	Response to IR
0039	12/06/2018	Response to IR
0042	12/11/2018	Response to IR
0044	12/13/2018	Response to IR

1.14 Labeling

Information Request dated 5/24/2018

Microbiological studies in support of the post-constitution or post-dilution storage time (as stated in the proposed product labeling) have not been provided. Provide results from studies that demonstrate adventitious microbial contamination does not grow under the specified storage conditions (i.e., for up to 24 hours at approximately 2-8°C after reconstitution in SWFI and for up to 24 hours at approximately 2-8°C after further dilution with the 0.9% Sodium Chloride Injection, USP). Include a description of the test methods and results that employ a minimum

countable inoculum (10-100 CFU) to simulate potential microbial contamination that may occur during product reconstitution and dilution. Perform the test using the storage conditions (temperature and duration) and diluents specified in the product labeling. Provide justification for the selected test conditions and/or diluents as necessary. Periodic intermediate sample times are recommended, as well as extended sample time points demonstrating that the reconstituted or diluted product does not support microbial growth for at least the maximum storage periods under the specified storage conditions. Challenge organisms may include strains described in USP <51> Antimicrobial Effectiveness Testing, plus typical skin flora or species associated with hospital-borne infections. In lieu of this data, the product labeling should recommend that the post-reconstitution and/or post-dilution storage period is not more than 4 hours.

Summary response amendment 0039

A microbial challenge study was conducted in triplicate using one batch of SB3 DP. The study was conducted as two studies: post-reconstitution and post-dilution. For the reconstitution study, each vial containing 150 mg was reconstituted using 7.2 mL of SWFI and spiked with less than 100 CFU of the following organisms described in USP <51>: *S. aureus*, *P. aeruginosa*, *E. coli*, *C. albicans*, *A. brasiliensis*, and the common skin organism *M. luteus*. Data demonstrating inoculum verification of less than 100 CFU is presented in Table 6 of the response (table not shown). After reconstitution and spiking, the vials were stored up to 48 hrs. at 2-8°C. Samples were taken at 6, 24, and 48 hrs. and CFUs were counted using microbial enumeration. All test organisms were incubated on tryptic soy agar (TSA) at 30-35°C for no more than 3 days. *C. albicans* and *A. brasiliensis* were also incubated on saubourad dextrose agar (SDA) and incubated at 20-25°C for no more than 5 days. To meet acceptance criteria, the average number of CFUs recovered after incubation should not exceed 0.5log₁₀ of CFU recovered at time 0. The results of the post-reconstitution challenge are presented in Table 7 (table not shown). The average number of CFU recovered after incubation at 48 hrs at 2-8°C does not exceed 0.5log₁₀ of the initial inoculum. This data indicates that the reconstituted DP does not support microbial growth after 48 hrs.

For the post-dilution study, vials containing 150 mg were reconstituted using 7.2mL SWFI and stored up to 24 hrs at 2-8°C. The vial contents were pooled and diluted in 250mL of 0.9% sodium chloride solution in a polypropylene bag to produce a final concentration of 2.24 mg/mL (560 mg in 250 mL) which represents the worst case highest dose. The dilute DP was then spiked with less than 100 CFU of the same organisms as previously described. Inoculum verification is presented in Table 6 of the response (table not shown). The incubation and sampling conditions are the same as previously described. To meet acceptance criteria, the average number of CFUs recovered after incubation should not exceed 0.5log₁₀ of CFU recovered at time 0. The results of the post-dilution study are presented in Table 8 of the

response (table not shown). The average number of CFU recovered after incubation at 48 hrs at 2-8°C does not exceed 0.5log₁₀ of the initial inoculum for all organisms tested. The data presented in Table 8 indicates that the dilute DP does not support microbial growth after 48 hrs at 2-8°C.

Negative controls samples for the post reconstitution and post dilution study include buffer, media, sample bags, and DP samples. All negative controls are negative for growth. The results are presented in Table 9 and Table 10 of the response (tables not shown).

Reviewer's Comment: The sponsor agreed to conduct the post-reconstitution and post-dilution growth promotion studies in amendment 0015 to support a hold of up to 24 hours at 5 ± 3°C after reconstitution with SWFI and for up to 24 hours at 5 ± 3°C after further dilution with the 0.9% sodium chloride for injection. The data indicates that the reconstituted and diluted SB3 DP does not support bacterial growth up to 48 hrs. The data supports at post-reconstitution hold up to 24 hrs at 2-8°C and a post-dilution hold up to 24 hrs at 2-8°C.

Satisfactory

3.2.P.1 Composition of the Drug Product

SB3 drug product (DP) is manufactured as a sterile lyophilized powder for concentrate for solution for infusion. SB3 is reconstituted with 7.4mL of sterile water for injection (WFI) to produce 21mg/mL drug product. Prior to use the concentrated solution is further diluted with 0.9% sodium chloride and is delivered by infusion. The reconstitution diluents are not provided with the drug product. The composition of a vial of SB3 is presented in Table 1 (table not shown).

Description is Satisfactory

3.2.P.2 Pharmaceutical Development

(b) (4)

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3.2.P.8 Stability

3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment

The stability program will be used to assess the stability of SB3 DP. Data from stability testing data conducted in accordance to the guidelines specified in ICH Q5C and Q1A(R2) will be used to evaluate and extend the shelf life. The proposed shelf-life for SB3 DP is 36 months

when stored at 2-8°C. One batch per year will be placed in stability testing, unless no batches of SB3 are produced that year. The stability testing plan with regards to microbial quality is summarized below.

Test		Time Points (Months)				
		0	12	24	36	48
Container Closure Integrity	Pass		X	X ²	X ¹	X ¹
Sterility	No microbial growth observed	X			X ²	X ¹

1. Post-approval stability plan endpoints if the approved shelf-life is 48 months.

2. Post-approval stability plan endpoints if the approved shelf-life is 36 months.

Reviewer's Comment: Endotoxin testing was removed in the drug product stability program in amendment 0015. However, current stability samples will be monitored for endotoxin until the end of the stability study. The stability program should be evaluated by OBP.

3.2.P.8.3 Stability Data

Container Closure Integrity Testing Method Validation

Limit of Detection

Container closure integrity of the SB3 DP vials was evaluated using immersion in a 1% methylene blue solution. To determine the limit of detection, 10µl of 1:10 dilution and 5µl of 1:10, 1:100, dilutions of 1% methylene blue was added to the vial neck and lyophilized cake of separate vials. The vials were inspected by two analysts. Once the dye was visible to both analysts, the vials were reconstituted using 3mL and reanalyzed. The lowest concentration of dye that was visible in the neck and cake and is still visible after reconstitution is the limit of detection for the assay. The results of this study are presented in Table 5-1 (table not shown). The limit of detection is 5µl of 1:10 dilution of 1% methylene blue.

Repeatability/Specificity

To validate the CCIT method by dye ingress, 20 vials were punctured with a 20µm capillary. Three negative control samples were punctured with a sealed 20µm capillary. The positive and negative controls, as well as three non-punctured test samples were immersed in 1% methylene blue and exposed to 20psi of pressure for 30 min. The acceptance criteria are as follows:

- All 20 positive test samples but show evidence of dye penetration and must contain more dye that the reconstituted limit of detection vials.
- The three negative test samples with capillaries and thee unpunctured test samples must not show evidence of dye penetration.

For the first trial, the acceptance criteria were not met. Only 16 of the positive control vials were positive for dye penetration. One negative test sample with a capillary gave a false positive. For the second trial, only 15 positive control vials were positive for dye penetration. All negative control vials were negative. An investigation established that the positive control capillaries were blocked prior to use. For trial 3, all 20 positive control vials were positive for dye penetration. All negative control vials were negative for dye penetration. One vial was a false positive in trial 3 caused by improper sealing around the capillary. For trial 4, all 20 positive control vials were positive for dye penetration. All negative control vials were negative for dye penetration.

Information Request 11/15/2018

Regarding the container closure integrity test, clarify whether test samples are reconstituted after the CCIT prior to inspection. Non-reconstituted samples may result in false negatives because the seal may cover the dye. If your test does not include reconstitution of the samples, modify the test to include that step and update the BLA accordingly.

Summary response amendment 0036

CCIT validation was submitted in the initial submission. The impact of reconstitution on the limit of detection was evaluated. The results presented in Table 5-1 of validation report 073134-01-08 indicate that both analysts could detect dye ingress (5µl of 0.001% solution) in the neck and cake of the vial prior to reconstitution. Dye ingress was not detected in the reconstituted vials. To comply with the request, (b) (4)

[Redacted text block]

STN 761100/SB3 (Samsung Bioepis Co., Ltd)

PMC 3: Update the dye-ingress container closure integrity test to include vial reconstitution prior to visual inspection.

