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APPLICATION NUMBER:

761100Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	BLA, Original 351(k)
Application Number(s)	76100
Priority or Standard	Standard
Submit Date	10/20/2017
Receipt Date	10/20/2017
BSUFA Goal Date	01/20/2019
Division / Office	DOP1/OHOP
Reviewer Name(s)	Tatiana Prowell, MD Laura Fernandes, PhD Yutao Gong, PhD
Review Completion Date	12/19/2018
Established Name	Trastuzumab-dttb
(Proposed) Trade Name	Ontruzant
Therapeutic Class	HER2-binding humanized monoclonal antibody
Applicant	Samsung
Formulation(s)	IV
Dosing Regimen	8 mg/kg IV loading dose, then 6 mg/kg IV q3 wks
Proposed Indication(s)	Ontruzant is a HER2/neu receptor antagonist indicated for: • Treatment of HER2 overexpressing breast cancer. • Treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma.
Recommended Indication	Ontruzant is a HER2/neu receptor antagonist indicated for: • Treatment of HER2 overexpressing breast cancer. • Treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma. Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.

*In this review, FDA generally refers to the applicant's proposed product by the applicant descriptor "SB3". Herceptin licensed for use in the European Union is referred to as "EU-Herceptin". Herceptin licensed for use in the United States is referred to as "US-Herceptin".

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1. Recommendations/Risk Benefit Assessment

1.1. Recommendation on Regulatory Action

This biologics license application (BLA 761100) seeks approval of the product SB3 (trade name: Ontruzant), which is a proposed biosimilar to US-licensed Herceptin (which will be referred to as US-Herceptin for the remainder of this review).

The biosimilar licensure pathway under section 351(k) of the Public Health Service Act (PHS Act) requires that the proposed 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 reference products in terms of safety, purity and potency. Both parts of the statutory definition need to be met to demonstrate biosimilarity, but the foundation of the data demonstrating biosimilarity is extensive structural and functional characterization to support a demonstration that the products are highly similar.

From a clinical standpoint, the data submitted to the 351(k) BLA from the clinical development program of SB3 support a demonstration of no clinically meaningful differences between SB3 and EU-approved Herceptin (which will be referred to as EU-Herceptin for the remainder of this review). A demonstration that SB3 is highly similar to US-Herceptin, notwithstanding minor differences in clinically inactive components together with the clinical data discussed in this review, will support licensure of SB3 as a biosimilar to US-Herceptin under section 351(k) of the PHS Act.

1.2. Risk Benefit Assessment

Breast cancer is the number one cancer in women, with more than 200,000 women newly diagnosed in the United States and about 40,000 women dying of breast cancer annually. HER2 is a tyrosine kinase transmembrane receptor that is amplified in about 20-30% of breast cancers. HER2-positive breast cancer is associated with a more aggressive phenotype.

Gastric cancer is much more common in less-developed countries than it is in the United States today. In 2017, about 28,000 new cases of gastric cancer and 11,000 deaths due to it are estimated in the United States, with about 7-34% of them overexpressing HER2. Known risk factors for gastric cancer are male sex, increasing age, ethnicity, geography, Helicobacter pylori infection, diet, and smoking, to name a few. As in breast cancer, HER2-positive gastric cancer has been associated with a more aggressive phenotype and resulting poorer prognosis.

Treatment of HER2-positive breast and gastric cancer with targeted therapy such as trastuzumab increases response rates compared to chemotherapy alone. Trastuzumab

is one of the key agents used to target these tumor subtypes throughout the world and thus plays a central role in treatment of patients with breast and gastric cancer.

Testing for HER2 status is commonly performed in all new diagnoses of invasive breast cancer as well as at the time of recurrence. Targeted therapy such as trastuzumab has led to significant increases in response rates compared to chemotherapy alone. For the adjuvant treatment of HER2 positive breast cancer, trastuzumab is given for 1 year, in combination with 4-6 cycles of taxane-based chemotherapy. For the treatment of HER2 positive metastatic breast cancer (MBC), trastuzumab is FDA approved in combination with paclitaxel for first-line treatment. For patients who progress on first line treatment, subsequent FDA-approved HER2-targeted treatment options include ado-trastuzumab emtansine (T-DM1, Kadcyla) and lapatinib (Tykerb). For the treatment of metastatic HER2 positive gastric adenocarcinoma, trastuzumab is FDA-approved to be used in the first-line setting in addition to chemotherapy with fluoropyrimidine (capecitabine or 5-fluorouracil) and cisplatin.

SB3 is a proposed biosimilar to trastuzumab (US-Herceptin). The applicant has submitted a BLA for SB3 with the same proposed indications as for US-Herceptin:

1. Adjuvant breast cancer:
 - a. As part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
 - b. With docetaxel and carboplatin
 - c. As a single agent following multi-modality anthracycline based therapy
2. Metastatic breast cancer (MBC):
 - 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
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

The clinical team recommends approval of SB3 for the following indications:

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

2. Metastatic breast cancer (MBC):
 - 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
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.

Study SB3-G31-BC (which will be referred to as Study G31 for the remainder of this review) supports the determination of no clinically meaningful differences between SB3 and US-Herceptin. This was a double-blind, parallel group, equivalence study in which 875 patients were randomized to receive chemotherapy with either SB3 or EU-Herceptin in the neoadjuvant setting. After completing neoadjuvant therapy and undergoing surgery, patients were to continue with the same trastuzumab product as adjuvant monotherapy to complete a total of 1 year of HER2-directed therapy. The primary endpoint of breast pathological complete response (bpCR) ratio (the bpCR rate with SB3 divided by the bpCR rate with EU-Herceptin) as assessed by local review of the per-protocol set (PPS) of 1.259 (90% CI 1.112, 1.426) was within the pre-specified equivalence margin: (90% CI 0.785, 1.546). Secondary endpoints of total pathological complete response (tpCR) rate, overall clinical response rate, event-free survival (EFS), and overall survival (OS) were similar between the treatment arms.

The safety findings of Study G31 were reviewed, with special focus on cardiac dysfunction, infusion reaction, and embryo-fetal toxicities. Overall there were no clinically meaningful differences in safety between the two arms.

The neoadjuvant setting for breast cancer used in Study G31 is an acceptable, homogenous, and sensitive patient population to evaluate for the absence of clinically meaningful efficacy and safety 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 in neoadjuvant breast cancer patients is expected to be the same as the mechanism of action for trastuzumab in the indications for which the applicant is seeking licensure. For these reasons, the study population and primary endpoint used in Study G31 is acceptable to support approval of SB3 for the indications for which US-Herceptin has been previously approved.

The analytical data supports the conclusion that SB3 is highly similar to US-Herceptin, notwithstanding minor differences in clinically inactive components. The clinical data, which includes pharmacokinetics, efficacy, safety, and immunogenicity, supports the finding of no clinically meaningful differences between the two products. Thus, the totality of the evidence supports the biosimilarity of SB3 and US-Herceptin.

The applicant is seeking indications that are the same as those for US-Herceptin. The applicant has provided the following justification for extrapolation of the data and information submitted in the application to support licensure, under section 351(k), as a biosimilar for the conditions of use for which US-licensed Herceptin is approved:

- The mechanism of action of trastuzumab 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 identify any significant differences in expected toxicities for each condition of use and patient population
- There are no toxicities 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 trastuzumab and route of administration is similar across all indications
- Pharmacokinetic (PK) results support a demonstration of no clinically meaningful differences between SB3 and US-Herceptin
- Immunogenicity was low and similar between SB3 and Herceptin

The applicant has demonstrated high similarity of SB3 with respect to analytical attributes, and no clinically meaningful differences in efficacy and safety, which supports approval for all indications for which US-Herceptin is approved (adjuvant and metastatic breast cancer and metastatic gastric cancer). A scientific bridge between US-Herceptin, EU-Herceptin, and SB3 has been established, based in part on the results from Study SB3-G11-NHV, which evaluated the pharmacokinetic similarity of EU-Herceptin, US-Herceptin, and SB3. The totality of the analytical data supports a demonstration that SB3 and US-Herceptin are highly similar, notwithstanding minor differences in clinically inactive components. The clinical data, including PK, efficacy, safety, and immunogenicity, support the finding of no clinically meaningful differences between US-Herceptin and SB3, and the reviewers find extrapolation for use in all of the proposed indications to be scientifically justified based on the bullets above. Thus, the totality of evidence supports biosimilarity of SB3 and US-Herceptin.

The applicant conducted the following clinical studies to support the application:

- Study SB3-G11-NHV (referred to hereafter as Study G11), a Phase I study in healthy male volunteers, and

- Study SB3-G31-BC (referred to hereafter as Study G31), a Phase III efficacy and safety study in female patients with newly diagnosed HER2-positive Early Breast Cancer (EBC) or Locally Advanced Breast Cancer (LABC).

Study SB3-G31-BC (comparative clinical study, this study will be referred to as Study G31 for the remainder of this review)

- Study G31 is a Phase III, randomized, double-blind, parallel group, multi-center study to compare the efficacy, safety, pharmacokinetics, and immunogenicity of SB3 and Herceptin in women with HER2 positive early breast cancer or locally advanced breast cancer in the neoadjuvant setting. A total of 875 study participants were randomly assigned in a 1:1 ratio to receive either SB3 or EU-Herceptin in the neoadjuvant setting for 8 cycles given concurrently with 8 cycles of chemotherapy [4 cycles of docetaxel followed by 4 cycles of 5-fluorouracil/epirubicin/cyclophosphamide (FEC)]. Following surgery, patients received further 10 cycles of adjuvant SB3 or EU-Herceptin per randomization assignment to complete a total of one year of trastuzumab product. All patients were female.
- Study G31 was designed as an equivalence study, with a primary endpoint of breast pathologic complete response (bpCR) after 8 cycles of neoadjuvant treatment. The definition of bpCR was no histologic evidence of residual invasive tumor cells in the breast specimen removed at surgery (bpCR). For the primary endpoint, residual non-invasive breast cancer (carcinoma in situ) was allowed, and the pathological status of the axillary lymph nodes was not considered (ypT0/is, ypN0/+). If the 90% CI of the ratio in bpCR proportions of responders was entirely bound by the interval 0.785 to 1.546, then the study supports the assertion of no clinically meaningful differences between the products. The primary population for this analysis was the per-protocol set (PPS), with a supportive analysis also conducted using the intention to treat (ITT) patients. The PPS included all randomized patients who completed the 8 cycles of neoadjuvant therapy and surgery and excluded patients according to pre-specified rules prior to the unblinding of treatment codes for analyses. Patients who were excluded from the PPS per the statistical analysis plan either did not have a pathologic response assessment and/or had a pre-specified major protocol violation. Secondary endpoints included total pathological clinical response (tpCR), overall response rate (ORR), event-free survival (EFS), and overall survival (OS).
 - o The safety findings of study G31 were reviewed, with a special focus on cardiac dysfunction, infusion reaction, and embryo-fetal toxicities. Overall no clinically meaningful differences were found in the safety analysis.
 - o The totality of the analytical data supports a demonstration that SB3 and US-Herceptin as highly similar, notwithstanding minor differences in clinically inactive components. The clinical data which includes pharmacokinetics, efficacy, safety, and immunogenicity, supports the finding of no clinically meaningful differences between SB3 and US-

Herceptin. Extrapolation of data to support approval for all of the proposed indications is justifiable.

- o In conclusion, the totality of evidence supports the biosimilarity of SB3 and US-Herceptin.

1.3. Recommendations for Postmarketing Risk Evaluation and Mitigation Strategies

No clinical postmarketing risk evaluation and mitigation strategies have been recommended.

1.4. Recommendations for Postmarket Requirements and Commitments

No PMRs or PMCs have been requested. The applicant has an ongoing extension study (Study SB3-G31-BC-E) described later in this review, in which patients enrolled in Study G31 who consented to participate in the extension phase, are followed for a total of 5 years.

At the time Study G31 was designed and conducted, a pregnancy registry and pharmacovigilance program was in place for Genentech's US-Herceptin. Given that the risks of oligohydramnios have been adequately characterized in the US-Herceptin labeling, FDA has determined that the US-Herceptin pregnancy registry and pregnancy pharmacovigilance program are no longer necessary for US-Herceptin; therefore, no registry or pharmacovigilance program has been recommended for SB3.

2. Introduction and Regulatory Background

2.1. Product Information

SB3 (trade name: Ontruzant) is a proposed biosimilar to US-Herceptin (trastuzumab). Trastuzumab is a humanized IgG1 monoclonal antibody of the kappa isotype consisting of two identical glycosylated heavy chains and two identical light chains. The target of trastuzumab is the cell surface receptor human epidermal growth factor receptor 2 (HER2). HER2 is part of the HER family of transmembrane tyrosine kinases that play a role in the regulation of cellular survival, proliferation, adhesion, and differentiation.

2.2. Tables of Currently Approved Trastuzumab Products for Proposed Indications

Table 1 below lists the current FDA approved trastuzumab products.

