

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761100Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	<i>Electronic Stamp Date</i>
From	Jennifer Gao, M.D. (Acting CDTL) Laleh Amiri-Kordestani, M.D. (Associate Division Director)
Subject	Cross-Discipline Team Leader Review
BLA #	351(k) BLA 761100
Applicant	Samsung Bioepis Co., LTD.
Date of Submission	10/20/2017
BsUFA Goal Date	1/20/2019
Proprietary Name / Nonproprietary Name	ONTRUZANT/trastuzumab-dttb ¹ SB3 ² Lyophilized Powder for Intravenous Infusion
Dosage forms / Strength	For Injection: 150 mg lyophilized powder in a single-dose vial for reconstitution
Proposed Indication(s)	<p>ONTRUZANT is a HER2/neu receptor antagonist indicated for:</p> <ol style="list-style-type: none"> 1. Adjuvant breast cancer: <ul style="list-style-type: none"> Adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature) breast cancer <ol style="list-style-type: none"> a. As part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel b. As part of a treatment regimen with docetaxel and carboplatin c. As a single agent following multi-modality anthracycline based therapy <p>Select patients for therapy based on an FDA-approved companion diagnostic for Ontruzant.</p> <ol style="list-style-type: none"> 2. Metastatic breast cancer: <ol style="list-style-type: none"> a. In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer b. As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease <p>Select patients for therapy based on an FDA-approved companion diagnostic for Ontruzant.</p>

¹ The proposed proprietary name (Ontruzant) and proposed nonproprietary name (trastuzumab-dttb) for this proposed product have been conditionally accepted.

² For purposes of this review, the proposed product is referred to by the Sponsor's descriptor SB3, which was the name used to refer to this product during development.

	<p>3. Metastatic gastric cancer:</p> <p>a. In combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease</p> <p>Select patients for therapy based on an FDA-approved companion diagnostic for Ontruzant.</p>
Recommended Regulatory Action:	<i>Approval</i>
Recommended Indication	<p>ONTRUZANT is a HER2/neu receptor antagonist indicated for:</p> <p>1. Adjuvant breast cancer: Adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature) breast cancer</p> <p>a. As part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel</p> <p>b. As part of a treatment regimen with docetaxel and carboplatin</p> <p>c. As a single agent following multi-modality anthracycline based therapy</p> <p>Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.</p> <p>2. Metastatic breast cancer:</p> <p>a. In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer</p> <p>b. As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease</p> <p>Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.</p> <p>3. Metastatic gastric cancer:</p> <p>a. In combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease</p>

	Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.
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REVIEW TEAM**Product Quality (CMC) Review Team:****Drug Substance and Analytical Similarity:** Kristen Nickens**Drug Product and Immunogenicity Assay:** Wen Jin Wu and Wendy Weinberg (TL)**Drug Substance Microbiology:** Maria Lopez-Barragan**Drug Product Microbiology:** Lindsey Brown**Facility:** Wayne Seifert and Peter Qiu (Branch Chief)**Labeling:** Vicky Borders-Hemphill**Product Quality Team Lead:** Qing (Joanna) Zhou**Microbial QAL:** Patricia Hughes**RBPM:** Oumou Barry**Application Team Lead:** Qing (Joanna) Zhou**CMC Statistics:** Yu-Ting Weng and Meiyu Shen (TL)**Pharm/Tox:** George Chang and Tiffany Ricks (TL)**Clinical Pharmacology:** Sriram Subramaniam and Olanrewaju Okusanya (TL)**Clinical Reviewers:** Tatiana Prowell and Jennifer Gao (Acting CDTL)**Statistics:** Laura Fernandes and Shenghui Tang (TL)**OSI:** Lauren Iacono-Connor and Susan Thompson (TL)**OSE/DMEPA:** Tingting Gao and Chi-Ming (Alice) Tu (TL)**OSE/DRISK:** Ingrid Chapman and Elizabeth Everhart (TL)**OPDP:** Kevin Wright**RPM:** Fatima Rizvi and Alice Kacuba (TL)**DOP1 Division Director:** Julia Beaver**DOP1 Associate Division Director:** Laleh Amiri-Kordestani

1. Introduction

On October 20, 2017, the applicant submitted a biologics license application (BLA) 761100 under Section 351(k) of the Public Health Service Act for SB3, a proposed biosimilar to US-licensed Herceptin (trastuzumab; henceforth referred to as US-Herceptin)³. The Applicant is seeking licensure of SB3 for the same indications as US-Herceptin:

Adjuvant breast cancer:

Adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature) breast cancer

- a. As part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
- b. As part of a treatment regimen with docetaxel and carboplatin
- c. As a single agent following multi-modality anthracycline based therapy

Metastatic breast cancer:

- a. In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer
- b. As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease

Metastatic gastric cancer:

- a. In combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease

Section 351(i) of the Public Health Service Act (PHS Act) defines the terms “biosimilar” or “biosimilarity” to mean that “the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components” and that “there are no clinically meaningful differences between the proposed biosimilar and the reference product in terms of the safety, purity, and potency of the product.”