Reviewer's Comment: CCIT has been successfully validated to detect a 20µm defect in a vial.

Satisfactory

Conclusion

- I. The BLA, as amended, was reviewed from a sterility assurance and product quality microbiology perspective and is recommended for approval.
- II. Product quality aspects other than microbiology should be reviewed by OBP.
- III. See panorama for the GMP status of the relevant facilities.

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Candau-Chacon

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PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

Reviewer: Maria Jose Lopez-Barragan, Ph.D.
Secondary Reviewer: Reyes Candau-Chacon, Ph.D.

Date: 12/17/2018
BLA: 761100
Applicant: Samsung Bioepis Co., LTD.
US License: 2046
Subject: Biologic License Application
Facilities:  (b) (4)

Product: ONTRUZANT™ (SB3; a proposed biosimilar to US-licensed Herceptin®)
Indication: Treatment of patients with HER2-positive metastatic breast cancer and HER2-positive gastric cancer
Dosage: Lyophilized powder in single dose vial (150 mg) for intravenous infusion
BsUFA date: 1/20/2019

Recommendation for approvability: The drug substance section of BLA 761100, as amended, is recommended for approval from a microbial control and microbiology product quality perspective.

SUMMARY

Samsung Bioepis Co., Ltd. has submitted BLA 761100 to obtain approval of SB3, a proposed biosimilar to US-licensed Herceptin® (trastuzumab). BLA 761100 was submitted in eCTD format on 10/20/2017. This review contains the assessment of SB3 drug substance from a microbiology product quality perspective. Microbiology product quality and sterility assurance of SB3 drug product were reviewed by Dr. Lindsey Brown.

Drug Substance Microbiology Quality Information Reviewed

Description	eCTD Sequence	Date
Original BLA	0001	10/20/2017
Amendment (response to Information Request)	0013	4/19/2018
Amendment (response to Information Request)	0016	6/21/2018
Amendment (response to Information Request)	0020	7/18/2018
Amendment (response to Information Request)	0022	7/27/2018
Amendment (response to Information Request)	0044	12/13/2018

3.2.S DRUG SUBSTANCE

S.1 GENERAL INFORMATION

SB3 (trastuzumab) is a recombinant immunoglobulin G1 that contains human framework regions with the complementarity-determining regions of a murine antibody (4D5) that binds to the extracellular domain of HER2 receptor. SB3 is expressed in a Chinese Hamster Ovary (CHO) cell line.

The description is satisfactory

S.2 MANUFACTURE

S.2.1 MANUFACTURE(S)

(b) (4)



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S.7 STABILITY

S.7.1 Stability Summary and Conclusions

The proposed shelf-life for SB3 DS is (b) (4) at the recommended storage temperature (b) (4). Stability testing at long term (b) (4) and intermediate (b) (4) conditions include bioburden and endotoxin testing annually and at 30 and 42-month time-points.

Reviewer's comment: Microbial (bioburden and endotoxin) monitoring was eliminated from the DS stability program in amendment 0044.

Satisfactory

S.7.3. Stability Data

Bioburden and endotoxin results accrued during stability studies were provided in tables 5, 6, 8, 9, 11, and 12 of the submission. All results were below the limits of detection.

Reviewer's comment: Microbial attributes (bioburden or endotoxin) were monitored during the stability. Microbial growth is not expected to occur in stability samples held at (b) (4).

Satisfactory

CONCLUSION

- I. The Drug Substance section of this BLA, as amended, was reviewed from a microbial control and microbiology product quality perspective and it is recommended for approval.
- II. Non-microbial information and data from the Drug Substance section of this BLA should be reviewed by OBP.
- III. A pre-license inspection (PLI) of [REDACTED] (b) (4) [REDACTED] (Drug Substance manufacturing facility) was conducted by CDER/OPQ/OPF/DIA and CDER/OPQ/OBP from [REDACTED] (b) (4) through [REDACTED] (b) (4) (see under FACTS assignment [REDACTED] (b) (4)). Refer to Panorama for cGMP status of the relevant facilities.

Information request submitted on 4/9/2018. Responses provided in amendment 0013 dated 4/19/2018.

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

(b) (4)



Maria Jose
Lopez-Barragan

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Reyes
Candau-Chacon

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**Memorandum
(Immunogenicity Assay Review)**

Date: November 28, 2018

To: File for BLA 761100 (Seq. 0001)

From: Milos Dokmanovic, Ph.D., RAC, Product Quality Reviewer, DBRRI/OBP

Through: Brian Janelsins, Ph.D., Product Quality Reviewer, DBRRI/OBP

Product: SB3, a proposed biosimilar to US-licensed Herceptin (trastuzumab)

Indication(s): Adjuvant and metastatic HER2-overexpressing breast cancer and metastatic HER2-overexpressing gastric or gastroesophageal junction adenocarcinoma

Sponsor: Samsung Bioepis Co., Ltd.

Received by FDA: October 20, 2017

Action date: January 20, 2019

Recommendation: BLA 761100 is recommended for approval with respect to OBP's evaluation of the immunogenicity assays. Sufficient information and data were provided to support the suitability of the immunogenicity assays (binding and neutralizing anti-drug antibody assays) that were used to generate clinical anti-drug antibody data to support the BLA.

Note: Figures were copied directly from the submission. Reviewer's comments are emphasized in *italics*.

Background

Clinical development of SB3 included a PK study SB3-G11-NHV (Randomized, double-blind, three-arm parallel group, single-dose study to demonstrate similarity in PK, efficacy, and safety profiles between SB3, US-licensed Herceptin, and EU-approved trastuzumab in healthy males) and a confirmatory study SB3-G31-BC (Randomized, double-blind, parallel-group, multicenter study in woman with HER2 positive early breast cancer [EBC] or locally advanced cancer [LABC] in neoadjuvant setting to evaluate the efficacy, safety/tolerability and immunogenicity of SB3 compared to EU-approved trastuzumab). The clinical samples from PK study SB3-G11-NHV were evaluated for the presence of binding anti-drug antibodies (ADAs) using a single

ECL-based bridging assay with labelled SB3 reagents. The results showed that SB3, US-licensed Herceptin, and EU-approved trastuzumab treatment groups did not result in any patients developing ADAs; however, the study was not designed to allow for meaningful conclusions regarding the comparative incidences of immunogenicity between the treatment groups. Because study SB3-G31-BC is a multi-dose parallel arm study in the indicated population and is appropriately powered, this study is more informative about the comparative immunogenicity between the products. The study SB3-G31-BC clinical samples (approximately 4375 samples from 875 patients at pre-dose of cycles 1, 5, 9, and 14 and at end of study) were evaluated for the presence of binding ADAs using the same assay that was used to evaluate the study SB3-G11-NHV samples. The ADA incidences were reported both as 0.7% for the SB3 treatment group (3/423) and the EU-approved trastuzumab treatment group (3/426). Antibody titer values were reported for the samples containing ADAs. Two patients in each group contained neutralizing antibodies (Nabs) as determined by an ECL-based ligand-binding assay.

Reviewer comment: Because a determination of whether the ADA incidences are similar between the products was largely made by the analysis of ADA data generated from study SB3-G31-BC, this review memo focuses on the assay validation of the binding ADA and Nab assays that were used to analyze the SB3-G31-BC clinical samples (validation studies 8306929 and 8306930, respectively). During the review cycle, an information request (IR) was conveyed to the sponsor on 04/09/18 (i) to determine a confirmatory cut-point based on a 1% false positive rate and to use that cut-point to re-analyze the clinical samples that screened positive for ADAs, (ii) to provide the antibody titer values that consider the minimal required dilution (MRD) in the final titer value for samples that contain ADAs, and (iii) to re-calculate a Nab assay cut-point based on a 1% false positive rate and to use that cut-point to re-analyze the clinical samples that are confirmed positive for ADAs. The sponsor's responses received on 04/19/18 are acceptable and incorporated in the appropriate sections of the review memo.

Section 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

I. Immunoassay for detection, confirmation and titration of binding antibodies (Validation study 8306929)

The samples from the clinical study SB3-G31-BC were evaluated for the presence of binding ADAs using a multi-tier approach, consisting of screening, confirmatory and titration assays. The summary of the validated parameters is included in the Table 18 of the section 2.7.1.