Table 1: Summary of FDA Approved Trastuzumab Products

Name	Indication	Approval	Dosing	Efficacy	Safety and Tolerability
Trastuzumab-dkst (IV, Ogivri, biosimilar)	Same as Herceptin	2017	Same as Herceptin	Studies conducted to support a finding of biosimilarity	Studies conducted to support a finding of biosimilarity
Trastuzumab (IV, Herceptin)	HER2 overexpressing breast cancer HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma	1998	Adjuvant breast cancer (52 weeks total): 1) 4 mg/kg load, then 2 mg/kg weekly with taxane, then 6 mg/kg every 3 weeks; 2) after anthracycline-based chemotherapy 8 mg/kg load, then 6 mg/kg every 3 weeks Metastatic breast cancer: 4 mg/kg load, then 2 mg/kg weekly Metastatic gastric cancer: 8 mg/kg load, then 6 mg/kg every 3 weeks	Adjuvant breast cancer: 4 studies showing benefit in DFS and OS with addition of trastuzumab to chemotherapy Metastatic breast cancer: 2 studies showing benefit in TTP and ORR Metastatic gastric cancer: 1 study showing benefit in OS	Cardiomyopathy Infusion reactions Embryo-fetal toxicity Pulmonary toxicity Exacerbation of chemotherapy-induced neutropenia

2.3. Availability of Proposed Active Ingredient in the United States

SB3 is not currently marketed in the United States.

Reference Product:

US-Herceptin was initially licensed in the United States on September 25, 1998. Subsequently, two additional indications were approved based on supplements to the BLA. The indications for which US-Herceptin is licensed are:

- The treatment of HER2 overexpressing breast cancer.
- The treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma.

2.4. Important Safety Issues with Consideration to Related Drugs

Boxed warnings from the FDA prescribing information for US-Herceptin include cardiomyopathy, infusion reactions, embryo-fetal toxicity, and pulmonary toxicity. Additional warnings and precautions from the FDA label include exacerbation of chemotherapy-induced neutropenia.

2.5. Summary of Presubmission Regulatory Activity Related to Submission

The key clinical pre-submission regulatory activity with the FDA was as follows (note: conducted under pre-IND 123,158):

October 7, 2014: Biologics Product Development (BPD), Type 2 Meeting

- FDA advised applicant that a second comparative clinical study using US-Herceptin would not be necessary if an adequate scientific bridge were established to justify the relevance of data from the comparative study using EU-Herceptin to demonstrate biosimilarity to US-Herceptin.

March 24, 2017: BPD, Type 3 Meeting

- Applicant noted that as a scientific bridge to US-Herceptin, three pair-wise comparisons of SB3, EU-Herceptin, and US-Herceptin in analytical similarity assessments and a Phase I PK study in volunteers were conducted demonstrating PK similarity. FDA agreed that an additional Phase 3 study would not be required in support of the planned 351(k) biologics licensing application for SB3.

August 3, 2017: BPD, Type 4 Meeting

- FDA discussed content and format of planned 351(k) biologics licensing application for SB3. Discussed that an agreed iPSP should be in place prior to submission of the application. FDA noted that whether extrapolation of data intended to support a demonstration of biosimilarity, including clinical data using SB3 to treat patients with breast cancer, to other conditions of use would be a review issue. FDA also noted that US-licensed Herceptin has orphan drug exclusivity for some indications which would preclude approval of a biosimilar to US-licensed Herceptin for the protected indication until the expiration of orphan drug exclusivity. FDA stated that submission of the 120 day safety update was necessary. For additional information pertaining to other disciplines, please refer to official meeting minutes from the Type 4 meeting.

Oct 20, 2017: BLA 761100 submitted to FDA.

2.6. Other Relevant Background Information

None

3. Ethics and Good Clinical Practices

3.1. Submission Quality and Integrity

The overall data quality and integrity are acceptable to the reviewers. The submitted datasets are generally consistent, and variables are clearly labeled and/or explained. The tumor response datasets included all assessment values and time points. The applicant responded to information requests in a timely manner and resolved identified issues and/or review questions satisfactorily. Based on the submitted data and reports, the reviewers believe that analyses and results are adequate for regulatory decision making.

3.2. Compliance with Good Clinical Practices

The applicant stated that Study G31 was conducted in accordance with the Declaration of Helsinki, International Council for Harmonization (ICH) Guidance for Industry E6 Good Clinical Practice (GCP), and all applicable regulations.

The applicant certified that it did not use in any capacity in the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Participant identification information was with a code number and did not include the participant name, Investigator, site number, or other information that could re-identify them. A list linking the code and the participant's name was kept in site files as required by Good Clinical Practice (GCP) to protect patient confidentiality. The Investigator was required to maintain essential study documents (protocol and protocol amendments, completed electronic case report forms (eCRFs), signed informed consent forms, relevant correspondence, and all other supporting documentation) until at least 2 years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years after the formal discontinuation of clinical development of SB3 or 15 years from completion of Study G31. These documents were to be retained for a longer period if required by the applicable regulatory requirements or the Investigator site, institution or private practice in which the study was being conducted. Any correction to the data entered into the eCRF was to be carried out by the Investigator or a designated member of staff. These changes were

permitted be made either on the initiative of the site staff or in response to monitoring or data queries. Any changes to written data were to be made using GCP corrections, and any change to electronic data made in a system with an audit trail. Monitors and clinical data managers reviewed the eCRF for accuracy and generated queries to the investigational staff for resolution. Corrections were to be recorded in an audit trail that recorded the old information, the new information, and identification of the person making the changes, date of correction made and reason for change.

Study G31 was monitored by an independent data safety monitoring board (DSMB) composed of external experts (medical oncologist, cardiologist, clinical pharmacologists, and biostatisticians) assigned to meet at least four times (30% randomization, 70% randomization, after last participant completes neoadjuvant therapy and surgery, after treatment completion of last participant enrolled) to review the safety and tolerability data from the study at pre-specified intervals. There was also blinded review of adverse events (AEs), including clinical laboratory data, performed on a continuous basis by the applicant's medical monitor and pharmacovigilance team. As no interim analysis for efficacy was planned, there was no review of the efficacy data by the DSMB.

Due to regional instability in the Eastern Ukraine, it was impossible to conduct any source data verification activities for 11 patients from two sites (SB31203 and SB31210), and hence the applicant decided to exclude these patients from PPS.

3.3. Financial Disclosures

In accordance with 21 CFR part 54 Financial Disclosures by Clinical Investigators, the applicant certified that it has not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). The applicant also certified that all clinical investigators required to disclose to the applicant whether the investigator had a proprietary interest in this product or a significant equity in the applicant as defined in 21 CFR 54.2(b) disclosed no such interests. The applicant further certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1. Product Quality

The analytical similarity program consisted of two parts: 1) an analytical comparison between SB3 and EU-Herceptin to support the demonstration that the products are highly similar, and 2) pairwise analytical comparisons between EU-Herceptin, US-Herceptin, and SB3 to establish the analytical portion of the scientific bridge to justify the use of clinical and animal data generated using EU-Herceptin as the comparator in Study G31. The results of the analytical similarity comparison show that for the critical

functional assays, EU-Herceptin, US-Herceptin, and SB3 met the predefined statistical criteria for analytical similarity. These results support that SB3 and US-Herceptin are highly similar. Minor differences observed in other quality attributes do not preclude a demonstration that SB3 is highly similar to US-Herceptin, as the differences have been determined not to have clinical impact. Therefore, the data presented supported both a demonstration that US-Herceptin and SB3 are highly similar and the analytical portion of the scientific bridge between EU-Herceptin, US-Herceptin, and SB3.

Please refer to Drs. Wen Jin Wu, Kristen Nickens, and Yu-Ting Weng's reviews for BLA 761100.

4.2. Clinical Microbiology

The manufacturing process of SB3 bulk drug substance and drug product aspects were assessed and recommended for approval from a microbial control and microbiology product quality perspective.

Please refer to Drs. Maria Lopez-Barragan and Lindsey Brown's reviews for BLA 761100.

4.3. Immunogenicity

The incidence of immunogenicity for SB3 and EU-Herceptin was compared in Study G31. The results indicate a very low and similar incidence of anti-drug antibodies between the two arms. There was no apparent relationship between ADAs and efficacy, safety, or pharmacokinetic parameters.

Please refer to Dr. Milos Dokmanovic's review for BLA 761100.

4.4. Preclinical Pharmacology/Toxicology

Please refer to Dr. George Chang's review for BLA 761100.

4.5. Clinical Pharmacology

The applicant submitted the results of Study G11, which evaluated the pharmacokinetic similarity of EU-Herceptin, US-Herceptin, and SB3. Overall, the results of Study G11 adequately demonstrate the PK similarity of EU-Herceptin, US-Herceptin, and SB3. Study G11, conducted in healthy volunteers, is considered sufficiently sensitive to detect clinically significant differences in PK between the three relevant products.

Please refer to Dr. Sriram Subramaniam's review for BLA 761100.

4.5.1. Mechanism of Action

Trastuzumab is a humanized IgG₁K monoclonal antibody directed against an epitope on the extracellular juxtamembrane domain of HER2. Multiple mechanisms of action have been proposed for trastuzumab, including inhibition of HER2 receptor dimerization, increased destruction of the endocytic portion of the HER2 receptor, inhibition of extracellular domain shedding, and activation of cell-mediated immune defenses such as ADCC activity. Trastuzumab has not been shown to inhibit the dimerization of HER2 with the other isoforms; therefore, signaling through the other three receptor isoforms is maintained in the presence of the antibody. Studies have supported a mechanism by which trastuzumab is bound to the HER2 receptor and taken up by the target cell through endocytosis and subsequently degrades the receptor leading to a downregulation of downstream survival signaling, cell cycle arrest and apoptosis. Trastuzumab has also been shown to block the cleavage/shedding of the HER2 receptor extracellular domain thereby preventing the formation of the activated truncated p95, which has been correlated with a poor prognosis based on the detection of the released extracellular domain of HER2 in the serum of metastatic breast cancer patients.

4.5.2. Pharmacokinetics

The applicant conducted Study G11, which evaluated the PK similarity of EU-Herceptin, US-Herceptin, and SB3. Study G11 was a randomized, double-blind, parallel group study designed to compare the PK of EU-Herceptin (n=39), US-Herceptin (n=36), and SB3 (n=36) administered over 90 minutes as a single-dose IV infusion to 109 healthy male volunteers. The 90% confidence intervals (CI) of the geometric mean ratios for all three pairwise comparisons (SB3 vs. US-Herceptin, SB3 vs. EU-Herceptin, and EU-Herceptin vs. US-Herceptin) of AUC_{0-inf} and C_{max} were within the pre-specified limits of 80 to 125% in Study G11. The results of the study established the PK similarity between US-Herceptin and SB3 and provide the PK portion of the scientific bridge between EU-Herceptin, US-Herceptin, and SB3 to justify use of EU-Herceptin in the comparative clinical study, Study G31.

Based on the Guidance for Industry entitled, "Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product," a single-dose, parallel group design is appropriate for trastuzumab because the product has a long half-life (ranging from 2 to 12 days) and avoids repeated exposures that can lead to an increased immune response and affect the PK similarity assessments. A study in healthy subjects is considered safe and more sensitive compared with that in patients with potentially confounding factors such as underlying disease, concomitant medications, and other factors.

Please refer to Dr. Sriram Subramaniam's review for BLA 761100.

5. Sources of Clinical Data

5.1. Tables of Studies/Clinical Trials

A listing of clinical studies applicable to this BLA is provided below.