The applicant conducted an analytical comparison between the proposed biosimilar to US-Herceptin to support the demonstration that the products are highly similar. The applicant also conducted analytical comparisons between the proposed biosimilar to US-Herceptin and EU-approved Herceptin (henceforth referred to as EU-Herceptin) to establish the analytical portion of the scientific bridge to justify the relevance of data generated using EU-Herceptin as the comparator to an assessment of biosimilarity with US-Herceptin. The applicant also conducted a head-to-head comparison of the non-clinical PK and toxicity profiles of SB3, US-Herceptin, and EU-Herceptin via intravenous administration in cynomolgus monkeys. Further, the applicant conducted a human PK similarity study, SB3-G11-NHV, and a comparative clinical study, SB3-G31-BC, to support the demonstration of no clinically meaningful differences between SB3 and

³ In this document, any reference to “Herceptin” should be considered a reference to US-licensed Herceptin. EU-approved Herceptin will be referred to as EU-Herceptin. References to unknown sources of trastuzumab (e.g., based on historical studies) will use “trastuzumab”.

US-Herceptin. The results of SB3-G11-NHV also established the pharmacokinetic component of the scientific bridge between SB3, EU-Herceptin, and US-Herceptin.

In the US, Herceptin is approved as a multi-dose vial containing 420 mg of lyophilized drug product and as a single-dose vial containing 150 mg of lyophilized drug product. In the EU, trastuzumab is marketed only as a single-dose vial containing 150 mg of lyophilized drug product. The applicant developed SB3 as a 150 mg single-dose presentation. The applicant is currently only seeking licensure of the 150 mg presentation.

The analytical data supports the determination that SB3 is highly similar to US-Herceptin notwithstanding minor differences in clinically inactive components. In addition, the data submitted from the clinical development program of SB3 support a demonstration of no clinically meaningful differences between SB3 and US-Herceptin. The applicant also provided adequate scientific justification for extrapolation of data and information to support licensure of SB3 under Section 351(k) as a biosimilar for the conditions of use for which the applicant is seeking licensure. Together, the totality of the data supports the demonstration of biosimilarity of SB3 to US-Herceptin, as summarized below.

The analytical similar program consisted of two parts. SB3 was evaluated and compared to US-Herceptin and EU-Herceptin using multiple orthogonal physicochemical and functional methods. The analytical similarity data support the conclusion that SB3 and US-Herceptin are highly similar, notwithstanding minor differences in clinically inactive components. The data indicate that the amino acid sequences of SB3 and US-Herceptin are the same. The results from the analysis of the secondary and tertiary structures and the biological activity analyses met the predefined analytical similarity acceptance criteria. In addition, the analytical component of the scientific bridge between SB3, US-Herceptin and EU-Herceptin has been adequately established to justify the relevance of clinical data generated using EU-Herceptin as the comparator.

The manufacturing and control data submitted in this application are sufficient to support a conclusion that the manufacture of SB3 is well controlled and will lead to a product that is pure and potent for the duration of the shelf -life.

The nonclinical pharmacokinetic and toxicity profile of SB3 was compared with US-Herceptin and EU-Herceptin via intravenous administration in cynomolgus monkeys. Overall, the animal studies provided in the BLA submission did not identify any safety concerns with SB3 or differences in the PK or toxicity profile of SB3 compared to US-Herceptin or EU-Herceptin. The Pharmacology and Toxicology discipline has not identified any residual uncertainties.

The pharmacokinetic profiles of SB3, US-Herceptin, and EU-Herceptin were evaluated in healthy subjects in study SB-G11-NHV. The results of this pharmacokinetic similarity study support a demonstration of no clinically meaningful differences between SB3 and US-Herceptin. The results of this study also established the pharmacokinetic component of the scientific bridge between SB3, US-Herceptin, and EU-Herceptin. Through analytical and pharmacokinetic data, the applicant established an adequate scientific bridge between SB3, US-Herceptin, and EU-Herceptin to justify the relevance of clinical data generated using EU-Herceptin as the comparator to support a demonstration of biosimilarity of SB3 to US-Herceptin.

The results of the comparative efficacy and safety study SB3-G31-BC support a demonstration of no clinically meaningful differences between SB3 and US-Herceptin. Specifically, the 90% confidence intervals for the pathologic complete response rate (pCR) ratio between SB3 and EU-Herceptin are within the pre-specified statistical equivalence margins. The safety analyses in study SB3-G31-BC did not show any meaningful differences in safety between arms.

Anti-drug antibodies were measured in study SB3-G31-BC comparing SB3 to EU-Herceptin. The data indicate that there is no increase in immunogenicity risk in terms of ADA development for SB3 when compared to EU-Herceptin, which supports the demonstration of no clinically meaningful differences to US-Herceptin.

The applicant provided adequate scientific justification for extrapolation of data and information to support licensure of SB3 under Section 351(k) as a biosimilar for the conditions of use for which the applicant is seeking licensure.

In considering the totality of the evidence, the data submitted by the applicant show that SB3 is highly similar to US-Herceptin, notwithstanding minor differences in clinically inactive components, and support a demonstration that there are no clinically meaningful differences between SB3 and US-Herceptin in terms of safety, purity, and potency.

2. Background

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

Section 351(k) of the PHS Act defines the terms “biosimilar” or “biosimilarity” to mean that “the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components” and that “there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.”

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

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

3. CMC

Source: OBP Executive Summary dated December 21, 2018; OPQ Drug Product Review dated December 21, 2018; OPQ Drug Product Microbiology Review and Evaluation dated December 17, 2018; OPQ Drug Substance and Analytical Similarity review dated December 20, 2018

Final Product Quality Team Recommendation: Approve.