Reviewer comment: The critical assay reagent sulfo-tagged SB3 was exhausted during patient sample evaluation. Therefore, new sulfo-tagged SB3 and biotinylated SB3 reagents were requalified from existing lot sources and used in the assay to perform the clinical sample evaluation. To support the use of the new reagents, new screening and confirmation cut points were determined and the assay signal generated from the old and the new assay reagents were compared to ensure appropriate system suitability criteria are implemented. Although it was unclear whether the assay with the new reagents was used to analyze all or some of the clinical

samples, the likelihood that the new reagents from the same lots would impact the ADA incidences is very low. See below for further discussion.

Screening assay design

Samples are immunodepleted with biotinylated anti-HER2 antibody. Streptavidin magnetic beads are added to the samples, and through magnetic separation, residual HER2 is removed from the samples. Acid dissociation is performed to release ADAs that are complexed with SB3 or EU-approved trastuzumab. Samples are then neutralized and incubated in the presence of a “master mix” that includes biotinylated and sulfo-tagged SB3, which allows a ternary complex to form. Following complex formation, the samples are added to the streptavidin coated plate to allow binding of biotinylated SB3 to streptavidin. Following a washing, the read buffer containing tripropylamine is added and electric voltage is applied to generate chemiluminescence; the signal is directly proportional to the ADA concentration.

Confirmatory assay design

The same procedures are followed as in the screening assay except that samples are either incubated or not with excess of unlabeled SB3 (concentration not specified) during the acid dissociation step. The percentage inhibition is calculated as $100 \times [1 - (\text{response of sample competed with SB3 excess} / \text{response of sample not competed with SB3 excess})]$.

Titration assay design

The same procedures are followed as in the screening assay, except that samples are serially diluted in the negative control (see below for details) prior to assay analysis. The titer is determined as the reciprocal of the highest serial dilution that was above the screening cut-point multiplied by the MRD (1:20). At least one sample in the serial dilution series must test negative.

Test matrix: Pooled normal human serum (NHS) was used to prepare the negative and positive controls (see below). Individual pre-dose patient samples (confirmatory study SB3-G31-BC) were used to determine the screening, confirmatory, and titer assay cut-points. Pooled and individual patient sera were used for the analysis of drug tolerance, selectivity/matrix effects (lipolysis/hemolysis), and stability (freeze/thaw and bench top).

Positive controls (PC): Commercially available, human anti-trastuzumab antibody (EU-approved trastuzumab specific Ab) obtained from AbD Serotec was used to prepare the low positive control (LPC) at 6.5 ng/ml and high positive control (HPC) at 10000 ng/ml.

Negative control (NC): Pooled NHS was used as the negative control.

Critical reagents: Critical reagents included unlabeled SB3, EU-approved trastuzumab, biotinylated SB3, sulfo-tagged SB3, Pierce streptavidin magnetic beads, and the NC.

System suitability: The ranges established for the controls correspond to the mean ± 3 SD from the data generated during the validation runs. The expected responses are ≤ 285 ECL for the NC, ≥ 183 and ≤ 733 ECL for the LPC, and ≥ 223118 and ≤ 511222 ECL for the HPC response. Of

note, the NC, LPC, and HPC ranges are for batch monitoring purposes, and investigations will be performed if values are outside the ranges.

Reviewer comment: *Because of the change in assay reagents, the system suitability criteria were re-assessed. First, the old and new assay reagents were compared by running the NC, LPC, and HPC (2 replicates, one analyst) in the same assay (see appendix 1, tables 1 and 2 for results; Study Report 8288854 and 8295025) to determine if the new reagents result in a difference in background signal and positive assay responses. The results indicated that NC and LPC responses were lower than those obtained using the old assay reagents (for example 104.7 versus 246.6 ECL for NC and 480 versus 519 ECL for LPC), and the values for HPC were higher using the new assay reagents (up to 40% higher). Based on the analysis of the NC, LPC, and HPC data generated from the new reagents, the updated system suitability criteria were provided (see appendix 1, Table 3; study reports 8288854 and 8295025); these include NC response of ≤ 157 ECL, LPC response of ≥ 288 and ≤ 680 ECL and HPC response of ≥ 370415 and ≤ 885925 ECL.*

Screening Assay Cut point: A total of 80 pre-dose samples were analyzed using a balanced design with eighteen runs (two analysts, 9 runs each, a total of 480 data points, see Table 2). Data from all runs were pooled into a single dataset, and potential outliers were identified as either greater than $Q3 + 1.5 \times IQR$ or lower than $Q1 - 1.5 \times IQR$ (where $Q1$ and $Q3$ stands for lower and upper quartile, respectively, and IQR stands for interquartile range); 24 outliers were excluded from analysis (5%). The linear regression analysis was run between sample means and the negative control means in each run, which showed correlation ($p < 0.0185$; R^2 value of 0.3007) for data on the raw scale (non-log transformed); therefore, normality was tested using non-transformed data (ECL values). Shapiro Wilk test indicated departure from normality ($p < 0.01$); it was decided that the screening cut-point be determined non-parametrically (95th percentile). Based on 456 data points, the screening cut-point value was established at 263.778. To determine the type of suitable cut-point (e.g., fixed or floating), ANOVA f-test was used to assess the equality of means across assay runs, and Levine's test was used to assess equality of variances across runs and analysts. As the results indicate statistically significant evidence for a difference in means across runs but not of variances, a floating cut point (plate-specific; PSCP) was implemented (see statistics memo for more details). The normalization factor at 1.26 was obtained by dividing the 95 percentile non-parametric value (263.778) by the mean of the negative control (208.824). The in-study plate-specific cut-point is determined by multiplying the normalization factor by the NC mean value for each given plate. Any in-study samples with a value above the cut point would be classified as "positive" and analyzed in the confirmatory assay. The screening cut-point was also used as titer assay cut-point.

Reviewer comment: *The cut-point determined by the analysis of pre-dose SB3-G31-BC clinical samples resulted in a false positive rate of 11%, which is considered acceptable when targeting a 5% false positive rate for the screening cut-point assay. We noted that multiple runs failed in the original validation study for cut point determination due to the use of a wrong lot of the PC*

antibody (lot HCA168 rather than HCA177), see appendix 3 for details. Importantly, however, all runs that tested the 80 samples (two analysts) for cut-point determination were repeated and passed the acceptance criteria (see appendix 1).

Because of the use of new SB3-labeled reagents during clinical sample analysis, a new screening floating cut point was determined with the new reagents by analyzing the same 80 pre-dose SB3-G31-BC patient samples that were analyzed to determine the original screening cut-point. Data and the statistical memo generated from the assessment are provided in Appendix 1, Table 4 and Appendix 4, respectively, of Report 8288854 and 8295025. Outliers were identified and excluded as described above. Non-transformed and log-transformed data gave evidence of a departure of normality (Shapiro-Wilk $p < 0.05$); therefore, a non-parametric approach was used to determine the 95th percentile of the normalized data set [cut-point value (126.834)/negative control mean value (92.2083)]. The normalization factor at the 95th percentile was calculated at 1.3. Therefore, the new in-study plate-specific cut-point is determined by multiplying 1.3 by the negative control mean on each plate. The new normalization factor is close to the previous value (1.26) and is not likely to cause a significant difference in the evaluation of the clinical samples. The new screening cut-point results in an acceptable false positive rate (5.6%). Therefore, the new cut-point appears to be appropriate to analyze the clinical samples with the new assay reagents.

Confirmatory assay cut-point: A total of 43 pre-dose samples were spiked with excess of SB3 and the level of % inhibition was determined relative to unspiked samples (a total of 258 data-points). Data from both runs were pooled into a single dataset, and potential outliers were identified as either greater than $Q3 + 1.5 \times IQR$ or lower than $Q1 - 1.5 \times IQR$ (where $Q1$ and $Q3$ stands for lower and upper quartile, respectively, and IQR stands for interquartile range); 6 outliers were excluded from analysis (2.3%). Assessment of normality of pooled data was done by Shapiro-Wilk test and there was no evidence of departure from normality ($p \geq 0.05$). The confirmatory cut-point was determined as the mean + 2.33 SD. As the mean of % inhibition was calculated at -2.85% and the SD of inhibition values at 10.2, the confirmatory cut point was established at 20.9% based on 1% false positive rate. Any sample with % inhibition greater than 20.9% will be confirmed positive.

Reviewer comment: The confirmatory cut-point was originally determined during validation as 28.7% signal inhibition based on targeting a 0.1% false positive rate, which is not appropriate for a confirmatory cut-point. The update in the confirmatory cut point from 28.7% to 20.9% signal inhibition was due to the Agency's request to re-determine the confirmatory cut-point based on a 1.0% false positive rate. Because of the use of new SB3-labeled reagents during clinical sample analysis, a new confirmatory floating cut point based on a 1.0% false positive rate was calculated (21.1% signal inhibition, see appendix 1, table 4 for raw data). The new confirmatory cut-point is appropriate (e.g., results in a 2% false positive rate).