The datasets, study reports and other documents reviewed as part of the application may be accessed at the following location on the network drive:

<\\CDSESUB1\evsprod\BLA761100\0001>

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen	Number of Subjects	Test Subjects	Duration of Treatment	Study Status; Type of Report

Phase I (Comparative PK, safety, tolerability, immunogenicity)	SB3-G11-NHV (EudraCT No. 2013-004112-21)	5.3.3.1	For FDA: To investigate and compare the PK profiles of SB3 to US Herceptin, SB3 to EU Herceptin, and US Herceptin to EU Herceptin in healthy male subjects. For EMA: To investigate and compare the PK profiles of SB3 and EU Herceptin in healthy male subjects.	Randomized, double-blind, three-arm, parallel group, single-dose study Active Control/Comparator	SB3, US Herceptin or EU Herceptin; single dose i.v. infusion 6 mg/kg	N=108 (36 per arm)	Healthy male subjects	Single dose followed by 8 weeks of safety follow-up	Completed; Final CSR
Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen	Number of Subjects	Test Subjects	Duration of Treatment	Study Status; Type of Report

Phase III (Comparative efficacy, safety, tolerability, PK, immunogenicity)	SB3-G31-BC (ClinicalTrials.gov identifier: NCT02149524, EudraCT No.: 2013-004172-35)	5.3.5.1	To demonstrate the comparable clinical efficacy of SB3 and Herceptin in terms of pathologic complete response (pCR) rate in female patients with HER2-positive EBC or LABC.	Randomized, double-blind, parallel group, multicentre study Active Control/Comparator	SB3 or EU Herceptin ; <i>i.v.</i> infusion 8 mg/kg (loading dose), then 6 mg/kg (maintenance dose) every 3 weeks	N=875 (SB3: 437; EU Herceptin: 438)	Female patients with newly diagnosed HER2-positive EBC or LABC	Approximately 54 weeks of active treatment (neoadjuvant therapy period and adjuvant therapy period) and 4 weeks of safety follow-up	Completed; Final CSR
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EBC: Early Breast Cancer; HER2: Human Epidermal Growth Factor Receptor 2; LABC: Locally Advanced Breast Cancer

Source: eCTD Module 5, Section 5.2

5.2. Review Strategy

The clinical review was conducted by Dr. Tatiana Prowell with safety data analytic support provided by Dr. Yutao Gong. The statistical review was conducted by Dr. Laura Fernandes. The clinical review included the following:

- Literature review of HER2-positive breast and gastric cancer
- Review of FDA regulatory history and meeting minutes pertaining to SB3 development
- Review of applicant submitted CSR, protocol, protocol amendments, and pertinent datasets for Study G31
- Review of selected case report forms (CRFs) for Study G31
- Review of selected patient narratives for adverse events of special interest and deaths in Study G31
- Drafting information requests to the applicant and review of response to clinical and biostatistical information requests sent to the applicant

- Review of consultation reports from the Office of Scientific Investigations and Center for Devices and Radiological Health
- Comparison to package insert for Herceptin and other approved biosimilar trastuzumab products

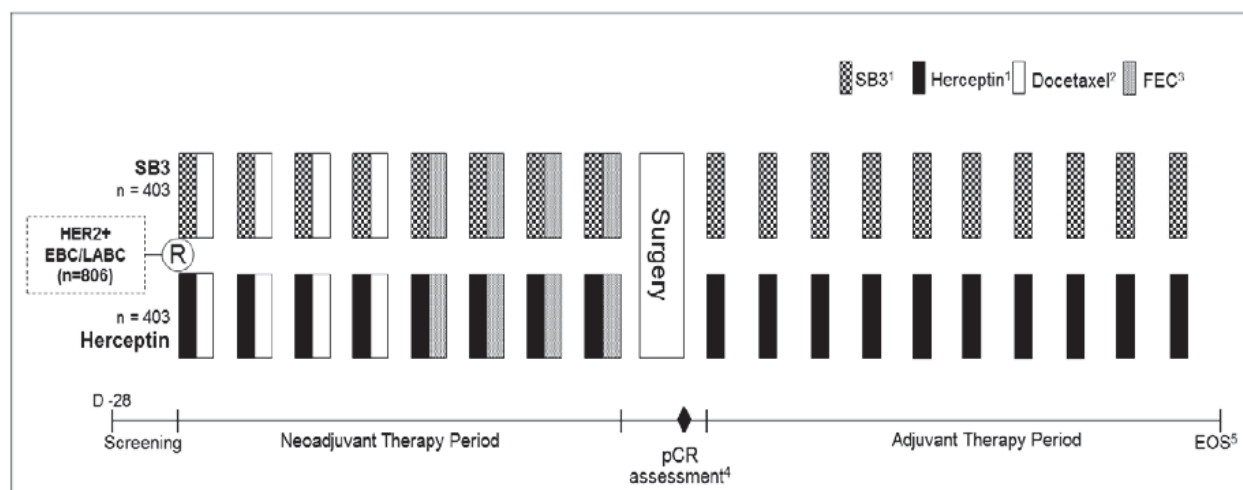
5.3. Discussion of Individual Studies/Clinical Trials

5.3.1. Study Design

Study G31 was a double-blind, randomized, parallel-group, multicenter clinical study to compare the efficacy and safety of SB3 and EU-Herceptin in the neoadjuvant and adjuvant treatment of patients with early or locally advanced HER2 positive breast cancer. In the neoadjuvant period, patients received 4 cycles of SB3 or EU-Herceptin plus docetaxel followed by 4 cycles of SB3 or EU-Herceptin given concurrently with FEC chemotherapy. In the adjuvant period, SB3 or EU-Herceptin was continued to complete a total of one year of HER2-directed therapy (10 cycles during the adjuvant period). Patients were randomized 1:1 and stratified by disease stage and hormone receptor status.

The study design is shown in Figure 1 below.

Figure 1: Study G31 Design



D = day; EBC = early breast cancer; EOS = end of study; HER2 = human epidermal growth factor receptor 2; LABC = locally advanced breast cancer, n = number of subjects; pCR = pathological complete response, R = randomisation.

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: pCR in breast tumour

⁵ EOS Visit was scheduled 30 days after the last dose of investigational product

Source: Study G31 Clinical Study Report

Reviewer comment: The design of the comparative clinical study is acceptable. The early breast cancer population studied and the efficacy endpoint of bpCR after neoadjuvant treatment were agreed upon by the applicant and FDA prior to the BLA submission. A definition of pCR that includes the status of lymph nodes (tpCR) is preferred by the FDA for regulatory purposes. An analysis by the applicant using the FDA's preferred definition has also been provided in the Clinical Study Report.

The schedule of activities for Study G31 is shown in the applicant's tables below.

Table 2: Schedule of Events - Study G31, Neoadjuvant Period

Assessments	Pre-screening ¹	Screening	Neoadjuvant Therapy Period										Surgery ²⁸	
Cycle			1	2	3	4	5	6	7	8			Pre-S	Post-S
Day of Cycle		-28 to -1	1	8	1	1	1	1	1	1	1			
Informed consent ²	✓	✓												
Randomisation ³			✓ ⁴											
Demographic, Medical history ⁵		✓												
Concomitant and previous medication ⁶		✓	continuously											
ECOG status ⁷		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Physical exam ⁷		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Vital signs ⁸		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Weight		✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	
Height		✓												
HER2 status ⁹	✓	✓												
Hormone receptor status (ER, PR) by IHC ¹⁰		✓												
EFFICACY ASSESSMENTS														
Chest X-ray		✓											✓	
Bilateral mammography		✓											✓	
Clinical breast exam ¹¹			✓			✓		✓		✓			✓	
Clinical tumour assessment by ultrasound or caliper ¹²		✓ ¹³						✓					✓	
CT scan (optional) ¹⁴		(✓)												
Liver imaging (optional) ¹⁴		(✓)												
Bone scan (optional) ^{14, 15}		(✓)												
Assessment of pathologic response														✓
SAFETY & LABORATORY ASSESSMENTS														

Assessments	Pre-screening ¹	Screening	Neoadjuvant Therapy Period								Surgery ²⁸		
Cycle			1		2	3	4	5	6	7	8	Pre-S	Post-S
Day of Cycle		-28 to -1	1	8	1	1	1	1	1	1	1		
Haematology and biochemistry ¹⁶		✓	✓ ¹⁷	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Pregnancy test ¹⁸		✓											
Urinalysis		✓						✓				✓	
Blood sample for PK ¹⁹			✓			✓		✓		✓	✓		
Blood sample for immunogenicity ²⁰			✓					✓					
Blood sample for serum HER2 level ²¹			✓								✓		
12-lead ECG		✓						✓				✓	
LVEF (ECHO or MUGA scan) ²²		✓						✓				✓	
Adverse events ²³		✓	continuously										
STUDY TREATMENT													
SB3 or Herceptin [®] IV ²⁴			✓ ²⁵		✓	✓	✓	✓	✓	✓	✓		
Docetaxel IV ²⁶			✓		✓	✓	✓						
5-Fluorouracil IV ²⁷								✓	✓	✓	✓		
Epirubicin IV ²⁷								✓	✓	✓	✓		
Cyclophosphamide IV ²⁷								✓	✓	✓	✓		

Cycle 1, Day 1 = first dose of study drug

Clinical visits must be scheduled within ± 3 days of the day specified. However, PK samples should be taken on the exact day of the scheduled visit.

- Pre-screening is defined as brief screening process only for checking HER2 status. Details of pre-screening are described in Section 5.1.1.
- Written informed Consent must be obtained before any study-specific screening assessments are performed.
- Randomisation will be stratified by hormone receptor status and disease stage.
- Subject should be received IPs or non-IPs within 1 week of randomisation.
- Medical history includes menopausal status, clinically significant diseases and surgical procedures within the last 5 years prior to randomisation.
- Concomitant and previous (within 1 month prior to Randomisation) medications will be recorded at Screening and concomitant medications are to be monitored continuously during the study.
- Must be performed pre-dose on dosing days.
- Vital signs include blood pressure, pulse rate, and body temperature.
- HER2 test must be performed in tissue from core biopsy or open biopsy (fine needle aspiration not acceptable). Tumour sample at Screening is to be used for local HER2 and hormone receptor status testing. Details of HER2 screening process are described in Section 5.2.4.
- Hormone receptor (ER/PR) status will be assessed by IHC test at local laboratory. ER or PR positive is defined as > 1% immunoreactive cells.
- Clinical breast exam including bimanual palpation of breast and locoregional lymph nodes is to be performed every 2 cycles within 3 days prior to dosing during neoadjuvant therapy period. Pre-operative clinical breast exam is allowed to performed within 7 days prior to surgery.
- Tumour assessments of breast and locoregional lymph nodes are to be performed within up to 7 days prior to dosing or surgery. If there is suspicion of disease progression based on clinical or laboratory findings before the next scheduled tumour assessment, an unscheduled assessment should be performed.
- Recommended to be performed within 2 weeks prior to randomisation.
- CT scan, liver imaging, or bone scan will be performed at the discretion of Investigator (optional), if there are symptoms or clinical suspicion of distant metastasis.
- Plain films (CT scan in the case of vertebral column abnormalities) are required to exclude metastatic disease if a bone scan is positive. In the absence of radioactive isotopes, MRI scan (with gadolinium enhancement if required) or PET scan is an acceptable form of assessment of the skeleton for the presence of bone metastases.
- Haematology and biochemistry should be completed pre-dose on Day 1 of each cycle (or up to 3 days before). Haematology tests include haemoglobin, total WBC, absolute neutrophil count (ANC)/neutrophils, platelet count. Biochemistry tests include creatinine, urea (BUN), SGPT (ALT), SGOT (AST), total bilirubin, alkaline phosphatase, albumin, sodium, potassium and calcium.
- Does not need to be repeated if baseline haematology and biochemistry was performed within 3 days prior to Cycle 1.
- For all women of childbearing potential including women who had menopausal onset within 2 years prior to randomisation, a serum or urine pregnancy test must be performed within 2 weeks prior to randomisation.
- Blood sampling for PK analysis will be performed only in PK populations. PK samples will be taken pre-dose on the exact day of the scheduled visit. If the treatment of scheduled cycle for PK analysis is delayed for any reasons after blood sampling for PK analysis, blood sampling for PK analysis does not need to be repeated in delayed visit for the treatment.
- Blood sampling for Immunogenicity will be performed in all randomised subjects. Blood sampling for immunogenicity will be taken pre-dose on Day 1 of each scheduled cycles. If the treatment of scheduled cycle for immunogenicity sampling is delayed for any reasons after blood sampling for immunogenicity, blood sampling for immunogenicity does not need to be repeated in delayed visit for the treatment.
- Blood sampling for serum HER2 level will be performed only in PK populations. Blood sampling for serum HER2 level will be taken pre-dose on Day 1 of Cycle 1 and Cycle 8. If the treatment of Cycle 8 is delayed for any reasons after blood sampling for serum HER2 level, blood sampling for serum HER2 level does not need to be repeated in delayed visit for the treatment.
- LVEF will be measured by echocardiography or MUGA scan. The same method should be used throughout the study for each subject. It is also recommended that same sonographer perform the echocardiography on a subject throughout the study. During study treatment, LVEF assessments should be performed within 7 days prior to dosing to allow evaluation of the results before the next treatment cycle.
- AEs will be recorded from the time the main informed consent form (ICF) is signed and are to be monitored continuously during the study.
- Loading dose for SB3 or Herceptin® is 8 mg/kg followed by maintenance doses of 6 mg/kg.
- Vital signs measurement will be performed before and after the first infusion of SB3 or Herceptin®.
- Docetaxel 75 mg/m² will be administered on Day 1 of Cycle 1 to Cycle 4. It may be given as an IV infusion over 60 (± 10) minutes. It is to be given after completion of SB3 or Herceptin® administration. Premedication with oral corticosteroids, such as dexamethasone 16 mg per day or equivalent for 3 days starting 1 day prior to docetaxel administration, unless contra-indicated, should be used.
- 5-Fluorouracil 500 mg/m² will be administered on Day 1 of Cycle 5 to Cycle 8. It may be given as an IV bolus over 3-5 minutes or as an infusion over 30 minutes. Epirubicin 75 mg/m² will be administered on Day 1 of Cycle 5 to Cycle 8. It may be given as an IV bolus over 3-5 minutes or as an infusion over 30 minutes. Cyclophosphamide 500 mg/m² will be administered on Day 1 of Cycle 5 to Cycle 8. It may be given as an IV bolus over 3-5 minutes or as an infusion over 30 minutes.
- After 8 cycles of neoadjuvant therapy, the subject will undergo surgery within 6 weeks after the last dose of neoadjuvant therapy. (Pre-S: Pre-surgery evaluation, Post-S: Post-surgery evaluation)

Source: Study G31 Protocol Version 1

Table 3: Schedule of Events - Study G31, Adjuvant Period

Assessments	Adjuvant Therapy Period										EOS ¹¹
Cycle	9	10	11	12	13	14	15	16	17	18	1 month after last dose of IP
Day of Cycle	1	1	1	1	1	1	1	1	1	1	
Physical exam ¹	✓					✓				✓	✓
ECOG status ¹	✓					✓				✓	✓
Vital signs ^{1,2}	✓					✓				✓	✓
Weight ¹	✓					✓				✓	✓
Bilateral mammography											✓
Chest X-ray											✓
CT scan (optional) ³											(✓)
Liver imaging (optional) ³											(✓)
Bone scan (optional) ^{3,4}											(✓)
Haematology and biochemistry ⁵	✓					✓					✓
Blood sample for immunogenicity (SB3 or Herceptin®) ⁶	✓					✓					✓
12-lead ECG						✓					✓
LVEF (ECHO or MUGA scan) ⁷						✓					✓
Adjuvant SB3 or Herceptin® IV ⁸	✓ ⁹	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Adverse events ¹⁰	continuously										
Concomitant medication ¹⁰	continuously										

Clinical visits must be scheduled within ± 3 days of the day specified.