General product quality considerations

Trastuzumab products target human epidermal growth factor receptor 2 (HER2) and when bound to HER2 on HER2-expressing cells, trastuzumab 1) inhibits HER2 receptor dimerization and downstream signaling, 2) increases destruction of the endocytic portion of the HER2 receptor 3) inhibits HER2 extracellular domain shedding, and 4) activates cell-mediated immune defenses such as ADCC activity through concomitant binding to Fcγ receptors on immune effector cells.

SB3 is a humanized IgG1κ monoclonal antibody produced in CHO cells. SB3 drug product is manufactured to the same strength and dosage form as US-Herceptin at a single-use 150 mg/vial and is supplied as a sterile, lyophilized powder for intravenous infusion.

SB3 monoclonal antibody consists of two identical heavy chains glycosylated at asparagine (Asn300) and two identical light chains. The molecular weight of SB3 is 148 kDa and consists of 1328 amino acids. The theoretical extinction coefficient was calculated to be $1.50 \text{ mL mg}^{-1} \text{ cm}^{-1}$, and it was determined experimentally to be $1.49 \text{ mL mg}^{-1} \text{ cm}^{-1}$. (b) (4)

SB3 is produced in CHO (b) (4) cells. The SB3 Master Cell Bank (MCB, lot 110170955) was developed (b) (4)

No animal-derived materials were used in the manufacture of both the MCB and WCB cell banks. The cell lines were appropriately tested to ensure product safety from adventitious and endogenous agents.

SB3 drug substance is manufactured (b) (4)

SB3 drug product manufacturing includes

(b) (4)

Bioburden and endotoxin are tested during manufacture and sterility and endotoxin are tested at release. Container closure integrity testing using a validated dye ingress method is included in the stability program.

SB3 drug product is manufactured as a sterile lyophilized powder for concentrate for solution for infusion. SB3 needs to be reconstituted with 7.4 mL of sterile water for injection (WFI) to produce 21 mg/mL drug product. The WFI is not provided with the SB3 drug product.

Post-marketing commitments were issued by OPQ – refer to Section 14 of this review below.

Microbiology Reviews

Drs. Maria Jose Lopez-Barragan and Reyes Candau-Chacon (DS microbiology reviewers) recommended approval of the BLA from a microbial control and a microbiological product quality perspective.

Drs. Lindsey Brown and Reyes Candau-Chacon (DP microbiology reviewers) recommended approval of the BLA from an assessment of sterility assurance and microbiology product quality perspective.

Facilities Review/inspection

Facilities review was performed by Wayne Seifert, OPF/DIA, with concurrence from branch chief Zhihao Peter Qiu. A pre-licensure inspection (PLI) was conducted from (b) (4) of SB3 DS at (b) (4) and for the SB3 DP at (b) (4). Both locations are multi-product manufacturing facilities. The BLA is recommended for approval from a facilities review perspective.

Analytical similarity assessment

The analytical similarity assessment was performed to demonstrate that SB3 and US-Herceptin are highly similar, notwithstanding minor differences in clinically inactive components and to justify the analytical component of the scientific bridge between SB3, US-Herceptin and EU-Herceptin to justify the relevance of data generated using EU-Herceptin as the comparator to an assessment of biosimilarity with US-Herceptin.

SB3 was evaluated and compared to US-Herceptin and EU-Herceptin using a battery of biochemical, biophysical, and functional assays, including assays that addressed each potential mechanism of action (see Section II A, OBP Executive Summary). The analytical data submitted support the conclusion that SB3 is highly similar to US-Herceptin. The amino acid sequences of

SB3, EU-Herceptin, and US-Herceptin are identical. A comparison of the secondary and tertiary structures and the impurity profiles of SB3 and US-Herceptin support the conclusion that the two products are highly similar. In addition, the analytical similarity data provided for SB3, US-Herceptin and EU-Herceptin are adequate to justify the analytical component of the scientific bridge to justify the relevance of data generated using EU-Herceptin as the comparator to an assessment of biosimilarity with US-Herceptin.

Inhibition of proliferation and ADCC activity, which reflect the presumed primary mechanisms of action of trastuzumab products, and HER2 binding, were determined to be similar for SB3, US-Herceptin and EU-Herceptin. The binding activities to FcγRIIIa and FcγRIIIb were slightly lower in SB3 as compared to US-Herceptin; however, binding to FcγRII in general is not expected to impact product safety, quality, potency, PK, and immunogenicity and this slight difference observed does not preclude the demonstration of highly similar between SB3 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 SB3, US-Herceptin and EU-Herceptin. A slight increase in the levels of non-glycosylated heavy chain (NGHC) was observed in SB3 as compared to those of US-Herceptin, which may have the potential to impact product potency through ADCC; however, similar ADCC activity was demonstrated among SB3, US-Herceptin and EU-Herceptin. Other size variants, including high and low molecular species, are similar among the three products. While higher amounts of basic variants were observed in SB3 compared to EU-Herceptin and US-Herceptin, these did not significantly impact product potency (HER2 binding and anti-proliferation) or FcRn binding activity. Further, the data submitted by the applicant support the conclusion that SB3 and US-Herceptin can function through the same mechanisms of action for the indications for which US-Herceptin is currently approved, to the extent that the mechanisms of action are known or can reasonably be determined. The extensive comparison of functional, physicochemical, and primary and higher order structural attributes, supports a demonstration that SB3 is highly similar to US-Herceptin, notwithstanding minor differences in clinically inactive components. SB3 meets the statutory “same strength” requirement under section 351(k)(2)(A)(i)(IV) of the PHS Act.