LPC concentration and sensitivity: The LPC was calculated from analysis of the dilution series as the concentration that would be equivalent to the floating cut-point. HPC sample was diluted in the 10000 to 0.1 ng/ml range in 2-fold dilution series (three independently prepared series), to span the screening cut-point. The analysis was conducted by at least two analysts, on a minimum of two days (a total of 12 independent dilution series, Table 4). Each assay run included three independently diluted series (analyzed in duplicate), and a minimum of three sets of duplicate NC (on different positions within a plate) and at least two sets of duplicate HPC and LPC. A log-log regression model was used to back calculate a concentration that was equivalent to the floating cut-point (PSCP). Based on the results from 12 series, a mean value was calculated at 3 ng/ml, and the sensitivity was determined as 5.34 ng/ml (mean +1.80*SD). The LPC was calculated at 6.54 ng/ml (mean +2.72SD) to ensure a 1% rejection rate.

Reviewer comment: *The results from an additional LPC assessment (Table 5) show that the PC at 6.5 ng/ml confirmed positive in 80% of samples prepared using pooled human sera (NC). This indicates that the LPC may be set too low and result in a greater rejection rate than 1%.*

However, this was not a concern because the clinical samples were analyzed on plates that included a LPC that generated a positive response and passed system suitability criteria. The results from the selectivity experiments (Tables 12, 13, 14 and 15), which used BC patient sera, indicate lower sensitivity at 25 ng/ml, likely due to matrix effects (see selectivity). Both sensitivity values are however sufficient for evaluation of binding ADA concentrations in screening and confirmatory assay formats.

Precision: Inter-assay and intra-assay precision were reported for the screening, confirmation and titration assay. Screening and confirmation assay precision was evaluated in the same runs (Table 6); titration assay precision was determined based on data from the runs that established the LPC (Table 4).

- Screening assay: HPC, LPC and NC samples were run on at least six different plates, by at least two different analysts, on a minimum two different days. Three sets of control samples (in duplicates) were included on each plate. The intra-assay precision (%CV) was 6.1-21.8% for five out of six runs for LPC and 3.5-19.1% for six out of six runs for HPC; one run for LPC had 30% CV. The inter-assay precision was 22.1%CV for LPC and 13.7% for HPC.

Reviewer comment: *A single point with slightly higher %CV is acceptable. In the sample analysis outline amendment 4, the sponsor indicated that during assay execution, the assay is also monitored based on LPC/Mean NC ratio and the obtained results were consistent between the runs, regardless of the higher value for intra-assay %CV.*

- Confirmation assay: LPC and HPC were run on at least six different plates, by at least two analysts, on a minimum of two different days. Three duplicate sets of HPC and LPC, with and without spiked SB3, were analyzed on different plate location. The intra-assay

precision for LPC was 7.6-24.3%CV, and for HPC was 0% CV; the inter-assay precision was 10% CV for LPC and 9% CV for HPC.

- Titration assay: As stated before, the inter and intra-assay precision was assessed from independently prepared dilution series that were used to determine LPC concentration (Table 4). The results for intra-assay precision in most runs were within the range of 1.8-20% CV. For the titer of 128000, two out of four runs were 43.9%CV and 85.8%CV; the other two were 16.3%CV and 5.4%CV. For the titer 256000, two out of four runs were 25.9%CV and 50.9% CV; the other two were 5% and 8.5%CV. For the titer 512000, two out of four runs were 28.3%CV and 46.3%CV; the other two were 7.9%CV and 3.2%CV. Overall, the inter-assay precision for all 12 series was 43.3%CV.

Reviewer comment: *The higher values for intra-assay precision are noted for titers at or greater than 128000. Of note, the assay sensitivity was determined at 5.34 ng/ml and would correspond to the median titer of 12800. The results for intra-assay precision for titers up to 64000 (corresponding to the concentration of 3.13 ng/ml) are sufficiently tight and acceptable to support assay performance in the indicated range.*

Drug tolerance: To investigate if clinically relevant EU-approved trastuzumab or SB3 drug levels may interfere with ADA detection, the maximum tolerated concentration of ADA was determined by spiking ADA samples (a range of 0-10000 ng/ml) with different concentrations of either SB3 and Herceptin (a range of 0-150 µg/ml). The replicate samples were incubated for 1 hour at 37°C and were tested by using appropriate dilutions. Drug tolerance data obtained from spiking either EU-approved trastuzumab or SB3 were also compared to test antigenic equivalence; antigenic equivalence was demonstrated by graphical comparison of plotted results and by determining the mean % difference between signals in the presence of either EU-approved trastuzumab or SB3.

The results indicate that ADA concentration of 6.5 ng/ml can be detected in the presence of up to 20 µg/ml of either SB3 or EU-approved trastuzumab and ADA concentration of 250 ng/ml and higher can be detected in the presence of up to 150 µg/ml of either SB3 or EU-approved Herceptin (Tables 9 and 10). Of note, by graphical comparison, there was similar decrease in signal (except for 6.5 ng/ml ADA concentration) with either SB3 or EU-approved Herceptin (Figure 2).

Reviewer comment: *Study SB3-G31-BC indicates that C_{through} levels for both drugs are similar and do not exceed 50.502-55.799 µg/ml (Table 9, section 2.7.2). This is within the range that was evaluated in the drug tolerance assessment; no interference is detected in that range and the assay is sufficiently sensitive to detect clinically relevant ADA incidences in the presence of either SB3 or EU-approved trastuzumab. In addition, the C_{max} levels for both drugs were generally within or near the evaluated range. Therefore, the true sensitivity of the assay is acceptable to evaluate the clinical study SB3-G31-BC samples for binding ADAs.*

The range for % mean difference between ECL values for the detection of ADAs in the presence of EU-approved trastuzumab and SB3 is between -33.4% to 11.2% (Table 11). Although this appears to be a wide range, there was no impact on the sample screening, and the titrations show similar trends across different levels of drug and ADAs (Figure 3, Section 2.7.1; see below). Therefore, the assay is likely to act similarly regardless whether samples have SB3 or EU-approved Herceptin. Antigenic equivalence is also supported by the fact that 95.6% of all clinical study SB3-G31-BC samples that screened and confirmed positive using excess of SB3 were additionally confirmed positive using excess EU-approved trastuzumab. Overall, the validation and clinical sample results support antigenic equivalence between SB3 and EU-approved trastuzumab.

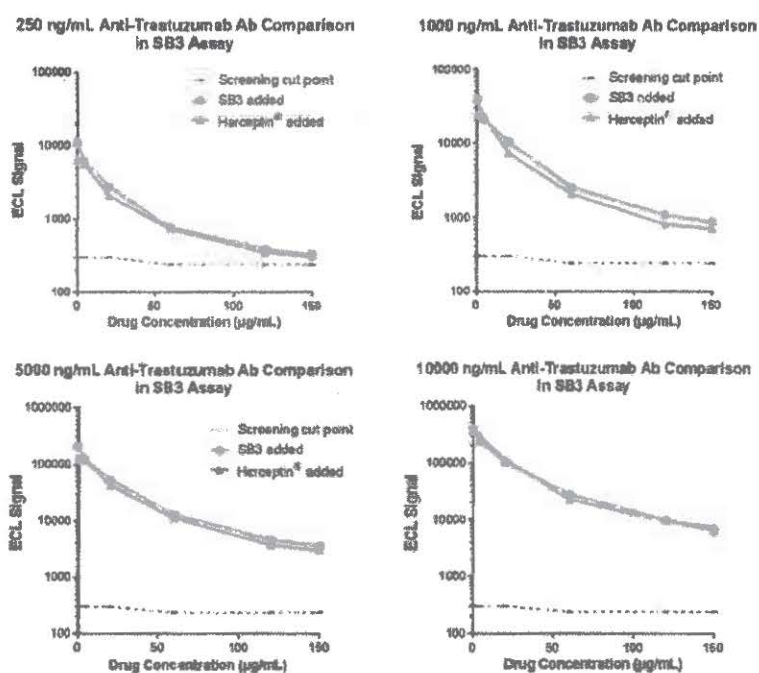


Figure 3: Antigenic Equivalence of SB3 Assay in Clinical Phase III ADA Method Validation

Selectivity: To support detection of ADAs in patient serum matrix, selectivity was analyzed in 6 analytical runs (VB30R-VB41) using individual sera from breast cancer patients. Ten individual samples were either spiked or not with LPC and HPC and analyzed in the screening and confirmatory assay. All unspiked samples screened negative (Table 12). All HPC spiked samples screened and confirmed positive (100%). For LPC spiked samples, all ten samples screened positive (100%); however, only 7 were confirmed positive (70%). Because of this discrepancy, the analysis was repeated in additional runs (Tables 13 and 14) using LPC at either 6.5 ng/ml (the same as before) or PCs at 7.5, 10, and 12.5 ng/ml; most samples tested as expected, however, one sample tested consistently negative in the confirmatory assay (IM15/11110718/140BRH1000651). To explore higher concentrations, a PC at 25 ng/ml was

used and the sample IM15/11110718/140BRH1000651 was confirmed as expected ("Positive"). Based on this, the sensitivity for confirmatory assay is 25 ng/ml (Table 15).