- Physical exam, ECOG status, vital signs, and weight should be measured before IP administration on Day 1 of Cycle 9, 14, 18 and at the end of study. These assessments may be done at more frequent intervals if clinically indicated.
- Vital signs include blood pressure, pulse rate, and body temperature.
- CT scan, liver imaging or bone scan will be performed at the discretion of Investigator (optional), if there are symptoms or clinical suspicion of recurrence.
- Plain films (CT scan in the case of vertebral column abnormalities) are required to exclude metastatic disease if a bone scan is positive. In the absence of radioactive isotopes, MRI scan (with gadolinium enhancement if required) or PET scan is an acceptable form of assessment of the skeleton for the presence of bone metastasis.
- Haematology and biochemistry should be completed pre-dose on Day 1 of each scheduled cycle (or up to 3 days before). Haematology tests include haemoglobin, total WBC, absolute neutrophil count (ANC)/neutrophils, platelet count. Biochemistry tests include creatinine, urea (BUN), SGPT (ALT), SGOT (AST), total bilirubin, alkaline phosphatase, albumin, sodium, potassium and calcium.
- Blood sampling for immunogenicity will be performed in all randomised subjects. Blood sampling for immunogenicity will be taken pre-dose on Day 1 of each scheduled cycle. If the treatment of scheduled cycle for immunogenicity sampling is delayed for any reasons after blood sampling for immunogenicity, blood sampling for immunogenicity does not need to be repeated in delayed visit for the treatment.
- LVEF will be measured by echocardiography or MUGA scan. The same method should be used throughout the study for each subject. It is also recommended that same sonographer perform the echocardiography on a subject throughout the study. During study treatment, LVEF assessments should be performed within 7 days prior to administration of IP to allow evaluation of the results before the next treatment cycle.
- Loading dose for SB3 or Herceptin® is 8 mg/kg followed by maintenance doses of 6 mg/kg.
- Re-loading of SB3 or Herceptin® is required at Cycle 9, since the interval between Cycle 8 and Cycle 9 is more than 6 weeks due to surgery. Details of re-loading rules are described in Section 6.2.1.
- AEs and concomitant medications will be recorded and be monitored continuously during study treatment.
- End of study (EOS) is defined as 1 month after the last dose of SB3 or Herceptin®.

Source: Study G31 Protocol Version 1

Reviewer comments: The schedule of study events is appropriate. Echocardiogram or MUGA scan was performed at baseline, after cycles 4 and at end of treatment in the neoadjuvant period, at the end of cycle 6, and end of treatment at during the adjuvant period. Laboratory, EKG, AE, and PK assessments are also appropriate.

5.3.2. Protocol Amendments

The original protocol for Study G31 was dated November 8, 2013. There were five global amendments and four country-specific amendments. The notable amendments are briefly summarized below:

- Global protocol amendment May 8, 2014 (Amendment 1)
Added language related to fertility, pregnancy, and lactation and related to administration of neoadjuvant chemotherapy as required by French authorities

- Global protocol amendment May 8, 2014 (Amendment 2)
Clarified several eligibility criteria: definition of multifocal/multicentric tumors, known HBV infection, and definition of surgery (excludes diagnostic biopsy); clarified that screening, randomization, and first study drug administration could occur on the same day; clarified that diagnostic biopsy results could be used for ER/PR status; clarified timing of FEC administration in case of docetaxel discontinuation due to toxicity; clarified protocol violations and durations of treatment delay that could lead to discontinuation of study treatment as criteria for premature withdrawal
- Global protocol amendment August 26, 2014 (Amendment 3)
Clarified that SLNB before neoadjuvant therapy is not considered exclusionary from standpoint of eligibility criteria excluding patients with recent surgery; extended period of contraceptive use for WOCBP from 6 to 7 months after last dose of study drug based on change to Herceptin product labeling; allowed bilateral mammography to be done within 6 weeks prior to randomization; clarified language regarding timing of clinical tumor assessment, LVEF assessment, and scheduled procedures prior to cycle 5 and pre-surgery; clarified that SISH or CISH result would be accepted from SISH-or CISH-accredited laboratory; clarified disease stage when tumor size was 2.0 cm; clarified definition of overall clinical response rate; updated axillary staging procedure for consistency with current ASCO & ESMO guidelines to clarify that some patients may be appropriate for sentinel lymph node biopsy alone after neoadjuvant therapy, most patients should undergo standard surgical evaluation of the axilla (axillary nodal dissection) after post-neoadjuvant therapy
- Global protocol amendment December 8, 2014 and December 17, 2014 (Amendments 4 & 4.1, which corrected errors introduced in Amendment 4)
Updated sample size and rationale based on recent literature; changed expected bpCR rate from 40% to 37.5%; changed the number of evaluable subjects to provide 80% power from 220 to 358 subjects per arm and the equivalence margin from within +/-15% to 0.785 to 1.546; changed number of total patients to be randomized from 498 to 806 and recruitment period from 12 to 15 months. Modified criteria for declaring equivalence from: Equivalence between the two treatment groups will be declared if the two-sided 95% (CI) of the difference in the pCR rate between treatments is entirely contained within the equivalence margin of [-15%, 15%] to instead state that equivalence will be declared if the two-sided 95% CI of the ratio in the pCR rate between treatments is entirely contained within the equivalence margin of [0.785, 1.546] or, if the 95% CI of the difference in the pCR rate between treatments is entirely contained within the equivalence margin of [-13%,13%]. The difference of pCR will be used for EMA submission, and relative ratio of pCR will be used for FDA submission.
- Global protocol amendment April 23, 2015 (Amendment 5)
Added references (different versions of NCI-CTCAE) to be used to grade the severity of AEs of CHF, left ventricular dysfunction and febrile neutropenia; amended sample size for PK population from 270 to 300 and updated expected non-evaluable rate from 22% to 30% and clarified PK sampling procedures; clarified dose modification and delay section; updated premature withdrawal criteria with regard to permitted treatment delays; added section on quality control of pCR by central

review; added language allowing use of G-CSF as primary prophylaxis for neutropenia in high-risk patients.

- Remaining amendments were country specific (Korea and France) and do not impact the overall conduct or interpretation of the study
- Statistical analysis plan amendment September 6, 2015
Analysis to be performed using the risk ratio of pCR with 90% confidence intervals for the US regulatory submission

Reviewer comment: The protocol amendments and changes appear reasonable. The original protocol used the risk difference of pCR rates for the primary efficacy analysis with the corresponding 95% CI to be contained within [-15%,15%]. The efficacy analysis has changed over various protocol amendments due to updated information. The current endpoint of bpCR with the 90% CI of the risk ratios was included in the later amendments for the purposes of submitting the data for U.S. regulatory review since the FDA recommends use of risk ratios of the proportions with a 90% CI to perform the two one sided test procedure with 5% type I error probability in the evaluation of biosimilarity of two biological products. The SAP was updated on September 6, 2015 to use the 90% CI of the risk ratios for consistency with FDA advice on biosimilars instead of the 95%CI specified in the protocol. The changes to the SAP and protocol are acceptable and did not bias the conduct or interpretation of the trial.

5.3.3. Study Objectives

Primary Objective

To demonstrate comparable clinical efficacy of SB3 and Herceptin in terms of pCR rate in the primary breast tumor in women with HER2 positive early breast cancer or locally advanced breast cancer in the neoadjuvant setting. Breast pCR (bpCR) was defined as no histological evidence of residual invasive tumor cells in the breast specimen removed at surgery. Non-invasive residual tumor cells (i.e. carcinoma in situ) were allowed, and the pathological status of the axillary lymph nodes was not considered in the definition of bpCR (ypT0/is, ypN0/+).

Secondary Objectives

To evaluate the efficacy of SB3 compared to Herceptin by:

- Total pathological complete response rate (tpCR, defined as absence of residual invasive cancer in both breast and lymph nodes)
- Overall clinical response rate during neoadjuvant therapy (using tumor size as measured by ultrasound or calipers)
- Event-free survival (EFS), defined as time from randomization to date that an event occurs. An event was defined as disease recurrence or progression (local, regional, distant, or contralateral) or death due to any cause.
- Overall survival (OS), defined as time from the date of randomization to the date of

death, regardless of the cause of death. Participants who were alive at the time of analysis were to be censored at the date of the last follow up assessment.

Reviewer comments: Total pathological complete response (tpCR) is the FDA's preferred endpoint for assessment of efficacy in the neoadjuvant setting given that lymph node involvement is known to be prognostic. A definition of pCR that includes nodal status (i.e. tpCR) has shown improved correlation with EFS and OS compared to a definition of pCR that considers the status of the breast specimen alone (i.e. bpCR) in an FDA pooled analysis (Cortazar et al. Lancet 2014). The presence or absence of residual non-invasive cancer (i.e. carcinoma in situ) is not believed to be of prognostic significance based upon the same FDA pooled analysis. The applicant and the FDA review team analyzed tpCR as a secondary endpoint, and results were consistent with the analysis of the primary endpoint (bpCR).

5.3.4. Eligibility Criteria

Inclusion Criteria:

1. Female aged 18-65 years
2. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1
3. Non-metastatic, unilateral newly diagnosed primary breast cancer of clinical stage II to III including inflammatory breast cancer with:
 - a. tumor size ≥ 2 cm
 - b. histologically confirmed primary invasive adenocarcinoma of the breast
 - c. HER2-positivity confirmed by a central laboratory or an accredited local laboratory and defined as immunohistochemistry 3+ or fluorescence in situ hybridization (FISH) +
4. Known hormone receptor (estrogen receptor [ER] and progesterone receptor [PR]) status
5. Baseline left ventricular ejection fraction (LVEF) $\geq 55\%$ measured by echocardiography or multiple gated acquisition (MUGA) scan
6. Subjects had to be able to provide informed consent, which had to be obtained prior to any study-related procedures

Exclusion Criteria:

1. Metastatic (stage IV) or bilateral breast cancer or clinically detectable two separate breast cancer masses by physical examination (palpation)
2. History of any prior invasive breast carcinoma, except for subjects with a past history of ductal carcinoma in situ and/or lobular carcinoma in situ treated with surgery only
3. Past or current history of malignant neoplasms within 5 years prior to randomization, except for curatively treated carcinoma in situ of uterine cervix, basal cell carcinoma of the skin or squamous cell carcinoma of the skin (malignant neoplasm occurring more than 5 years prior to randomization were permitted if curatively treated with surgery only)
4. Previous history of radiation therapy, immunotherapy, chemotherapy or biotherapy (including prior HER2 directed therapy)
5. Major surgery within 4 weeks prior to randomization and minor surgery within 2 weeks prior to randomization (major surgery was defined as surgery which required general anesthesia; the diagnostic procedures such as open and/or core-needle biopsies were not regarded as surgeries mentioned above; sentinel lymph node biopsy before initiation of neoadjuvant therapy was exempted from this criterion)
6. Serious cardiac illness that would preclude the use of trastuzumab such as:
 - a. History of documented congestive heart failure (CHF; New York Heart Association [NYHA] class II or greater heart disease)
 - b. LVEF $< 55\%$ by echocardiography or MUGA scan