Reviewer Comment: I concur with the CMC/OPQ review team’s conclusion that the analytical data supports a demonstration that SB3 is highly similar to US-Herceptin. A major amendment was made to this application to provide data and information needed to support the CMC/OPQ review of this application.

CDRH

CDRH consultation was requested pertaining to the product label for BLA 761100, under sections 1.1, 1.2, 1.3, and 2.1 regarding the statement for the companion diagnostic. Per CDRH reviewers (Drs. Soma Ghosh, Aaron Schetter, and Reena Philip), CDRH agreed with the CDER review team that sections 1.1, 1.2, and 1.3 of the label should indicate the following: “Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.” CDRH agreed with the CDER review team that section 2.1 of the label should have the language: “Select patients based on HER2 protein overexpression or HER2 gene amplification in tumor specimens [see Indications and Usage (1) and Clinical Studies (14)]. Assessment of HER2 protein overexpression and HER2 gene amplification should be performed

using FDA-approved tests specific for breast or gastric cancers by laboratories with demonstrated proficiency. Information on the FDA-approved tests for the detection of HER2 protein overexpression and HER2 gene amplification is available at: <http://www.fda.gov/CompanionDiagnostics>".

The applicant was requested to provide a rationale for why the approved companion diagnostics for trastuzumab could serve as companion diagnostics for SB3. The applicant provided a response on January 26, 2018 and February 9, 2018. CDRH reviewers concluded that Samsung's justification for why the approved companion diagnostics for trastuzumab could serve as companion diagnostics for SB3 is adequate. Moreover, for purposes of the HER2 tests approved as companion diagnostics for trastuzumab, CDRH believes that reference to trastuzumab in the device labeling includes not only Herceptin but also products determined to be biosimilar to Herceptin.

4. Nonclinical Pharmacology/Toxicology

Source: Pharmacology and Toxicology Primary Review (Drs. C.J. George Chang and Tiffany Ricks)

Final Pharmacology/Toxicology Team Recommendations: Approval.

A non-good laboratory practice (GLP) mouse xenograft efficacy study showed anti-tumor efficacy of SB3/BIIB604 and effects on body weight changes were similar to that of EU-Herceptin and US-Herceptin in an orthotopic BT474 human breast tumor mouse xenograft model.

A GLP 4-week study with weekly administration of SB3, EU-Herceptin, and US-Herceptin were conducted in cynomolgus monkeys to compare the toxicity profiles and the toxicokinetic (TK) profiles of SB3, EU-Herceptin, and US-Herceptin. Overall, based on the animal studies provided in this BLA submission, there was no evidence to indicate potential clinical safety concerns associated with SB3 administration. There were no toxicity findings in animals treated with either SB3, EU-Herceptin, or US-Herceptin. The toxicokinetic profile of SB3 was comparable to that of EU-Herceptin and US-Herceptin.

The cynomolgus monkey has been identified as a pharmacologically relevant species. SB3, EU-Herceptin, or US-Herceptin was administered to monkeys at 25 mg/kg on Days 1, 8, 15 and 22. The 25 mg/kg dose was selected based on previous results of non-clinical studies of US-Herceptin where 1, 5, and 25 mg/kg doses administered for 4-26 weeks. No apparent toxic response was observed in monkeys treated with SB3, EU-Herceptin, or US-Herceptin at 25 mg/kg. TK evaluation showed that animals were continuously exposed to SB3, EU-Herceptin, or US-Herceptin for the duration of the study. Following repeated administration of SB3, EU-Herceptin, or US-Herceptin at 25 mg/kg, similar systemic exposures were observed for both products. There were no detectable levels of SB3, EU-Herceptin, or US-Herceptin in serum samples obtained from vehicle treated animals on Day 1 and 22. Systemic exposure was comparable between SB3, EU-Herceptin, and US-Herceptin. No immunogenic (anti-drug

antibodies) responses to SB3, EU-Herceptin, or US-Herceptin were detected in samples taken from treated animals.

On July 26, 2018, the OBP review team requested an opinion from the Pharmacology/Toxicology review team regarding the applicant's safety assessment for extractables and leachables from the primary container closure system of SB3 DP. The Pharmacology/Toxicology review team reviewed the applicant's summary of study procedures and results, related risk assessments, and estimated Permissible Daily Exposures (PDEs) for all leachables while considering the recommendations made by the Product Quality Research Institute (PQRI) and concluded there is no need to conduct additional toxicology assessments.

Reviewer Comment: I concur with nonclinical team's conclusion that the submitted pharmacology and toxicology data were adequate to demonstrate similarity in the safety and PK profiles of SB3, EU-Herceptin, and US-Herceptin in cynomolgus monkeys. The similar safety and PK profiles of SB3 and US-Herceptin support a demonstration that SB3 is biosimilar to US-Herceptin.

5. Clinical Pharmacology

Source: Clinical Pharmacology Review (Drs. Sriram Subramaniam, Olanrewaju Okusanya, and Nam Atiqur Rahman) and Product Quality Review of immunogenicity (Drs. Milos Dokmanovic and Brian Janelins)

Final Clinical Pharmacology Team Recommendations: Approval

The objectives of the clinical pharmacology program were to demonstrate pharmacokinetic (PK) similarity between SB3 and US-Herceptin and to support the PK component of the scientific bridge between SB3, US-Herceptin, and EU-Herceptin. The applicant submitted study SB3-G11-NHV which evaluated the PK of SB3, EU-Herceptin, and US-Herceptin.