Reviewer comment: *There are no matrix effects that would impact the performance of the screening and confirmatory assays at ADA levels that are of likely clinical significance.*

Lipemic and hemolyzed matrix: The impact of serum matrix was evaluated by using samples with high triglyceride levels (300 mg/dL) and different blood hemolysis levels (2% and 5% hemolysis) and determining the screening and confirmation rates with blank, LPC and HPC (Tables 16 through 19). The results for the screening and confirmatory assay were as expected for lipemic and 2% hemolyzed sample matrices. For 5% hemolysis, one out of three blank samples tested positive in the screening assay (Table 18). Because of this, the analysis was repeated twice using 5% hemolyzed matrix; in the repeat analysis, five out of six blank samples screened negative, and six out of six confirmed negative.

Reviewer comment: *Overall, the results from different matrices support sufficient sensitivity for the screening and confirmatory assays.*

Hook effect: The ability of high ADA concentrations to interfere with screening assay performance and result in false negative results was evaluated in one analytical run (VB35). An ultra-high PC at 20000 ng/ml was prepared, diluted over the range of 20000-0.002 ng/ml and analyzed in screening assay. All PC preparations above the sensitivity of the assay (i.e., 20000, 2000, 200, and 20 ng/ml) screened positive; the concentration of the PC and the ECL values correlated at levels above the cut-point (Table 20).

HER-2 protein interference: Because of potential interference of HER-2 protein on ADA detection, the NC, LPC, and HPC samples were analyzed in the presence of different HER-2 protein concentrations (0, 50, 100, and 150 ng/ml). Of note, it was determined that the HER-2 levels in most patient sera were below 50 ng/ml. All LPC and HPC samples screened positive, as expected (Table 21). For NC, four samples were screened negative, as expected; the sample spiked at 100 ng/ml HER2 screened positive. Because of this anomaly, the NC analysis was repeated with two different sample preparations (run VB37R), using the same HER2 range (0-150 ng/ml). Most of samples screened negative, as expected; only two samples in one preparation (100 and 150 ng/ml) screened positive.

Reviewer comment: *The ability of HER-2 protein to interfere with assay performance and result in false positive results was addressed by incorporation of a HER-2 depletion step during sample preparation and prior to incubation with the master mix.*

Stability: The impact of freeze/thaw (F/T) manipulation (4 and 8 cycles thawed from either <-10 or <-50°C storage) and stability at room temperature (24, 48 and 72 hours) was evaluated using LPC and HPC in triplicates (Tables 23 and 24). No impact was detected, and all samples screened positive, as expected. The intra-assay variation was acceptable for most data-points: up

to 14.1% CV in F/T study and up to 13.1% CV in room temperature stability study. Only one measurement (8 F/T cycles for HPC) had a variation at 48.5% CV.

Reviewer comment: *Overall, the results support sample stability following freeze/thaw and room temperature exposure. Of note, additional stability data (up to 12 F/T cycles, and up to 210 hours at room temperature) were provided to ensure PC stability throughout assay re-validation that was performed because of updates in critical reagents. Overall, the data support that the clinical samples and PC controls will remain stable during clinical sample analysis.*

Re-analysis of clinical ADA data (SDN 13 in response to IR from April 9, 2018):

The sponsor updated the evaluation of the clinical samples using the confirmatory assay cut-point based on a 1% false positive rate (Tables 2 of IR response) and provided corrected titer values that include the MRD value (Table 5 of the IR response). Based on the 1% false positive confirmatory cut-point, two additional positive samples were detected in the SB3-treated group at baseline. These two additional samples are expected to have low titer. The overall immunogenicity incidence of the SB3-treated group (0.7%) did not change due to the two additional samples being detected positive at baseline.

II. Immunoassay for detection of neutralizing anti-SB3 and anti-Herceptin antibodies in breast cancer human serum (Validation study 8306930)

The samples from clinical study SB3-G31-BC that screened and confirmed positive for binding ADAs were evaluated for the presence of Nabs.

Reviewer comment: *The validated parameters for the Nab assay used to evaluate the incidences of immunogenicity in the study population were the same as those obtained during assay validation (see study reports 8288854 and 8295025). Out of five in-study runs, only one run failed system suitability (i.e., PC acceptance criteria); the run was successfully repeated and it passed the acceptance criteria.*

Nab detection assay design

The samples are prepared by using an acid dissociation step to release any ADAs complexed with drug (EU-approved trastuzumab or SB3). Biotinylated SB3 and streptavidin magnetic beads are used to form a complex with ADAs, and samples are washed to remove any free drug. A second acid dissociation step is applied to release ADA from the streptavidin beads, and after a neutralization step, the ADAs in the sample are incubated with plate-immobilized biotinylated SB3. Following complex formation, sulfo-tagged HER2 is added to bind with the free biotinylated SB3. To generate electrochemiluminescence signal, read buffer containing tripropylamine is added and electric voltage is applied; the signal is inversely proportional to the Nab concentration in a sample.

Reviewer comment: *The assay design is based on a direct competitive ligand binding approach. Because this approach reflects the presumed therapeutic mechanism of action, it is acceptable to use a competitive ligand binding assay in lieu of a cell-based assay for Nab detection.*

Test matrix: Pooled NHS was used to prepare the controls (NC, LPC and HPCs, see below for details). Individual pre-dose patient samples from the study SB3-G31-BC were used to determine the assay cut-point. Pooled and individual patient sera (BCS) were used for the analysis of drug tolerance, selectivity/matrix effects (lipolysis/hemolysis), and stability (freeze/thaw and bench top).

Positive controls (PC): Commercially available, human anti-trastuzumab obtained from AbD Serotec (generated against EU-approved trastuzumab) was used to prepare the low positive control (LPC) at 275 ng/ml and high positive control (HPC) at 2000 ng/ml in pooled NHS.

Negative control (NC): Pooled NHS was used as negative control.

Critical reagents: Critical reagents include biotinylated SB3, sulfo-tagged HER2, Pierce Streptavidin Magnetic Beads, and NC.

System suitability: NC response value of ≥ 15231 ECL, LPC response of ≥ 3628 and ≤ 21396 ECL, and HPC response of ≥ 782 and ≤ 2146 ECL. The ranges established for all three controls corresponded to the mean ± 3 SD analysis of the data generated from the validation runs.

Reviewer comment: *Of note, the data-set that was used to establish the system suitability criteria comes from inter- and intra-assay precision runs (Table 5). Some of the data from validation runs (see runs VB59 and VB60 in selectivity and lipemic/hemolysis matrix analysis) had unusually high variability and were not used to derive the ranges.*

Cut-point determination: A total of 80 pre-dose samples was analyzed in a balanced design, with eighteen runs (two analysts, 9 runs each, a total of 320 data points, see Table 2). All results were normalized relative to mean NC response (S/N ratio) in each run. The results from all runs were pooled into a single dataset, and potential outliers were identified as either greater than $Q3 + 1.5 \times IQR$ or lower than $Q1 - 1.5 \times IQR$ (where $Q1$ and $Q3$ stands for lower and upper quartile, respectively, and IQR stands for interquartile range); 11 outliers (3.4%) were excluded from the analysis. The analysis of 309 data-points by Shapiro-Wilk test indicated no departure from normality ($p \geq 0.05$) and the screening cut point was determined based on a 1% false positive rate using the following formula: mean + $2.33 \times SD$. Based on 309 data points, the screening cut-point value was established at 0.893 and any value below would be considered positive for Nabs. To determine the type of suitable cut-point (fixed, floating or dynamics), ANOVA f-test was used to assess the equality of means across assay runs and Levine's test was used to assess equality of variances across assay runs and analysts. As the results indicate no statistically significant evidence for differences in means or in variances across the runs, a fixed cut-point was

implemented. Any sample value that is below the pre-specified cut point would be “positive” for Nabs.