- c. Angina pectoris requiring anti-anginal medication
 - d. Evidence of transmural infarction on electrocardiogram (ECG)
 - e. Uncontrolled hypertension (systolic > 180 mmHg and/or diastolic > 100 mmHg)
 - f. Clinically significant valvular heart disease
 - g. High risk uncontrolled arrhythmias
7. Serious pulmonary illness enough to cause dyspnea at rest or requiring supplementary oxygen therapy
 8. Known history of hepatitis B virus (excluding immunized or fully recovered from the past infection), hepatitis C virus or human immunodeficiency virus infection
 9. Other concurrent serious illnesses that could interfere with planned treatment including severe cardiovascular, pulmonary, metabolic or infectious conditions
 10. Known hypersensitivity to the IPs, non-IPs or any ingredients or excipients of the IPs or non-IPs
 11. Known hypersensitivity to murine proteins
 12. Known history of dihydropyrimidine dehydrogenase deficiency
 13. Pre-existing peripheral sensory or motor neuropathy $\geq$ grade 2, defined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.0
 14. Any of the following abnormal laboratory tests:
 - a. Serum total bilirubin > $1.5 \times$ upper limit of normal (ULN); in cases of known Gilberts syndrome, level of total bilirubin within $3 \times$ ULN was permitted
 - b. Aspartate transaminase (AST) and/or alanine transaminase (ALT) > $1.5 \times$ ULN
 - c. Alkaline phosphatase (ALP) > $2.5 \times$ U
 - d. Serum creatinine > $1.5 \times$ ULN
 - e. Hemoglobin < 9 g/dl
 - f. Absolute neutrophil count (ANC) < $1500/\text{mm}^3$ (< $1.5 \times 10^9/\text{L}$)
 - g. Platelets count < $100000/\text{mm}^3$ (< $100 \times 10^9/\text{L}$)
 15. Pregnant or lactating women. A pregnancy test result was required for all women of childbearing potential including women who had menopause onset within 2 years prior to randomization. Women of childbearing potential had to agree to use non-hormonal contraceptive methods (as in Section 7.4.2 of the Study Protocol in Appendix 16.1.1) during the study and 7 months after the last dose of IP
 16. Concurrent hormonal therapy including birth control pills, ovarian hormone replacement for menopause, selective estrogen receptor modulator (SERM) either for osteoporosis or breast cancer prevention
 17. Subjects unwilling to follow the study requirements.

Reviewer comments: The inclusion and exclusion criteria are appropriate.

5.3.5. Drug Administration

Neoadjuvant Period

SB3 or EU-Herceptin: loading dose of 8 mg/kg body weight on day 1 of cycle 1, and then 6 mg/kg body weight every 3 weeks from cycles 2-8 (cycles 1-8).

Docetaxel: 75 mg/m² given on day 1 of each cycle and repeated every 3 weeks for a total of 4 cycles (cycles 1-4).

FEC: Fluorouracil 500 mg/m² IV, epirubicin 75 mg/m² IV, and cyclophosphamide 500 mg/m² IV given on day 1 of each cycle and repeated every 3 weeks for a total of 4 cycles, following 4 cycles of docetaxel (cycles 4-8).

Adjuvant Period

SB3 or EU-Herceptin was administered every 3 weeks at 6 mg/kg for up to 10 cycles after surgery to complete 1 year of a trastuzumab product (cycles 9-18).

5.3.6. Dose Modifications

- Trastuzumab product: No dose reductions are permitted. For grade 3/4 AEs (excluding congestive heart failure), trastuzumab is held until recovery to grade ≤ 2 . If recurrence of a grade 3/4 non-hematological AE occurs upon re-challenge or if toxicity of any grade 3/4 AE does not resolve to grade ≤ 2 within a maximum of 5 weeks from last dose, trastuzumab is permanently discontinued. For symptomatic congestive heart failure, trastuzumab is permanently discontinued.
- Docetaxel and/or FEC: Up to two 20% dose reductions permitted for grade 4 or prolonged (2-3 weeks) neutropenia, thrombocytopenia, and grade 3/4 febrile neutropenia, grade 3 neurosensory toxicity, grade 2/3 hepatic dysfunction, or grade 3/4 other clinically significant non-hematological AEs, such as mucositis or vomiting despite anti-emetics. Recurrence of grade ≥ 3 febrile neutropenia, grade ≥ 3 neurosensory toxicity, or first occurrence of grade 4 hepatic dysfunction resulted in permanent discontinuation.

5.3.7. Statistical Analysis Plan

The primary efficacy endpoint of this trial was bpCR, as assessed by local pathologist, and defined as no histologic evidence of residual invasive tumor cells in the breast specimen removed at surgery. Residual carcinoma in situ was allowed, and the pathological examination of axillary lymph nodes was not to be considered; ypT0is, ypN0/+, which means that subjects classified in pT0 or pTis categories would be considered as bpCR='Yes' regardless of pathological N category results. The bpCR rate is defined as the proportion of patients with pT0 or pTis within the patients who had pT category in pT0, pTis, pT1-pT4, and pTx.

The local pathologist will assess pathological staging (T and N category) according to the guidelines suggested in Cancer Staging Manual 7th edition on 2010 using results of residual invasive carcinoma, in situ carcinoma, skin invasion, chest wall invasion, sentinel lymph node dissection (SLND), and axillary lymph node dissection (ALND).

Sample Size Considerations:

The equivalence margin was based on three neoadjuvant studies found in literature that randomized patients to receive Herceptin® in combination with taxane- and/or anthracycline containing chemotherapies or only chemotherapies without Herceptin and reported bpCR in patients treated with these regimens.

The results from the three studies are summarized in Table 4. Buzdar and Chang studies included only operable EBC patients with stage II to III with resulting bpCR rate of 65% (26% for non-Herceptin arm) and 31% (9% for non-Herceptin arm), respectively, and NOAH study included only LABC patients in reporting bpCR rate of 43% (22% for non-Herceptin arm) [Buzdar, 2005, Gianni, 2010, Chang, 2008].

Table 4: bpCR Rates from Reference Studies

Study	Herceptin®	No Herceptin®	Diff	Ratio
	Event/Total	Event/Total		
Buzdar (2005)	15/23 (65%)	5/19 (26%)	39%	2.5
Gianni (2010) NOAH trial	50/117 (43%)	26/118 (22%)	21%	2.0
Chang (2008)	4/13 (31%)	1/11 (9%)	22%	3.4
Meta-analysis			23.3% [16.6;29.9] [†]	2.07 [1.546, 2.795] [‡]

[†] 80% CI, [‡] 90% CI

Source: Applicant's SAP

The estimated ratio of bpCR rates is 2.07 with the 90% CI of [1.546, 2.795] from meta-analysis using the three referenced studies. The asymmetric equivalence margin for the ratio of bpCR rates is calculated as [0.785, 1.546] where the lower limit preserves at least 50% of Herceptin® treatment effect over the placebo, i.e., $0.785 = 1/(1+0.5 \times (1.546-1))$. The upper equivalence limit of 1.546 is taken from the lower limit of 90% CI of the ratio between treatments

With the expected bpCR rate of 37.5%, 358 evaluable patients per arm would provide 80% power to detect the equivalence within the margin of [0.785, 1.546] under the assumption of no difference between two treatments in terms of bpCR rate. The difference of bpCR rates between treatments is calculated as 23.3% with the 80% CI of [16.6%, 29.9%] from meta-analysis using the three reference studies. The equivalence margin for the difference was derived as 13% ($= 16.6\% \times 0.8$).

The sample size of 358 patients per arm derived from the ratio-based approach would satisfy both primary analyses of the ratio and difference of bpCR rates to be submitted to the FDA and the EMA respectively.

Accounting for non-evaluable cases for bpCR (e.g., inoperable cases) and assuming an 11% dropout rate, a total of 806 patients per arm would be randomized with 1:1 ratio (403 patients per arm) into the study.

The applicant used the 90% asymptotic confidence region of the ratio of pCR in the SB3 arm versus the control arm as the primary analysis strategy. The primary analysis population was the per-protocol set as defined above; the intent to treat population was used for supportive analyses.

The study will be deemed successful if the 90% confidence interval for the ratio of bpCR rate between the two treatment arms is entirely contained within the equivalence margins of (0.785, 1.546) for the FDA submission or if the 95% CI of the difference in the bpCR rate between the two treatment arms is contained within (-13%, 13%) for the EMA submission.

The adjusted risk difference in bpCR rate (SB3 minus EU-Herceptin) between the two treatment groups will be estimated using a stratified Cochran-Mantel-Haenszel (CMH) test along with the 95% Wald confidence intervals (CIs); the adjusted risk ratio in bpCR rate (SB3/Herceptin) and its 90% CIs will also be estimated using stratified CMH test. The stratification factors for CMH tests are hormone receptor status, breast cancer type and region.

Secondary efficacy endpoints included the following:

- 1) Total pathological complete response (tpCR) defined as the absence of invasive residual in both breast and lymph nodes, which means that subjects classified in pT0/pN0 or pTis/pN0 categories will be considered as tpCR='Yes'. Patients with pNx category are considered 'not evaluable' and will not be included in the analysis of tpCR.
- 2) Overall response rate (ORR) assessed and classified by the investigator according to the criteria for clinical response evaluation modified from Response Evaluation Criteria in Solid Tumors (RECIST). ORR is defined as percentage of patients achieving CR or PR for the best overall response. Best overall response is defined as the best response among CR, PR, SD, and PD assessed at the mapped visit (Cycle 5 and Pre-surgery) during neoadjuvant therapy for each patient.
- 3) Event-free survival (EFS) defined as the time from the date of randomization to the date where an event occurs. An event is disease recurrence or progression (local, regional, distant or contralateral) or death due to any cause.

- 4) Overall Survival (OS) is defined as the time from date of randomization to the death date.

There are three main analyses populations:

Full analysis set [FAS]: FAS consists of all patients who are randomized at the randomization visit and follows the intent-to-treat principle. However, patients who do not qualify for randomization and are inadvertently randomized into the study will be excluded from the FAS, provided these patients did not receive IP during that study phase.

Per-protocol set [PPS]: PPS consists of all FAS patients who completed the 8 cycles of neoadjuvant therapy and surgery. The PPS will be the primary analysis set. Major protocol deviations that will lead to exclusion from this set will be pre-specified prior to unblinding the treatment codes for analyses. Patients who do not have a pathologic response assessment will be excluded from PPS.

Due to regional issues in the Eastern Ukraine it was impossible to conduct any source data verification (SDV) activities for 11 patients from two sites (SB31203 and SB31210) and hence the Applicant decided to exclude these patients from PPS.

Safety set [SAF]: SAF consist of all patients who received at least one dose of double-blind study drug during the study phase. Patients will be analyzed according to the treatment received.

Reviewer Comments:

The protocol and statistical analysis plan were written prior to any engagement with FDA. As a result, the original non-inferiority margins were chosen by the applicant without FDA input. FDA typically recommends symmetric efficacy margins for comparative clinical studies. In this case, if we were to consider the upper bound to be symmetric to the lower bound, the 90% CI for the risk ratio margin would be (0.785, 1.1.274). The primary endpoint of breast pathological complete response (bpCR) ratio (the bpCR rate with SB3 divided by the bpCR rate in the control arm) as assessed by local review of the per-protocol set (PPS) was 1.259, which still falls between these boundaries.

5.3.8. Charter and SOP Review

Blinding

Study site personnel, including local pathologists, were blinded to the treatments in study G31 and the randomization codes. Treatment group information was not to be revealed to patients, investigators, local pathologists, or any other blinded site staff until all final clinical data from the neoadjuvant, adjuvant, and post-treatment follow-up

periods had been entered into the database and the databased locked and released for analysis.

6. Review of Efficacy

Efficacy Summary

Study G31 together with other information in the application, supports the determination of no clinically meaningful differences between SB3 and US-Herceptin (discussed in Section 5.3). Specifically the point estimate for the bpCR ratio between SB3 and EU-Herceptin in Study G31 is 1.259, and its corresponding 90% CI of (1.112, 1.428) is entirely contained within (0.785, 1.546), the equivalence margin established for demonstration of biosimilarity between the two products. A scientific bridge between SB3, EU-Herceptin, and US-Herceptin has been established based in part on pharmacokinetic evaluation.

6.1. Indication

The applicant proposed indications that are the same as those for US-Herceptin.

6.2. Methods

Similarity in clinical efficacy was assessed in Study G31 comparing SB3 with EU-Herceptin in patients with early breast cancer. The primary efficacy analysis population was the per protocol set (PPS). The primary efficacy analysis was based on the bpCR rate at the time of surgery, as assessed locally, after completing 8 cycles of neoadjuvant treatment with chemotherapy and in the PPS population. Sensitivity analyses were performed as appropriate. Recalculation of the primary and secondary efficacy endpoints was conducted using the datasets submitted by the applicant. Analyses of the primary endpoint, key secondary endpoints, and safety are included in this review.