Evidence of PK similarity was demonstrated between SB3 and US-Herceptin, as well as the PK portion of the scientific bridge between SB3, US-Herceptin, and EU-Herceptin. Study SB3-G11-NHV was a single-dose, randomized, double-blind, 3-arm, parallel group study in 108 healthy subjects designed to determine the PK similarity of SB3, US-Herceptin, and EU-Herceptin following a single 6 mg/kg intravenous (IV) dose. The 90% confidence intervals (CI) for all three pairwise comparisons of AUC_{inf}, AUC_{last}, and C_{Max} were within the pre-specified limits of 80–125%. The results of the study established the PK similarity between SB3 and US-Herceptin and provide the PK element of the scientific bridge to justify the relevance of the comparative data generated using EU-Herceptin in study SB3-G31-BC to support a demonstration of biosimilarity to US-Herceptin. Overall, SB3-G11-NHV supports a demonstration of PK similarity between SB3 and US-Herceptin, as well as the PK component of the scientific bridge among SB3, US-Herceptin, and EU-Herceptin.

Immunogenicity

The incidence of immunogenicity for SB3, US-Herceptin, and EU-Herceptin was compared using clinical samples from the PK study SB3-G11-NHV. The results indicate similar incidence

and titers of anti-drug antibodies (ADA) for all products. These data indicate that there is no increase in immunogenicity risk for SB3 as compared to US-Herceptin or EU-Herceptin.

In conclusion, the PK and immunogenicity results support a demonstration of no clinically meaningful differences between SB3 and US-Herceptin and add to the totality of the evidence to support a demonstration of biosimilarity of SB3 and US-Herceptin.

Reviewer Comment: I concur with the clinical pharmacology team's conclusion that the submitted clinical pharmacology study adequately demonstrated PK similarity between SB3, US-Herceptin and EU-Herceptin. The evidence of PK similarity supports a demonstration of no clinically meaningful differences between SB3 and US-Herceptin. Also, the PK similarity data establish the PK component of the scientific bridge to justify the relevance of the comparative clinical data generated using EU-Herceptin to support a demonstration of the biosimilarity of SB3 to US-Herceptin. I agree with the product quality review team/s conclusion that the immunogenicity data indicate there is no increase in immunogenicity risk for SB3 when compared to US-Herceptin, which supports a demonstration of no clinically meaningful differences between SB3 and US-Herceptin.

6. Clinical Microbiology

Not applicable.

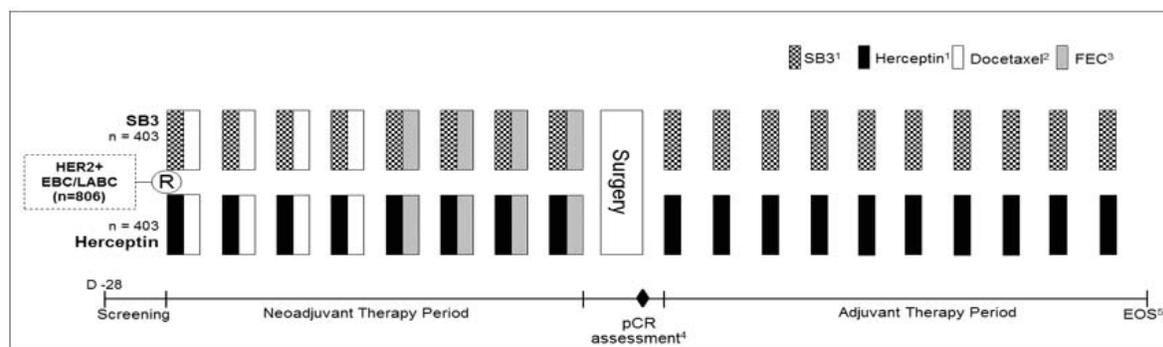
7. Clinical/Statistical- Efficacy

Source: Combined Clinical/Stat Review (Drs. Tatiana Prowell, Laura Fernandes, and Shenghui Tang)

Final Clinical/Statistical Team Recommendations: Approval

The applicant submitted one comparative clinical study SB3-G31-BC with a multicenter, randomized, double-blinded, parallel group design to assess the efficacy and safety of SB3 compared to EU-Herceptin to support a determination of no clinically meaningful differences between SB3 and US-Herceptin (see Fig. 1 below).

Study SB-G31-BC is a double-blind, randomized, parallel-group clinical study to compare the efficacy and safety of SB3 and EU-Herceptin in the neoadjuvant and adjuvant treatment of patients with early HER2 positive breast cancer. In the neoadjuvant portion, patients were treated with 4 cycles of SB3 plus docetaxel or EU-Herceptin plus docetaxel followed by 4 cycles of SB3 or EU-Herceptin with 5-fluorouracil, epirubicin, and cyclophosphamide chemotherapy. In the adjuvant portion, patients remained on SB3 or EU-Herceptin, as per original study randomization, to complete 1 year of treatment (up to 10 cycles during the adjuvant portion). Patients were randomized 1:1 and stratified by hormone receptor status (ER and/or PR positive vs. ER and PR negative) and breast cancer type (operable vs. locally advanced [including inflammatory]).