Reviewer comment: *The original cut-point determined during validation was based on 0.1% false positive rate, which resulted in a cut-point value of 0.866. Per the Agency’s request, the assay cut-point based on a 1% false positive was re-calculated as shown above.*

Sensitivity and LPC concentration: The sensitivity and LPC were determined from the analyses of a series of titrations. For each series, the HPC sample was diluted in the 2000 to 0.49 ng/ml range (three independently prepared series), to span the screening cut-point; the samples were tested by at least two analysts, on a minimum of two days (a total of 12 independent dilution series, Table 4). Each assay run had a minimum of three sets of duplicate NC (different positions within a plate) and a minimum of two sets of duplicate HPC and LPC. A regression model was used to back calculate a concentration that was equivalent to the fixed cut point. Based on the results from the 12 series, a mean value was calculated as 103.54 ng/ml, with SD of 60.738. The sensitivity was determined at 214 ng/ml based on mean + 1.83SD analyses to ensure higher consistency for reporting the sensitivity. The LPC was calculated at 274.82 ng/ml (mean +2.82SD) to ensure a 1% false rejection rate.

Inter/intra-assay precision

Inter and intra-assay precision was assessed in 6 analytical runs (VB49-VB54RRR); three sets of HPC and LPC controls were analyzed on each plate, by at least two analysts, over at least two days (a total of 36 data points for each control set, see Table 5). NC was included in each run. The intra-assay variation (%CV) for both control sets was below 25% (a range of 3.2-24.3% for LPC and a range of 6.9-25.6% for HPC). The inter-assay variation was also below 25% (21.4% CV for LPC and 15.5%CV for HPC).

Reviewer comment: *We note that during the precision runs, multiple failures occurred due to “negative PC response”. Details are not provided, but it appears that the LPC sample readings were above the cut point, and therefore were designated as “negative”. Of note, it appears that the LPC used in those runs could be 250 ng/ml and not 275 ng/ml as determined by titration analysis. It is possible that the value at 250 ng/ml was the originally intended value (see also analysis in Table 4 and original protocol that specified the use of lower LPCs). Importantly, however, the runs were repeated using 275 ng/ml LPC, and the results from the repeated runs were acceptable.*

Drug tolerance: To investigate if clinically relevant EU-approved trastuzumab or SB3 drug levels may interfere with Nab detection, the maximum tolerated concentration of Nab was determined by spiking the PC antibody (a range of 0-5000 ng/ml) with different concentrations of either SB3 and Herceptin (a range of 0-150 µg/ml). The replicate samples were incubated for 1 hour at 37°C and were tested by using appropriate dilutions. The obtained results were also compared to establish potential differences between the effects of EU-approved trastuzumab and SB3;

antigenic equivalence was demonstrated by graphical comparison of data plots and by determining mean % difference between signals.

The sample positivity was confirmed for all tested PC concentrations, including LPC at 275 ng/ml, in the presence of up to 150 µg/ml of either SB3 or EU-approved trastuzumab (Tables 8 through 10, not copied here). A similar decrease in signal was detected with increasing concentrations of SB3 and EU-approved trastuzumab (Figure 2, amendment to final report 1); the % difference for most results was in the range of -17.3 to 10.4%. Only the 2000 ng/ml PC sample in the presence of 120 µg/ml and 150 µg/ml of drug resulted in higher differences between SB3 and EU-approved trastuzumab (-41.9% and -34% ng/ml, respectively; Table 10).

Reviewer comment: Study SB3-G31-BC indicates that C_{trough} levels for both drugs are similar and do not exceed 50.502-55.799 µg/ml (Table 9, section 2.7.2). This is within the range that was evaluated in the drug tolerance assay; no interference is detected in that range and the assay is sufficiently sensitive to detect clinically relevant ADA incidences in the presence of either SB3 or EU-approved trastuzumab. In addition, the C_{max} levels for both drugs were generally within or near the evaluated range. Therefore, the true sensitivity of the assay is acceptable to analyze the SB3-G31-BC study samples that confirm positive for ADAs.

The results from the antigenic equivalence analysis support similar assay performance with either EU-approved trastuzumab or SB3 (Figure 4, Section 5.3.1.4; see below). Regarding any data-points with different mean results (such as data point with 2000 ng/ml ADA), there is no impact on the sample determination; all values are below the assay cut-point and therefore positive. Therefore, the assay is likely to act similarly regardless whether samples have SB3 or EU-approved Herceptin. In addition, considering the surrogate nature of PCs, there were no significant differences in assays responses when a PC directed against SB3, EU-approved trastuzumab, and US-licensed Herceptin were used in the assay (Figures 5 – 8, Table 14; Section 2.7.1), which further supports antigenic equivalence.

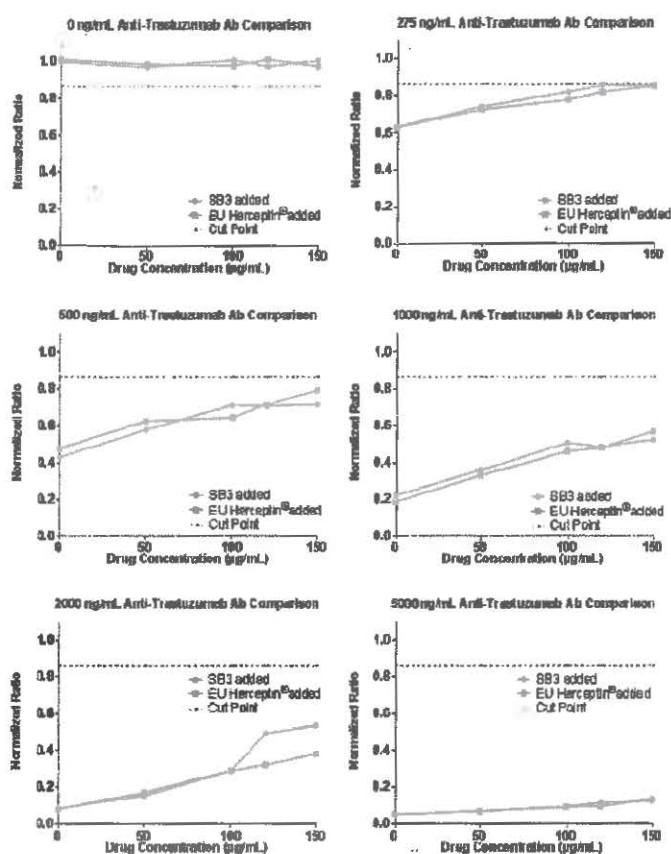


Figure 4: Antigenic Equivalence in SB3 Assay in Clinical Phase III Nab Method Validation

Selectivity: To support detection in patient serum matrix, selectivity was analyzed in 3 analytical runs (VB59, VB63 and VB63) using individual breast cancer patient sera (ten) that were either spiked or not with LPC and HPC. All control samples screened negative (Table 11). All HPC spiked samples screened positive (100%). For LPC spiked samples, only four samples screened positive (40%). Because of this anomaly, the analysis was repeated in additional runs using five out of six individual patient sera from the previous analysis (one sample was not repeated due to limited amounts) and eight additional patient samples that were not previously evaluated (Tables 12 and 13). All LPC samples screened positive in repeat analysis.

Reviewer comment: This is acceptable and demonstrates that there are no matrix effects that can impact the detection of a Nab response at the LPC and HPC levels.

Lipemic and hemolyzed matrix: The impact of serum matrix was evaluated for high triglyceride levels (300 mg/dL) and for different blood hemolysis levels (2% and 5% hemolysis); all evaluations included NC (blank), LPC (spiked at 275 ng/ml) and HPC (spiked 2000 ng/ml). All NC samples for lipemic matrix were negative and two out of three LPC and all three HPC samples were positive (Table 14, amendment to final report). Because of the LPC anomaly, the analysis was repeated (Table 15), and all LPC and HPC samples (three repeats from two

independent preparations) were positive. For 2% hemolysis matrix, all three NC samples were negative, and one out of two LPC samples three out of three HPC samples were positive (Table 16). For 5% hemolysis matrix, one out of three NC sample was positive, all three LPC were negative and two out of three HPC samples were negative. Because of anomaly with 2% and 5% hemolysis matrix, the analysis was repeated with two independent preparations of LPC and HPC (three repeats for each preparation); all LPC and HPC samples tested positive, as expected (Table 17).

Hook effect: The ability of high Nab concentrations to interfere with the screening assay performance and result in false negative results was evaluated in analytical run VB61. An ultra-high PC at 25000 ng/ml was prepared, diluted up to 256-fold and analyzed (a range of 25000-97 ng/ml). All results tested positive; the increasing PC concentration generally correlated with decreasing assay response values (Table 19).