6.3. Demographics

This was an international study with a total of 800 patients in the PPS population (875 in the full analysis set) enrolled in 14 countries, which are listed in Table 5.

Table 5: Enrollment by Country, PPS Population, Study G31

	Per Protocol Set	Full Analysis Set
--	------------------	-------------------

Country	SB3 N=402 n (%)	EU-Herceptin N=398 n (%)	SB3 N=437 n (%)	EU-Herceptin N=438 n (%)
Bosnia and Herzegovina	4 (1)	3 (1)	4 (1)	3 (1)
Bulgaria	3 (1)	0 (0)	3 (1)	1 (0)
Czech Republic	10 (2)	7 (2)	10 (2)	7 (2)
France	9 (2)	9 (2)	9 (2)	10 (2)
India	47 (12)	45 (11)	52 (12)	52 (12)
Malaysia	8 (2)	10 (3)	9 (2)	12 (3)
Mexico	0 (0)	0 (0)	0 (0)	1 (0)
Philippines	23 (6)	27 (7)	25 (6)	27 (6)
Poland	67 (17)	64 (16)	72 (16)	71 (16)
Korea	36 (9)	35 (9)	37 (8)	37 (8)
Romania	19 (5)	18 (5)	19 (4)	21 (5)
Russia	101 (25)	100 (25)	106 (24)	105 (24)
Ukraine	68 (17)	75 (19)	83 (19)	83 (19)
Vietnam	7 (2)	5 (1)	8 (2)	8 (2)

Source dataset: ADSL.xpt

Reviewer Comments: The top five countries for patient enrollment were Russia, Ukraine, Poland, India, and Korea. There were no patients enrolled from the United States.

The demographic and baseline disease characteristics of the PPS and FAS population are shown in Table 6 below.

Table 6: Demographic and Baseline Disease Characteristics in the Per Protocol and Full Analysis Population, Study G31

	Per Protocol Set		Full Analysis Set	
	SB3 N=402 n (%)	EU-Herceptin N=398 n (%)	SB3 N=437 n (%)	EU-Herceptin N=438 n (%)
Age (years)				
Mean (SD)	49.3	49.6	49.5	49.6

	Per Protocol Set		Full Analysis Set	
	SB3 N=402 n (%)	EU- Herceptin N=398 n (%)	SB3 N=437 n (%)	EU- Herceptin N=438 n (%)
	(9.5)	(9.4)	(9.5)	(9.4)
Median (range)	51 (24,65)	50 (22,65)	51 (24,65)	50 (22,65)
Age Categories				
20 - <30 years	8 (2)	10 (3)	9 (2)	12 (3)
30 - <40 years	66 (16)	49 (12)	69 (16)	53 (12)
40- <50 years	113 (28)	133 (33)	123 (28)	144 (33)
50- <60 years	153 (38)	137 (34)	166 (38)	155 (35)
>=60 years	62 (15)	69 (17)	70 (16)	73 (17)
Race				
Asian	124 (31)	124 (31)	134 (31)	138 (32)
White	269 (67)	264 (66)	294 (67)	289 (66)
Other	9 (2)	10 (3)	9 (2)	11 (3)
Ethnicity				
Hispanic/Latino	1 (0)	1 (0)	1 (0)	2 (0)
Not Hispanic/Latino	401 (100)	397 (100)	436 (100)	436 (100)
Region Category 1				
Region 1 (Korea)	36 (9)	35 (9)	37 (8)	37 (8)
Region 2 (Malaysia, Mexico, Philippines, Vietnam)	38 (9)	42 (11)	42 (10)	48 (11)
Region 3 (Bosnia and Herzegovina, Ukraine)	72 (18)	78 (20)	87 (20)	86 (20)
Region 4 (Bulgaria, Czech Republic, France, Romania)	41 (10)	34 (9)	41 (9)	39 (9)
Region 5 (Poland)	67 (17)	64 (16)	72 (16)	71 (16)
Region 6 (India)	47 (12)	45 (11)	52 (12)	52 (12)
Region 7 (Russian Federation)	101 (25)	100 (25)	106 (24)	105 (24)
Region Category 2 (EU)				
EU	108 (27)	98 (25)	113 (26)	110 (25)

	Per Protocol Set		Full Analysis Set	
	SB3 N=402 n (%)	EU- Herceptin N=398 n (%)	SB3 N=437 n (%)	EU- Herceptin N=438 n (%)
non-EU	294 (73)	300 (75)	324 (74)	328 (75)
ECOG at Baseline				
0	341 (85)	332 (83)	366 (84)	365 (83)
1	61 (15)	66 (17)	71 (16)	73 (17)
Tumor Number				
More than one	0 (0)	1 (0)	0 (0)	3 (1)
One	402 (100)	397 (100)	437 (100)	435 (99)
Histology Group				
Invasive ductal carcinoma NOS and other	394 (98)	393 (99)	426 (97)	432 (99)
Invasive lobular carcinoma	8 (2)	5 (1)	11 (3)	6 (1)
T Stage				
T1	2 (0)	2 (1)	2 (0)	4 (1)
T2	216 (54)	213 (54)	234 (54)	228 (52)
T3	77 (19)	86 (22)	84 (19)	99 (23)
T4	107 (27)	97 (24)	117 (27)	107 (24)
N-Stage				
N0	82 (20)	79 (20)	91 (21)	88 (20)
N1	227 (56)	212 (53)	243 (56)	232 (53)
N2	63 (16)	64 (16)	69 (16)	73 (17)
N3	30 (7)	43 (11)	34 (8)	45 (10)
M-Stage				
M0	402 (100)	398 (100)	436 (100)	438 (100)
M1	0 (0)	0 (0)	1 (0)	0 (0)
TNM Stage				
cT1N1M0	0 (0)	1 (0)	0 (0)	1 (0)
cT1N2M0	1 (0)	1 (0)	1 (0)	3 (1)
cT1N3M0	1 (0)	0 (0)	1 (0)	0 (0)
cT2N0M0	58 (14)	55 (14)	65 (15)	61 (14)
cT2N1M0	129 (32)	122 (31)	137 (31)	129 (29)

	Per Protocol Set		Full Analysis Set	
	SB3 N=402 n (%)	EU- Herceptin N=398 n (%)	SB3 N=437 n (%)	EU- Herceptin N=438 n (%)
cT2N2M0	19 (5)	21 (5)	22 (5)	23 (5)
cT2N3M0	10 (2)	15 (4)	10 (2)	15 (3)
cT3N0M0	12 (3)	14 (4)	13 (3)	17 (4)
cT3N1M0	42 (10)	46 (12)	46 (11)	51 (12)
cT3N2M0	15 (4)	19 (5)	16 (4)	22 (5)
cT3N3M0	8 (2)	7 (2)	9 (2)	9 (2)
cT4N0M0	12 (3)	10 (3)	13 (3)	10 (2)
cT4N1M0	56 (14)	43 (11)	60 (14)	51 (12)
cT4N2M0	28 (7)	23 (6)	30 (7)	25 (6)
cT4N3M0	11 (3)	21 (5)	13 (3)	21 (5)
cT4N3M1	0 (0)	0 (0)	1 (0)	0 (0)
Clinical Stage				
Stage IIA	58 (14)	56 (14)	65 (15)	62 (14)
Stage IIB	141 (35)	136 (34)	150 (34)	146 (33)
Stage IIIA	77 (19)	87 (22)	85 (19)	99 (23)
Stage IIIB	96 (24)	76 (19)	103 (24)	86 (20)
Stage IIIC	30 (7)	43 (11)	33 (8)	45 (10)
Stage IV	0 (0)	0 (0)	1 (0)	0 (0)
Tumor Baseline				
Inflammatory	15 (4)	15 (4)	16 (4)	15 (3)
Locally advanced	146 (36)	145 (36)	160 (37)	164 (37)
Operable	241 (60)	238 (60)	261 (60)	259 (59)
Hormone Status				
ER-/PR-	148 (37)	168 (42)	171 (39)	187 (43)
ER-/PR+	9 (2)	7 (2)	9 (2)	8 (2)
ER+/PR-	72 (18)	68 (17)	78 (18)	73 (17)
ER+/PR+	173 (43)	155 (39)	179 (41)	170 (39)
Hormone Status Group				
ER and PR negative	148 (37)	168 (42)	171 (39)	187 (43)

	Per Protocol Set		Full Analysis Set	
	SB3 N=402 n (%)	EU- Herceptin N=398 n (%)	SB3 N=437 n (%)	EU- Herceptin N=438 n (%)
ER and/or PR positive	254 (63)	230 (58)	266 (61)	251 (57)
Menopause Status				
No	204 (51)	200 (50)	217 (50)	222 (51)
Yes	198 (49)	198 (50)	220 (50)	216 (49)
Tumor Location				
Left/-	39 (10)	35 (9)	43 (10)	42 (10)
Left/Left	164 (41)	170 (43)	173 (40)	180 (41)
Right/-	42 (10)	43 (11)	47 (11)	45 (10)
Right/Left	0 (0)	0 (0)	1 (0)	0 (0)
Right/Right	157 (39)	150 (38)	173 (40)	171 (39)

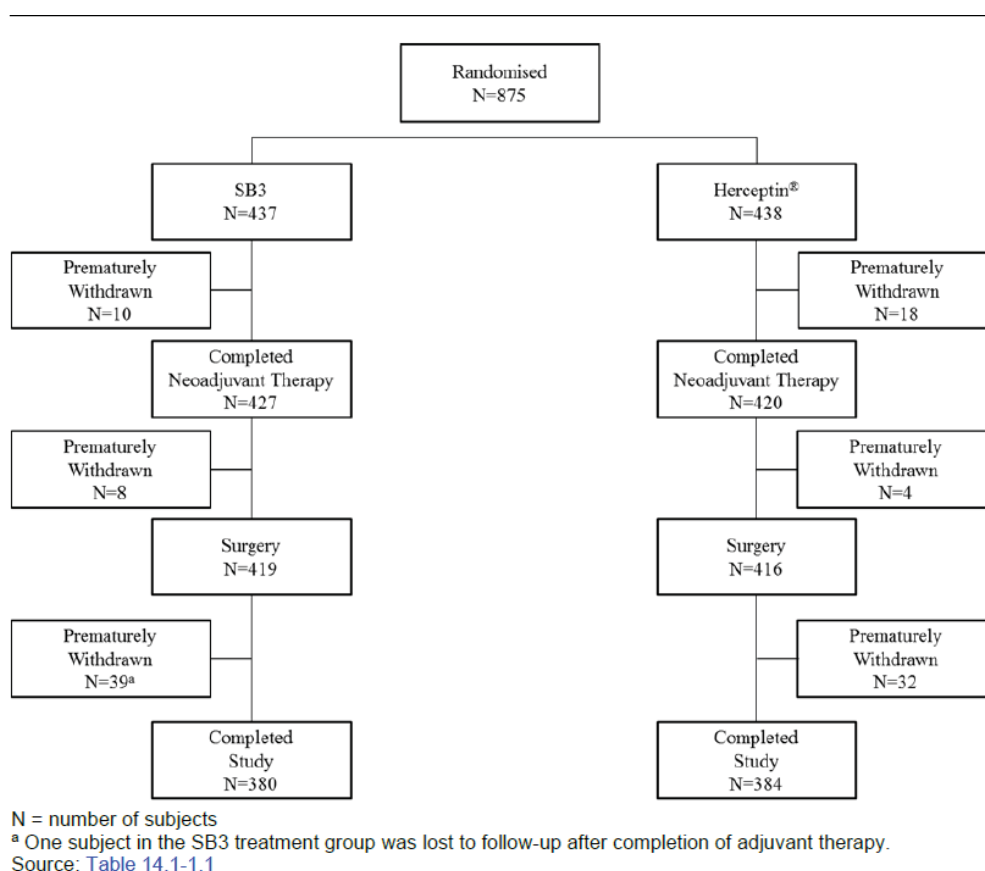
Source dataset: ADSL.xpt

Reviewer Comments: *Baseline patient demographics were well balanced between the two arms. All patients were female and a majority of patients were White (67%) and had stage IIB disease (35%) at baseline. Two-thirds of the patients had ER and/or PR positive hormone status. African American patients represent ~ 15% of the US population and are not represented in this study. This is unfortunate but does not alter our conclusion that the study supports a finding of no clinically meaningful differences between SB3 and US-Herceptin.*

6.4. Subject Disposition

A total of 875 patients were randomized, 437 to receive SB3 and 438 to receive EU-Herceptin. At the end of the study, 847 (96.8%) patients (427 [98%] in the SB3 and 420 [96%] in the EU-Herceptin treatment group) completed the 8 cycles of neoadjuvant therapy, and 835 (95.4%) patients (419 [96%] and 416 [95%], respectively) completed surgery. A total of 765 (87%) patients (381 [87%] and 384 [88%], respectively) completed the 10 cycles of adjuvant therapy, and 764 (87%) patients (380 [87%] and 384 [88%], respectively) completed the study. The overall patient disposition for the Study G31 is shown below in the applicant's figure, Figure 2.