EBC = Early breast cancer, LABC = Locally advanced breast cancer

1. Loading dose of 8 mg/kg and then a maintenance dose of 6 mg/kg every 3 weeks
2. Docetaxel 75 mg/m²
3. 5-fluorouracil 500 mg/m², epirubicin 75 mg/m² and cyclophosphamide 500 mg/m²
4. Primary endpoint: pathologic complete response (pCR) in breast tumor
5. EOS (End of Study) visit is scheduled 30 days after the last dose of IP

Figure 1. SB3-G31-BC Study Schema

Source: SB3-G31-BC Clinical Study Report

The primary efficacy endpoint of this trial was pathological complete response (pCR), defined as the absence of invasive tumor cells in the breast, regardless of DCIS. Pathological examination of axillary lymph nodes was not considered. The pCR was determined at the time of surgery, using hematoxylin and eosin evaluation of the resected breast specimen. The applicant used the 90% asymptotic confidence region of the ratio of pCR in the SB3 arm vs. the EU-Herceptin arm as the primary analysis strategy. The primary analysis population was the per-protocol set (those without major protocol violations and completed 8 cycles of neoadjuvant therapy, surgery, and pathologic assessment); the intention to treat population was used for supportive purposes.

The study was deemed positive if the 90% confidence region for the ratio was entirely contained within the interval (0.785-1.546). To calculate this interval, the applicant reviewed three study control arms to obtain pCR rates for the control arm and the treatment arms. A meta-analysis using the three studies calculated a ratio of breast pCR rate to be 2.07 with 90% CI of 1.546-2.795. The overall expected breast pCR rate was 37.5% and the difference of breast pCR rates between treatment arms was calculated as 23.3%, with the 80% CI of 16.6-29.9%. The equivalence margin for the difference was derived as 13%. Using a 50% retention rate, the applicant derived their equivalence margin for the ratio of 0.785-1.546. The applicant sized their study to achieve 80% power for the primary endpoint. The applicant calculated that 358 patients per arm would provide sufficient power and account for a 11% dropout.

Key secondary endpoints included total pCR rate (defined as absence of invasive residual tumor cells in both breast and lymph nodes), overall clinical response rate (defined as percentage of patients achieving clinical complete response or clinical partial response for the best overall response during the neoadjuvant period), event-free survival, and overall survival. Analysis of total pCR as a secondary endpoint showed results consistent with those of the primary endpoint of breast pCR. For the radiological evaluation, scans were done in the neoadjuvant and adjuvant periods. The local investigator determined whether an individual had a response or progression event. No central imaging review was performed.

The protocol had 5 global amendments and 4 country-specific amendments. Protocol changes include a change from using risk difference to risk ratio in the primary analysis, the use of a 90% confidence interval instead of a 95% confidence interval for the primary analysis, determination of sample size and rationale updated due to newly found literature, and quality control of pCR by central review of selected samples added.

In summary, study SB3-G31-BC demonstrates no differences in terms of efficacy between SB3 and EU-Herceptin, which supports a demonstration of no clinically meaningful differences between SB3 and US-Herceptin. Specifically, the 90% confidence interval for the pCR ratio between SB3 and EU-Herceptin in SB3-G31-BC is within the equivalence margin.

Reviewer Comment: I concur with clinical team's conclusion that the submitted clinical study demonstrated no differences in terms of efficacy between SB3 and EU-Herceptin. As the applicant established an appropriate scientific bridge comprised of comparative PK and analytical data for SB3, EU-Herceptin, and US-Herceptin, the efficacy results of SB3-G31-BC support a demonstration of no clinically meaningful differences between SB3 and US-Herceptin.

8. Safety

Source: Combined Clinical/Stat Review (Dr. Tatiana Prowell)

Final Clinical/Statistical Team Recommendations: Approval

The safety evaluation for this application is based on the neoadjuvant and adjuvant study portions of study SB3-G31-BC and a long term follow-up study for cardiac safety of patients who completed study SB3-G31-BC. The safety assessments for study SB3-G31-BC are adequate. There was particular attention to assessment of cardiac adverse events (AEs) due to the known cardiac effects of trastuzumab. The safety population in the neoadjuvant and adjuvant portions of study SB3-G31-BC consisted of 875 patients, 437 in the SB3 and 438 in the EU-Herceptin arms and is defined as all patients who received at least 1 dose of study drug in any amount. A total of 367 patients (186 in the SB3 and 181 in the EU-Herceptin arms) were enrolled in the long term follow-up study for cardiac safety monitoring after they had completed study SB3-G31-BC.

The frequency of TEAEs, serious events, and events leading to discontinuation of study drug had no meaningful differences between the treatment arms. Major events of interest which are listed as Black Box Warnings in the prescribing information for US-Herceptin include cardiomyopathy, infusion reactions, pulmonary toxicity, and embryo-fetal toxicity. There were no reports of pregnancy or embryo-fetal toxicity in study SB3-G31-BC. Most cardiac adverse events were grade 1-2 and most patients recovered in both groups. The safety results of study SB3-G31-BC showed no meaningful differences between SB3 and EU-Herceptin.

Reviewer Comment: The comparative safety results obtained in study SB3-G31-BC, for which EU-Herceptin was the comparator, support a demonstration of no clinically meaningful differences between SB3 and US-Herceptin, as the applicant established an

appropriate scientific bridge comprised of comparative PK and analytical data for SB3, US-Herceptin, and EU-Herceptin. Safety results from the long term follow-up study for cardiac safety for patients with HER2 positive early or locally advanced breast cancer who completed study SB3-G31-BC also support a support a demonstration of no clinically meaningful differences between SB3 and US-Herceptin. I concur with clinical team's conclusion that the submitted clinical studies adequately support a finding that there are no clinically meaningful differences in terms of safety between SB3 and US-Herceptin.