HER-2 protein interference: Because of potential interference of HER-2 protein on Nab detection, the NC, LPC and HPC samples were prepared in NHS, and analyzed in the presence of different HER-2 protein concentrations (0, 50, 100, and 200 ng/ml). All blank samples were negative, and all LPC and HPC samples were positive. (Table 20).

Stability: The impact of freeze/thaw (F/T) manipulation (4 and 6 F/T cycles from <-50°C) and stability at room temperature (24, 48 and 72 hours) was evaluated using NC (single), and LPC and HPC (triplicates); all samples were prepared using pooled BC sera. No significant impact was detected in either study (Tables 21 and 22). The intra-assay variation (%CV) was up to 6.1 % for F/T stability study; the maximum decrease relative to baseline was 7.7%. The intra-assay variation (%CV) was up to 15.4% for room temperature stability study; the maximum variation relative to baseline was up to 5.5% decrease and up to 8% increase.

Re-analysis of Nab incidences with recalculated confirmatory cut point (SDN 13 in response to IR from April 9, 2018)

The sponsor updated the evaluation of clinical samples using the Nab assay cut-point based on a 1% false positive rate (Tables 6 and 7 of IR response). Based on the updated assessment, three additional samples tested positive (total of 7 samples). The additional samples that tested positive belonged to two patients in the EU-approved trastuzumab group. Thus, there were a total of two patients in the SB3 treatment group and two patients in the EU-approved trastuzumab treatment group that developed Nabs.



**Milos
Dokmanovic**

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**Brian
Janelsins**

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

Date: 06/14/2018
To: Administrative File, STN 761100/0
From: Wayne Seifert, Reviewer, CDER/OPQ/OPF/DIA
Endorsement: Zhihao (Peter) Qiu, Ph.D., Supervisory Consumer Safety Officer
CDER/OPQ/OPF/DIA, Branch 1 Chief
Subject: New Biologic License Application (BLA)
US License: 2046
Applicant: Samsung Bioepis Co., Ltd
Mfg Facility: Drug Substance: [redacted] (b) (4)
Product: (SB3) trastuzumab
Dosage: Single-dose vial, 150 mg, Intravenous infusion
Indication: For Adjuvant Breast Cancer, Metastatic Breast Cancer, and Metastatic Gastric Cancer.
Due Date: 10/28/2018, Expedited Review 06/22/2018

RECOMMENDATION: This submission is recommended for approval from a facilities assessment perspective.

SUMMARY

The subject BLA proposes manufacture of SB3 (trastuzumab) DS at the [redacted] (b) (4) and DP at [redacted] (b) (4). Both locations are multi-product manufacturing facilities. The final dosage form is a lyophilized 150 mg presentation consists of a 15cc clear glass vial, 20 mm [redacted] (b) (4) rubber [redacted] (b) (4) stopper, and 20mm Red flip-off cap.

SB3 is a recombinant DNA-derived, humanized monoclonal antibody (IgG1 kappa) that contains human framework regions with the complementarity determining regions of a murine antibody (4D5) that binds to HER2. SB3 consists of 1,328 amino acids and has a molecular weight of approximately 148 kDa. Its molecular formula without the N-glycan moiety is C₆₄₆₀H₉₉₇₂N₁₇₂₄O₂₀₁₄S₄₄.

The facilities supporting SB3 DS manufacture, testing and storage are provided under Table 1, with facilities supporting SB3 DP manufacture, testing and storage included under Table 3.

ASSESSMENT

3.2.S.2. DRUG SUBSTANCE FACILITIES

The proposed SB3 DS Manufacturer, Testing and Storage Facilities are provided in Table 1.

Table 1: Manufacturers for SB3 DS

Site Name	Address	FEI #	Responsibility	
(b) (4)			Manufacture of the MCB and WCB and Storage.	
			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, 21987 Republic of Korea	3010031951	(b) (4)	
(b) (4)				DS storage.
				DS manufacture and packaging, QC release testing (protein concentration, appearance, endotoxin, and microbial enumeration). Stability testing (all tests). IPT testing (all
				QC release testing (all tests excluding protein concentration, appearance, endotoxin, and microbial enumeration).

	(b) (4)	Stability testing (all tests excluding endotoxin and microbial enumeration).
	(b) (4)	Stability testing (endotoxin and microbial enumeration).
(b) (4)		

Reviewer Comment 1: *The facilities used for Manufacture, Testing and Storage of SB3 DS were adequately described.*

➤ **Prior Inspection History for DS Manufacturing, Testing and Storage Sites**

- (b) (4) – Manufacture of the MCB and WCB and Storage
 - Inspection Conducted (b) (4): This was a GMP of a of a contract testing laboratory for biotech drug products, with coverage for profile code CTX. Quality and Laboratory Systems were covered. The firm's cell banking operations include production of MCBs and WCBs; however, the firm does not maintain any cell banks at this location. A 3-Item Form FDA 483 was issued, with verbal observation discussed with the firm. The inspection was classified VAI. The prior two GMP inspections conducted (b) (4) were NAI.
- (b) (4) - MCB and WCB Storage
 - Inspection Conducted (b) (4): This was a routine and comprehensive GMP inspection of a contract testing laboratory for profile codes (b) (4). The firm performs mycoplasma, pyrogen, and viral contamination testing on both NDA and BLA human drugs. The firm is also a contract testing facility and manufacturer for medical devices and components, and conducts the in-life phase of GLP toxicology studies. Quality, Material, and Facilities and Equipment and Laboratory Control Systems were covered. No Form FDA 483 was issued, with 4 observations discussed with the firm. The prior two GMP inspections conducted (b) (4) were classified NAI.
- (b) (4) - MCB and WCB Storage
 - Inspection Conducted (b) (4): This was a GMP inspection of a control testing laboratory for profile code CTL. Quality, Facilities and Equipment, Materials and Laboratory Controls Systems were covered. No Form FDA 483 was issued, with verbal observations discussed with the firm. The inspection was classified NAI. The prior two GMP inspections conducted (b) (4) were NAI.
- (b) (4) - MCB and WCB Storage
 - Inspection Conducted (b) (4): This was a GMP inspection of a contract testing laboratory for profile code CTL. Quality and Laboratory System were covered, with cursory coverage for Facilities and Equipment Systems. A 4-Items Form FDA 483 was issued, with the inspection classified VAI. The prior two GMP inspection conducted (b) (4) were NAI and VAI, respectively.

- Samsung Bioepis Co., Ltd. (FEI: 3010031951) - DS Testing
 - Inspection Conducted 03/05 - 07/2018 by CDER-DIA: This was a PAI of contract testing laboratory for profile code CTL. Quality and Laboratory Control Systems were covered. No Form FDA 483 was issued, with seven verbal observations discussed with the firm. The inspection was classified NAI. The prior two GMP inspection conducted 11/06/2017 and 08/19/2016 were NAI and VAI, respectively.
- (b) (4) - DS Testing
 - Inspection Conducted (b) (4)
This was a GMP inspection of a contract manufacturer of licensed bulk vaccine and biologic therapeutic bulk DS, and human drug control test laboratory for (chemical/physical, microbiological sterility/non-sterility, and biological) for profile codes CBI and CTX. Quality, Facilities and Equipment, Production, and Laboratory Control Systems were covered. A 3-item Form FDA483 was issued, with the inspection classified VAI. The prior two GMP inspections conducted (b) (4) were VAI and NAI, respectively.
- Source (b) (4) - DS Storage
 - Inspection Conducted (b) (4) This was a GMP inspection of a freezer storage warehouse for profile code CBI. This was the firm's first Agency inspection, with Quality and Material Systems covered. No Form FDA 483 was issued, with the inspection classified NAI.
- (b) (4) - DS Manufacture and Testing
 - Inspection Conducted (b) (4): This was a PAI of a DS manufacturing facility for profile codes CBI. Quality, Facilities and Equipment, Materials, Production, and Laboratory Control Systems were covered. A 6-Item Form FDA 483 was issued, with verbal observations discussed with the firm. The inspection was classified VAI. The prior two GMP inspections conducted 06/ (b) (4) were NAI and VAI, respectively.
- (b) (4) - Testing
 - Inspection Conducted (b) (4): This was a GMP and PAI of a control testing laboratory for profile code CTL. Quality and Laboratory Systems were covered. No Form FDA 483 was issued, with one verbal observation discussed with the firm. The inspection was classified NAI. A prior GMP and initial inspection conducted 1 (b) (4) was OAI to VAI.
- (b) (4) - Testing
 - Inspection Conducted (b) (4): This was a GMP inspection of a contract laboratory for profile code CTL. Quality and Laboratory systems were covered. No Form FDA 483 was issued with the inspection classified NAI. The prior two GMP inspections conducted (b) (4) were NAI.