Figure 2: Study G31 Overall Patient Disposition



Source: CSR Page 66, Figure 10-1

Reviewer Comment: The majority of patients completed the neoadjuvant and adjuvant periods of the trial.

Table 7 below lists the patient disposition for the PPS, which was the primary population set used for the primary endpoint of bpCR. Of note, patients with certain major protocol deviations were excluded from the PPS per the statistical analysis plan (SAP).

Table 7: All Enrolled Patient Disposition, Study G31

	SB3		Herceptin®		Total	
	n (%)		n (%)		n (%)	
Screened					1254	
Screening failures					379	
Reasons for screening failure						
Did not meet inclusion criteria					254	(67.0)
Met exclusion criteria					95	(25.1)
Subject lost to follow up					2	(0.5)
Withdrew consent					34	(9.0)
Other					6	(1.6)
Randomised	437		438		875	
Completed 8 cycles of neoadjuvant therapy	427	(97.7)	420	(95.9)	847	(96.8)
Completed surgery	419	(95.9)	416	(95.0)	835	(95.4)
Completed 8 cycles of neoadjuvant therapy and surgery	419	(95.9)	416	(95.0)	835	(95.4)
Did not complete 8 cycles of neoadjuvant therapy but completed surgery	0	(0.0)	0	(0.0)	0	(0.0)
Withdrew before surgery	18	(4.1)	22	(5.0)	40	(4.6)
Completed 10 cycles of adjuvant therapy	381	(87.2)	384	(87.7)	765	(87.4)
Withdrew during adjuvant therapy	38	(8.7)	32	(7.3)	70	(8.0)
Completed study	380	(87.0)	384	(87.7)	764	(87.3)

n = number of subjects

Percentages for screening failure reasons were based on the number of screening failures. Multiple screening failure reasons were possible.

Otherwise percentages were based on the number of subjects in the Randomised Set.

One subject in the SB3 treatment group was lost to follow-up after completion of adjuvant therapy.

Source: Table 14.1-1.1

Source: CSR page 67, Table 10-1.

Reviewer Comments: The PPS was the population used for efficacy analysis for the primary endpoint. All patients completed the neoadjuvant period. The majority of patients initiated and completed the adjuvant period. The patients that discontinued prior to end of the adjuvant period are few and unlikely to impact the overall efficacy conclusions.

Table 8 below lists the number of patients for each of the different analysis populations in the study.

Table 8: Analysis Populations, Study G31

	SB3 n (%)	EU-Herceptin n (%)
All randomized patients	437 (100)	438 (100)
FAS population	437 (100)	438(100)
PPS population	402 (92)	398 (90.9)
Safety population	437 (100)	438 (100)

Source: CSR Page 70, Table 11-1

Percentages are based on the number of randomized patients

FAS=Full Analysis Set; PPS=per protocol set

Reviewer Comments: The primary efficacy analysis was performed using the PPS population.

Protocol Violations/Deviations

The PPS consists of all patients who completed the 8 cycles of neoadjuvant therapy and surgery and excluded patients with certain major protocol violations and/or missing pathologic response assessment. Major protocol deviations that led to exclusion from this set were pre-specified prior to unblinding the treatment codes for analyses. A total of 37 (4.2%) patients were excluded from the PPS due to protocol violations, similar rates on both treatment arms; 17 (3.9%) on the SB3 arm and 20 (4.6%) on the Herceptin arm. The primary reasons for the protocol violations leading to exclusion were violation of the efficacy criteria, study procedure criteria and eligibility criteria. Major protocol deviations for the PPS set are listed below in Table 9.

Due to regional issues in the Eastern Ukraine, the applicant decided to exclude 11 randomized patients from two sites (SB31203 and SB31210) from the PPS since it was impossible to conduct any source data verification activities for these patients. This exclusion of the patients was done before the database lock.

A total of 443 (51%) patients had at least one major protocol deviation (including the 11 subjects from the aforementioned Eastern Ukraine sites); 224 (51%) patients from the SB3 arm and 219 (50%) patients from the EU-Herceptin arm. A total of 37 (4%) patients were excluded from the PPS due to specific major protocol deviations, 17 in the SB3 arm and 20 in the control arm. The most common major protocol deviations that led to exclusion from the PPS were associated with efficacy criteria (10 and 9 patients in the SB3 and EU-Herceptin arms, respectively) and study procedures criteria (6 and 5 patients in the SB3 and EU-Herceptin arms, respectively). The protocol violations do not impact the overall assessment of SB3 efficacy and safety.

Table 9: Major Protocol Deviations by Treatment Group, All Randomized Patients, Study G31

Table 10-3. Summary of Major Protocol Deviations by Treatment Group (Randomised Set)						
	SB3		Herceptin®		Total	
	N=437		N=438		N=875	
Subjects with protocol deviation	n (%)		n (%)		n (%)	
With at least one major protocol deviation	224	(51.3)	219	(50.0)	443	(50.6)
Subjects excluded from PPS as a result of major protocol deviation	17	(3.9)	20	(4.6)	37	(4.2)
Efficacy criteria	10	(2.3)	9	(2.1)	19	(2.2)
Study procedures criteria	6	(1.4)	5	(1.1)	11	(1.3)
Eligibility and entry criteria	1	(0.2)	4	(0.9)	5	(0.6)
IP and non-IP compliance	1	(0.2)	3	(0.7)	4	(0.5)
Withdrawal criteria	0	(0.0)	1	(0.2)	1	(0.1)
Subjects with other major protocol deviations	219	(50.1)	213	(48.6)	432	(49.4)
Study procedures criteria	154	(35.2)	143	(32.6)	297	(33.9)
Randomisation criteria	36	(8.2)	37	(8.4)	73	(8.3)
IP and non-IP compliance	31	(7.1)	36	(8.2)	67	(7.7)
Non-IP compliance	25	(5.7)	37	(8.4)	62	(7.1)
IP compliance	23	(5.3)	17	(3.9)	40	(4.6)
Eligibility and entry criteria	15	(3.4)	26	(5.9)	41	(4.7)
Withdrawal criteria	1	(0.2)	0	(0.0)	1	(0.1)

IP = investigational product; N = number of subjects in the Randomised Set; n = number of subjects with protocol deviations; PPS = Per-protocol Set.

Percentages were based on the number of subjects in the Randomised Set.

Source: Table 14.1-1.4

Source: Study 3.2 Adjuvant Period CSR Page 126

Reviewer Comments:

In response to an information request dated 8/2/2018, the applicant clarified the reasons for high protocol deviations (PDs) and the impact on the efficacy analysis. Among all major PDs that were reported during the study period, most of the patients were classified as 'other major protocol deviations', which means that these patients, although flagged as having major PDs, were not excluded from the PPS. Relatively few patients (3.9% in the SB3 and 4.6% in the control arm, respectively) were excluded from the PPS as a result of the major PDs.

Additional details of the protocol deviations leading to exclusion from the PPS set are provided in Table 10 below. Most of the patients (n=18) had a deviation in the schedule for the efficacy measurements. Only patients with a PD considered to impact assessment of efficacy of the study drug were excluded from the PPS in the SAP, and these patients were excluded prior to database lock. Other PDs

that were not considered to have an impact on the efficacy of the study drug were classified as ‘other major protocol deviations,’ and included in the PPS for primary efficacy analysis. The number of patients with ‘major PDs leading to exclusion from PPS’ was small and comparable between the SB3 and EU-Herceptin arms, thus the impact of excluding these patients from the PPS was considered negligible for the purposes of assessing the efficacy of SB3.

Table 10: Major Protocol Deviations Leading to Exclusion of the Patients from the PPS

Table 3: Major Protocol Deviations Leading to Exclusion of the Patients from the Per-protocol Set in Study SB3-G31-BC

Category	Protocol Deviation (PD) Description	Number of Cases with the Pertinent PD (n)
Eligibility and Entry Criteria	(1) Tumour size < 2 cm without proper staging evidence, or (2) clinical stage at Screening is T1N0 or missing unless inflammatory breast cancer is confirmed.	2
	Histologically not confirmed primary invasive carcinoma of the breast at Screening	2
	No positive (IHC3+ or FISH+) HER2 result confirmed by a central lab/accredited local lab during study period	0
	Hormone receptor status (either ER or PR, or both) is missing.	0
	Missing informed consent	1
	Metastatic (stage IV) or bilateral breast cancer or clinically detectable two separate breast cancer masses by physical examination (palpation) at Screening	2
	Any prior invasive breast carcinoma, except for subjects with a past history of DCIS and/or LCIS treated with surgery only at Screening	0
	History of malignant neoplasms within 5 years prior to Randomisation, except for curatively treated carcinoma in situ of uterine cervix, basal cell carcinoma of the skin or squamous cell carcinoma of the skin at Screening	0
Withdrawal Criteria	Subject still receive IPs and non-IPs during the neoadjuvant period despite treatment delay of > 3 weeks (6 weeks from the previous IP)	1
Efficacy Criteria	No surgery after completion of Cycle 8	0
	Window deviation from Day 1 of Cycle 8 to Surgery (> 6 weeks)	18
	pCR assessment was not evaluable for patients completed the surgery.	1
Study Procedures Criteria	Unable to ensure data integrity (Ukraine)	11
IP Compliance	IP infusion was missing during the neoadjuvant period.	0
IP and non-IP compliance	(1) Overall relative dose intensity (RDI) of IP < 85%, or (2) overall RDI of docetaxel and FEC < 80% during neoadjuvant period	4

n = number of patients with the pertinent PD; IP = investigational product; Non-IP = non-investigational product;
pCR = pathologic complete response; IHC+3 = immunohistochemical score 3+; FISH = fluorescence in situ hybridization;
HER2 = human epidermal growth factor receptor 2; ER = estrogen-receptor; PR = progesterone receptor;
DCIS = ductal carcinoma in situ; LCIS = lobular carcinoma in situ; FEC = fluorouracil, epirubicin, cyclophosphamide.
Source: Section 5.3.5.1 SB3-G31-BC CSR, Listing 16.2.2-1.1

Source: Information request response dated 8/2/2018

Reviewer Comments: *In response to an information request dated 8/2/2018, the applicant clarified the reasons for high protocol violations and the impact on the efficacy analysis. Since the number of patients excluded from the PPS set is small and similar on both the arms, it is unlikely to have a significant effect on the primary efficacy analysis.*

6.5. Analysis of Primary Endpoint

Breast pathological complete response (bpCR), assessed locally, was the primary analysis endpoint for this trial. The bpCR rate was 51.7% and 42% on the SB3 and EU-Herceptin arms, respectively. The results of the primary analysis are summarized in Table 11. The results demonstrate that the 90% confidence interval for the pCR response rate ratio fell entirely inside the pre-defined equivalence margin (0.785, 1.546), thus the study met its primary endpoint.

The results of the primary endpoint in the PPS population are shown in Table 11. The risk ratio confidence interval (both the 90% and 95%) fell within the predefined equivalence margins.

Reviewer Comment: *The trial met its primary objective of demonstrating equivalence of the bpCR rates. Additional sensitivity analyses further support the equivalence of the bpCR rates.*

Table 11: Breast Pathological Complete Response (bpCR) in Per Protocol Population, Study G31

	SB3 N=402	EU-Herceptin N=398
Responders	208	167
Response rate	51.7%	42.0%
95% CI	(46.7, 56.7)	(37.1, 47.0)
Response rate difference (SB3 – EU-Herceptin)	10.70%	
95% CI	(4.13%, 17.26%)	
Response rate ratio (SB3/EU-Herceptin)	1.259	
90% CI*	(1.112, 1.428)	
95% CI	(1.086, 1.463)	

**The 90% CI for the response rate ratio served as the primary analysis strategy for the FDA review. The pre-defined equivalence margin specified that the 90% CI would be entirely contained within (0.785, 1.546). The other results are presented to support the primary analysis strategy.*

Source dataset: ADEF.xpt

Table 12: Total Pathological Complete Response (tpCR) in PPS Population, Study G31

	SB3 N=382	EU-Herceptin N=380
Responders	175	136
Response rate	45.8%	35.8%
95% CI	(40.7, 51.0)	(31.0, 40.8)
Response rate difference (SB3 – EU-Herceptin)	11.05%	
95% CI	(4.44% - 17.66%)	
Response rate ratio (SB3/EU-Herceptin)	1.315	
90% CI	(1.137, 1.523)	
95% CI	(1.107, 1.567)	

Source dataset: ADEF.xpt

Reviewer Comment: *In response to an information request dated 7/9/2018 the applicant clarified that there are fewer patients in the tpCR evaluation compared to the bpCR evaluation because patients with a pathological N category of pNx were excluded from the tpCR assessment. A total of 38 patients, 20/402 (5%) and 18/398 (5%) on the SB3 and EU-Herceptin arms, respectively, were excluded. This exclusion is consistent with the pre-specified statistical analysis plan.*

Secondary Endpoints

Key secondary endpoints include overall response rate, event-free survival (EFS), and overall survival (OS).