9. Considerations for Extrapolation of Biosimilarity

Source: Combined Clinical/Stat Review (Dr. Tatiana Prowell)

The applicant seeks licensure for all indications for which US-Herceptin is licensed. The applicant has provided adequate justification for extrapolation of the data and information in the application, including comparative clinical efficacy and safety data from a clinical program in patients with early HER2 positive breast cancer, to support licensure of SB3 under Section 351(k) for which the applicant is seeking licensure.

Study SB-G31-BC compared the efficacy and safety of SB3 and EU-Herceptin in the neoadjuvant and adjuvant treatment of patients with early HER2 positive breast cancer. The neoadjuvant setting for breast cancer used in study SB3-G31-BC is an acceptable, homogenous, and sensitive patient population for evaluating whether there are clinically meaningful differences between SB3 and US-Herceptin. The patient population receiving HER2-based treatment is the same in the neoadjuvant and adjuvant settings, differing only in the timing of surgery. The primary endpoint of pCR is an acceptable endpoint in breast cancer. The mechanism of action of trastuzumab products in HER2+ neoadjuvant and adjuvant breast cancer patients is expected to be the same as the mechanism of action for trastuzumab products in the indications for which the applicant is seeking licensure but that were not studied in the submitted clinical program (HER2+ metastatic breast cancer and HER2+ metastatic gastric cancer).

The applicant has submitted the following scientific justifications for extrapolation of data and information to support licensure of SB3 as a biosimilar for the conditions of use for which the applicant is seeking licensure:

- The mechanism of action of trastuzumab products is the same across all indications as the target receptor involved (HER2) is the same across indications
- The available safety data of the reference product does not indicate that there are any significant differences in expected toxicities for each condition of use and patient population
- There are no toxicities that are related to off-target activities in patients treated in the neoadjuvant setting compared with adjuvant/metastatic breast cancer or metastatic gastric cancer
- The dose of US-Herceptin and route of administration is the same across all indications
- PK results support a demonstration of no clinically meaningful differences between SB3 and US-Herceptin
- PK characteristics are similar across the patient population in all indications

- Immunogenicity was low and similar between SB3 and US-Herceptin and expected to be low across the patient population in all indications

As described in the Guidance for Industry: “Scientific Considerations in Demonstrating Biosimilarity to a Reference Product,” if a biological product meets the statutory requirements for licensure as a biosimilar product under section 351(k) of the PHS Act based on, among other things, data derived from a clinical study or studies sufficient to demonstrate safety, purity, and potency in an appropriate condition of use, the potential exists for that product to be licensed for one or more additional conditions of use for which the reference product is licensed. The clinical team considered extrapolation to be scientifically justified based on the bullets above.

Reviewer Comment: I concur with clinical team’s conclusion that the evidence indicates that the extrapolation of data and information, including clinical data, to support licensure of SB3 for the indications for which US-Herceptin has previously been approved is scientifically justified.

10. Advisory Committee Meeting

An advisory committee meeting was not held for this application.

11. Pediatrics

Samsung requested a full waiver of pediatric studies for the requested indications and submitted an agreed iPSP with the BLA.⁴ The Oncology Center of Excellence Subcommittee of the Pediatric Review Committee met on September 12, 2018 and concurred with the applicant’s request for a full waiver in HER-2 overexpressing breast and gastric cancers. The minutes were entered to DARRTS September 12, 2018.

12. Other Relevant Regulatory Issues

Application Integrity Policy (AIP)

The application contained statements from Samsung Bioepis Co., Ltd. that they certified that they did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Exclusivity

Not applicable.

Financial disclosures

In accordance with 21 CFR Part 54 Financial Disclosures by Clinical Investigators, the applicant requested statements of financial interest from 121 principal investigators (PIs) and 520 sub-investigators for study SB3-G31-BC and 18 investigators for study SB3-G11-NHV. All investigators were assessed for equity interest, significant payments of other sorts, and other compensation by the applicant and propriety interest. The applicant has stated that none of the clinical investigators involved with the SB3 studies have financial interests or arrangements to

⁴ Breast cancer is included on the list of adult-related conditions that may qualify the drug product for disease-specific waivers in FDA’s September 2005 Draft Guidance (How to Comply with the Pediatric Research Equity Act).

disclose as defined in 21 CFR 54.2(f). All returned the financial disclosure information except for 4 pathologists (sub-investigators) for study SB3-G31-BC, as they had left their study site before the end of the study and were unable to be reached. However, this does not preclude approval of this BLA, as this was a small number of sub-investigators and quality control of pCR was conducted by central review of selected samples.

Bioequivalence Inspections

In a review entered into DARRTS on April 24, 2018, Shila Nkah of the Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without on-site inspection. The rationale for this approach was that OSIS had recently inspected one clinical and one analytical site. Although the last inspection outcomes were classified as Voluntary Action Indicated (VAI), based on the inspectional outcome, OSIS determined additional inspections were not needed. The clinical site previously inspected was PAREXEL International GmbH, Klinikum Westend, Haus 31, Spandauer Damm 130, 14059, Berlin, Germany. The analytical site previously inspected was

(b) (4)

Clinical Inspections

Lauren Iacono-Connors, Susan Thompson (Team Leader) and Kassa Ayalew (Branch Chief) from the Division of Clinical Compliance Evaluation, OSI, completed the clinical inspection summary (CIS) on July 19, 2018. FDA selected three clinical sites and the study sponsor for audit. There were no significant inspectional findings for clinical investigators Dr. Seock-Ah Im, Dr. Maximino Bello, Dr. Tomasz Sarosiek, and the study sponsor, Samsung Bioepis Co., Ltd. OSI review concluded that the data from study SB3-G31-BC submitted to the Agency in support of BLA 761100, appear reliable based on available information.