➤ **Current Prior Approval Inspection Decision**

- (b) (4) - MCB and WCB Manufacture and Storage

- No further evaluation required
- (b) (4) - MCB and WCB Storage
 - No further evaluation required
- (b) (4) - MCB and WCB Storage
 - No further evaluation required
- (b) (4) - MCB and WCB Storage
 - No further evaluation required
- (b) (4) - DS Testing
 - Approve facility based on profile
- (b) (4) - DS Testing
 - Approve facility based on profile
- Source (b) (4) - DS Storage
 - Approve facility based on profile
- (b) (4) - DS Manufacture and Testing
 - Inspection Conducted (b) (4) by CDER-DIA: This was a PLI inspection of a DS manufacturing facility for the subject application for profile code CBI. Quality, Production, Materials, Facilities and Equipment, and Laboratory Systems were covered. A 3-Item Form FDA 483 was issued, with the inspection classified VAI. See CMS Work # (b) (4), with a district office recommendation of approval.
- (b) (4) - DS Testing
 - Approve facility based on profile
- (b) (4) - DS Testing
 - Approve facility based on profile

Reviewer Comment 2: *The proposed facilities for manufacture and testing of SB3 DS are currently in a state of compliance and are acceptable from a facilities assessment standpoint.*

3.2.A.1. DS SITE FACILITIES AND EQUIPMENT

(b) (4)



➤ **3.2.P.3. DRUG PRODUCT FACILITIES**

SB3 (trastuzumab) DP: The container closure system for SB3 DP consists of (b) (4) glass vial with (b) (4) rubber stopper and aluminum seal with crimp. Secondary packaging consists of a carton box and package insert, with the carton box guarding the product from the potential risk of damage and light.

ASSESSMENT

The proposed SB3 DP manufacture, testing, storage and release facilities are listed in Table 3.

Table 3: Manufacturers Proposed for SB3 DP

Site Name	Address	FEI #	Responsibility
(b) (4)			DP manufacture, QC release testing (Sterility), Stability testing (CCIT), and in-process test (IPT) all tests.
			Stability testing (all tests excluding CCIT).
			QC release testing (all tests excluding endotoxin and sterility). Stability testing (all tests excluding endotoxin and sterility).
			Stability testing (anti-proliferation assay).

	USA		
		(b) (4)	QC release and stability testing (endotoxin and microbial enumeration).
			Secondary packaging.
			Secondary packaging.

Reviewer Comment 11: *The facilities used for manufacture, testing and storage of SB3 DP were adequately described.*

➤ **Prior Inspection History for DP Manufacturing, Testing, Storage and Release Sites**

- (b) (4) - DP Manufacture and Testing
 - Inspection Conducted (b) (4): This was a PAI for a finished dose manufacturer of human prescription DPs for profile code SVL. Quality, Materials Management, Facilities and Equipment, Production and Laboratory Systems were covered. A 2-item Form FDA 483 was issued with the inspection classified VAI. The prior two GMP inspections conducted (b) (4) for profile codes LVP, SVS, and SVT and (b) (4) were NAI and VAI, respectively.
- (b) (4) - DP Testing
 - See Section 3.2.S.2, DS facilities section for history.
- (b) (4) - DP Testing
 - See Section 3.2.S.2, DS facilities section for history.
- (b) (4) - Testing
 - Inspection Conducted (b) (4): This was a GMP inspection of a contract analytical laboratory. The inspection covered in vitro bioequivalence studies and respiratory group studies. A 1-Item Form FDA-483 was issued, with the inspection classified VAI. The prior two GMP inspections conducted (b) (4) included profile code CTL, with a classification of NAI.
- (b) (4) - DP Testing
 - See Section 3.2.S.2, DS facilities section for history.
- (b) (4) - Secondary Packaging
 - The firm has no inspectional history and is used for secondary packaging only.
- (b) (4) - Secondary Packaging
 - Inspection Conducted (b) (4) This was an inspection of a combination product packaging manufacturer and included profile code SVL. The firm continues to operate as a primary and/or secondary contract re-packager of solid and liquid oral dosage pharmaceuticals for humans. No Form FDA 483 was issued, with the inspection classified NAI. The prior two GMP inspections conducted (b) (4) were NAI and VAI, respectively.

➤ **Current Prior Approval Inspection Decision**

- (b) (4) - DP Manufacture and Testing
 - Approve facility based on district office recommendation and DP Waiver Memo.
- (b) (4) - DP Testing
 - Approve facility based on district office recommendation and inspectional assessment
- (b) (4) - DP Testing
 - Approve facility based on profile
- (b) (4) - Testing
 - Approve facility based on profile
- (b) (4) - Testing
 - Approve facility based on profile
- (b) (4) - Secondary Packaging
 - No further evaluation required
- (b) (4) - Secondary Packaging
 - No further evaluation required

Reviewer Comment 12: *The proposed facilities for manufacture and testing for SB3 DP are currently in a state of compliance and are acceptable from a facilities assessment standpoint.*

3.2.A.1. DP SITE FACILITIES AND EQUIPMENT





CONCLUSION

Adequate descriptions were provided for the facilities proposed for SB3 DP manufacture. The subject BLA is recommended for approval from a facilities assessment perspective.

Wayne Seifert
Consumer Safety Officer
OPF Division of Inspectional Assessment
Branch 1

Wayne E.
Seifert -S



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Zhihao (Peter) Qiu, Ph.D.,
Supervisory Consumer Safety Officer
OPF Division of Inspectional Assessment
Branch 1 Chief

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**Determining When Pre-License / Pre-Approval Inspections are Necessary
Inspection Waiver Memorandum**

Date: 06/18/2018
From: Wayne Seifert, OPQ/OPF/DIA
To: BLA File, STN 761100/0
Through: Zhihao (Peter) Qiu, Ph.D., Branch Chief, OPQ/OPF/DIA Branch 1
Subject: Inspection waiver memo for manufacture of SB3 DP at (b) (4)

Applicant: Samsung Bioepis Co., Ltd.

Facility: (b) (4)

Product: SB3 (trastuzumab)

Dosage: Single-dose vial/150 mg/Intravenous infusion

Indication: Adjuvant Breast Cancer (ABC), Metastatic Breast Cancer (MBC), and Metastatic Gastric Cancer (MGC).

Waiver Recommendation

The applicant for BLA STN 761100/0 proposes to manufacture SB3 DP at (b) (4). The proposed manufacturing process is similar to other licensed or approved products produced in the (b) (4) manufacturing department.

A PAI for the (b) (4) facility was conducted by IOG from (b) (4) for profile code SVL that resulted in a VAI conclusion. A prior ORAHD level I inspection was conducted (b) (4) for profile codes LVP, SVL, SVS, and SVT that resulted in a NAI conclusion, with a PAI conducted by CDER-DIA (b) (4) for profile code SVL, with a classified VAI.

The (b) (4) proposed for SB3 manufacture is (b) (4) located within the (b) (4) manufacturing department. The (b) (4) is used for the commercial manufacture of U.S. licensed biological products that includes (b) (4)

(b) (4) Based on the compliance history of the firm, the current GMP status, and the fact that (b) (4) (b) (4) has been approved to manufacture other Agency approved and licensed products, we recommend that the pre-license inspection for the facility be waived for BLA 761100/0 (action date 10/20/2018, primary review date 06/20/2018).

Summary

BLA STN 761100/0 proposes manufacture of SB3 DS at (b) (4) and SB3 DP at (b) (4) (b) (4). This waiver recommendation is in regards to SB3 DP at (b) (4).

Facility and Process Information

(b) (4)



Approvals:

Wayne E. Seifert -S
Wayne Seifert., DIA/OPF Reviewer _____ DATE _____
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Zhihao Qiu -S
Zhihao (Peter) Qiu, Ph.D., DIA/OPF, Branch Chief _____ DATE _____
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date=2018.06.18.08:48:45-0400

Wen J. Wu -S
Wen Jin Wu, Ph.D., DBRRI/OBP DP Reviewer _____ DATE _____
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Rachel L. Novak -S
Rachel Novak, Ph.D., DBRRI/OBP ATL _____ DATE _____
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Wendy C. Weinberg -S
Wendy Weinberg, Ph.D., DBRRI/OBP _____ DATE _____
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Patricia F. Hughestroost -S
Patricia Hughes, Ph.D., DMA/OPF Branch Chief _____ DATE _____
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Hughestroost -S
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Kathleen A. Clouse Strebel -S
Kathleen Clouse, Ph.D., DBRRI/OBP Division Director _____ DATE 6/19/2018
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Clouse Strebel -S
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