Other Discipline Consultations

Tingting Gao and Chi-Ming (Alice) Tu from the Office of Medication Error Prevention and Risk Management (OMEPRM), Division of Medication Error Prevention and Analysis (DMEPA) completed a review dated July 11, 2018 that concluded that the proposed proprietary name, Ontruzant, was conditionally acceptable.

Tingting Gao and Danielle Harris from OMEPRM completed a review dated July 12, 2018 that determined that the suffix “dttb” for the nonproprietary name is conditionally acceptable (trastuzumab-dttb).

Tingting Gao and Chi-Ming (Alice) Tu completed a review dated August 16, 2018 that defined recommendations relating to carton and container and product labeling. The recommendations were incorporated in revised product labeling.

Pediatric and Maternal Health

At the time of the submission of this BLA, a pregnancy registry and pharmacovigilance program was in place for US-Herceptin. Because the risks of oligohydramnios have been adequately characterized in the Herceptin labeling, FDA has determined that the Herceptin pregnancy registry and pregnancy pharmacovigilance program are no longer necessary for Herceptin and

therefore, no registry or pharmacovigilance program is required for this biosimilar. Additional details may be found in the primary clinical review.

13. Labeling

Proposed labeling submitted by Samsung was generally consistent with recommendations contained within FDA's draft Guidance for Industry "Labeling for Biosimilar Products" which recommends that the biosimilar product labeling incorporate relevant data and information from the reference product labeling, with appropriate product specific modifications. Some information in the labeling was revised to reflect SB3-specific information as well as to comply with current labeling practices.

14. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

The applicant is seeking licensure for indications that are the same as those licensed for US-Herceptin. The applicant is seeking licensure for the adjuvant treatment of HER-2 overexpressing breast cancer, treatment of HER2 overexpressing metastatic breast cancer, and treatment of HER-2 overexpressing metastatic gastric cancer indications. The data submitted to the BLA from the clinical development program of SB3 support a demonstration of no clinically meaningful differences between SB3 and US-Herceptin. These data also contribute to the totality of the data in support of a demonstration of biosimilarity of SB3 to US-Herceptin. The applicant provided adequate scientific justification for extrapolation of data and information to support licensure of SB3 for the metastatic breast cancer and metastatic gastric cancer indications. The applicant demonstrated that SB3 is highly similar to US-Herceptin based on extensive analytical data and that SB3 has no clinically meaningful differences from US-Herceptin in terms of safety, purity, and potency. Accordingly, in considering the totality of the evidence, the data submitted support licensure of SB3 as biosimilar to US-Herceptin for all indications for which the applicant is seeking licensure.

I recommend approval of BLA 761100 for SB3 to receive licensure as a biosimilar product to US-Herceptin for each of the following indications for which Herceptin is currently licensed and for which the applicant is seeking licensure:

ONTRUZANT is a HER2/neu receptor antagonist indicated for:

1. Adjuvant breast cancer:
Adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature) breast cancer
 - a. As part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
 - b. As part of a treatment regimen with docetaxel and carboplatin
 - c. As a single agent following multi-modality anthracycline based therapy

Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product

2. Metastatic breast cancer:

- a. In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer
- b. As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease

Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product

3. Metastatic gastric cancer:

- a. In combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease

Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product

Recommendation for Postmarketing Risk Evaluation and Management Strategies

None.

Recommendation for other Postmarketing Requirements and Commitments

The following Post-marketing Commitments were agreed upon with the applicant:

- 3532-1 Monitor [REDACTED] (b) (4) and provide [REDACTED] (b) (4).
- 3532-2 Conduct a study to determine the [REDACTED] (b) (4) using SB3 drug product at the pump speed setting used for the PPQ batches.
- 3532-3 Update the dye-ingress container closure integrity test used on the SB3 drug product vials to include vial reconstitution prior to visual inspection.
- 3532-4 Perform a method validation study to confirm the suitability of the FcγRIIIa AlphaScreen assay for use as a potency assay for SB3 drug substance and drug product stability testing. Submit the results in a final study report to the BLA.
- 3532-5 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 SB3 drug substance and drug product lot release and stability testing. Submit the results in a final study report to the BLA.

- 3532-6 Perform a qualification study using production (b) (4) to confirm the suitability of the (b) (4) for the detection of product-specific host cell protein impurities in SB3 drug substance. Submit the results in a final study report to the BLA.
- 3532-7 Implement a two-tiered reference standard program that includes the qualification of a working reference standard to be used for SB3 primary reference standard stability testing, routine SB3 drug substance and drug product release and stability testing. Submit the qualification results of the working reference standard to the BLA in a prior-approval supplement.

Recommended Comments to Applicant

None.

Recommended Regulatory Action

Approve.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JENNIFER J GAO
01/17/2019 04:42:49 PM

LALEH AMIRI KORDESTANI
01/17/2019 04:50:55 PM