The ORR is based on the number of patients with best overall response during neoadjuvant therapy period and without inflammatory breast carcinoma. Overall response rate data is presented in Table 13. The results demonstrate that the two arms have very similar response rates, i.e. within 1-2% of each other. EFS and OS data are presented in Table 14. Since this is a non-metastatic setting, progression and death events are very limited. Since this is a non-metastatic setting with a median duration of follow-up of only 1.2 years as of data cut-off for the Clinical Study Report, the number of recurrences and deaths is limited. Nevertheless, the data do not show a difference in either EFS or OS.

Table 13: ORR in PPS Population, Study G31

	SB3 N=383	EU-Herceptin N=374
Responders	369	341
Response rate	96.3%	91.2%
95% CI	(93.9,98.0)	(87.8, 93.9)
Response rate difference (SB3 – Herceptin)	5.03%	
95% CI	(1.74% - 8.31%)	
Response rate ratio (SB3/Herceptin)	1.055	
90% CI	(1.023, 1.091)	
95% CI	(1.017, 1.099)	

Source dataset: ADEF.xpt

Reviewer Comment: In response to an information request dated 7/9/2018 the Applicant clarified that there are lower number of patients in the ORR evaluation as compared to the bpCR evaluation in the PPS population because a total of 43 patients, 19/402 (5%) and 24/398 (6%) on the SB3 and EU-Herceptin arms respectively were excluded. The reasons for exclusion are as follows:

- Patients with inflammatory breast cancer (15 in the SB3 vs. 15 in the EU-Herceptin treatment group) were excluded because the measurement of breast tumor size was not available.
- By the definition of best overall response, patients who have no overall response among CR, PR, SD, and PD (3 in the SB3 vs. 9 in the EU-Herceptin treatment group) were excluded from the analysis.
- Patients with inconsistent methods of clinical tumor assessments throughout the study or using different methods other than caliper or ultrasound (1 in the SB3 vs. 0 in the EU-Herceptin treatment group) were also excluded.

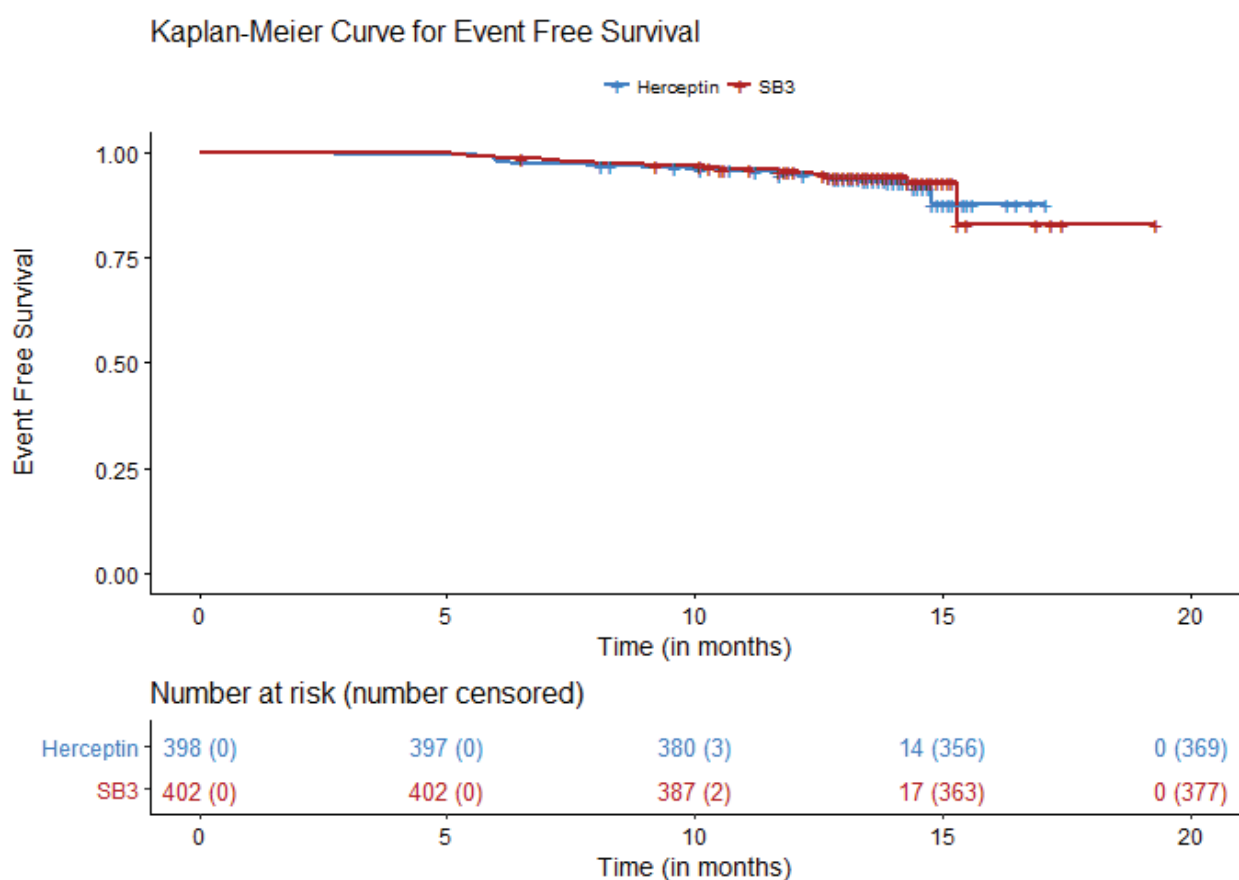
All exclusions were based on medical monitor's decision prior to database lock.

Table 14: Event Free and Overall Survival in Per-Protocol Population, Study G31

	SB3 N=402	EU-Herceptin N=398
EFS Events	25 (6.2%)	29 (7.3%)
Median (95% CI)	NR	NR
Stratified HR (95% CI)	0.92 (0.53, 1.60)	
OS Events	0	2 (0.5%)
Median (95% CI)	NR	NR
Stratified HR (95% CI)	0	

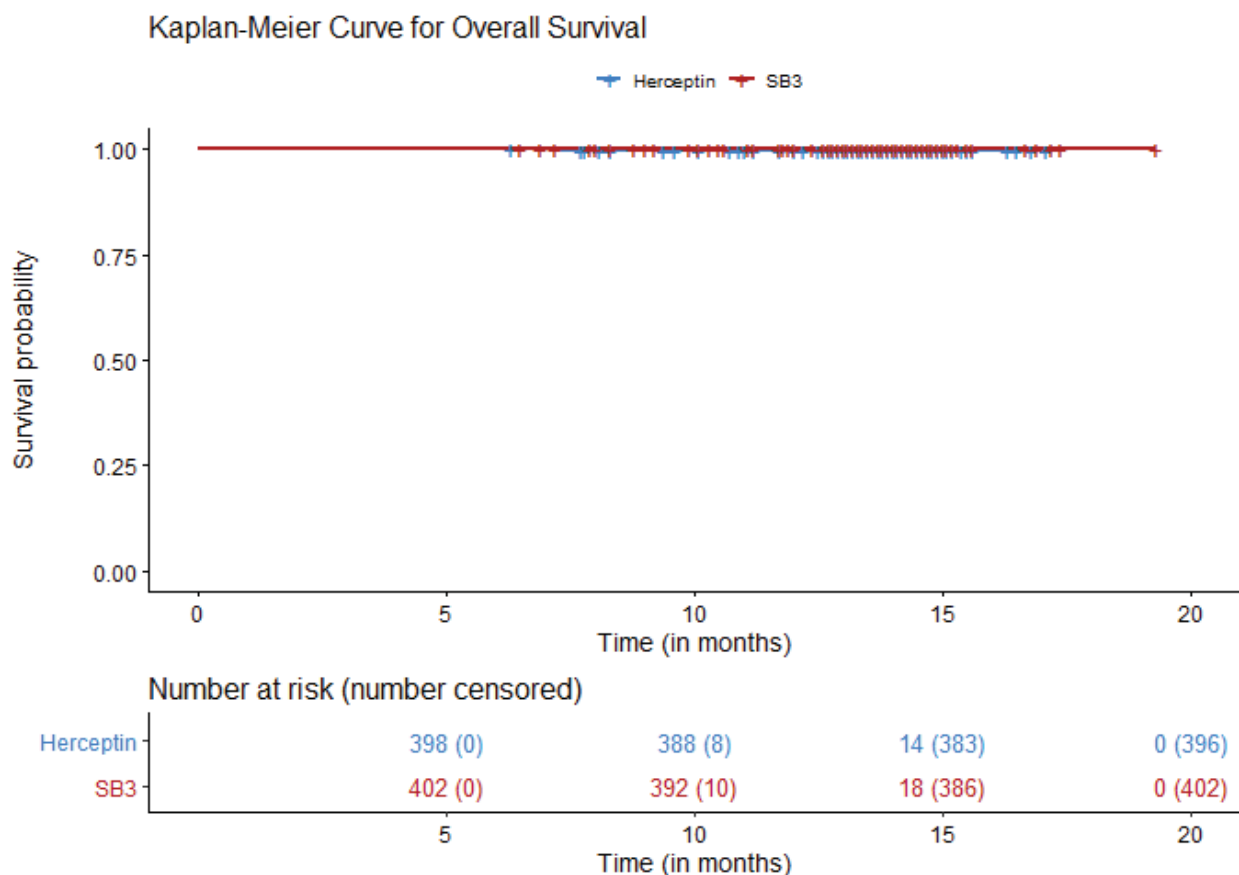
Source dataset: ADEF.xpt

Figure 3 Event Free Survival KM Curve in the PPS Population, Study G31



Source dataset: ADEF.xpt

Figure 4 Overall Survival KM Curve in the PPS Population, Study G31



Source dataset: ADEF.xpt

Reviewer Comment: The median follow-up duration was relatively brief (437 days in the SB3 arm and 438 days in the EU-Herceptin arm) at the clinical cut-off date for the initial Clinical Study Report. Accordingly, the number of recurrences and deaths observed is limited as would be expected in a neoadjuvant/adjuvant setting. The rates of EFS events are similar in both the arms, and the medians have not yet been reached. The results further support the equivalence of SB3 to US-Herceptin. There had been only two deaths reported in follow-up, both in the control arm, at the time of the Clinical Study Report, which precludes any meaningful analysis of OS. Long-term outcomes, including OS, should continue to be followed in the post marketing setting.

6.6. Subpopulations

Subgroup analyses of bpCR

Subgroup analyses of bpCR were done in demographic subgroups and important clinical subgroups. As shown in Table 15, the 90% CIs of the bpCR ratio are contained within the biosimilarity confidence interval of (0.785, 1.546) used for the primary

endpoint.

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Table 15: FDA Subgroup Analyses of bpCR in the Per-Protocol Population, Study G31

	SB3 N=402 n/N % (95%CI)	EU-Herceptin N=398 n/N % (95%CI)	pCR Ratio (90% CI)
Age			
<50 (N=379)	89/187 47.6 (40.3,55)	71/192 37 (30.1,44.2)	1.287 (1.055,1.576)
≥50 (N=421)	119/215 55.3 (48.4,62.1)	96/206 46.6 (39.6,53.7)	1.188 (1.014,1.395)
Region			
EU (N=206)	53/108 49.1 (39.3,58.9)	44/98 44.9 (34.8,55.3)	1.093 (0.856,1.403)
Non-EU (N=594)	155/294 52.7 (46.8,58.5)	123/300 41 (35.4,46.8)	1.286 (1.112,1.49)
Race			
White (N=533)	135/269 50.2 (44.1,56.3)	112/264 42.4 (36.4,48.6)	1.183 (1.014,1.383)
Asian (N=248)	68/124 54.8 (45.7,63.8)	51/124 41.1 (32.4,50.3)	1.333 (1.07,1.673)
Other (N=19)	5/9 55.6 (21.2,86.3)	4/10 40 (12.2,73.8)	1.38 (0.599,3.444)
Disease Stage			
Operable (N=479)	120/241 49.8 (43.3, 56.3)	97/238 40.8 (34.5, 47.3)	1.221 (1.035,1.446)
Inoperable (N=321)	88/161 54.7 (46.6, 62.5)	70/160 43.8 (35.9, 51.8)	1.249 (1.036,1.514)
Menopausal Status			
Yes (N=396)	105/198 53 (45.8, 60.1)	92/198 46.5 (39.4, 53.7)	1.141 (0.966,1.351)
No (N=404)	103/204 50.5 (43.4, 57.5)	75/200 37.5 (30.8, 44.6)	1.346 (1.117,1.631)
Progesterone/Estrogen Receptor Status			
Positive (N=484)	119/254 46.9 (40.6, 53.2)	78/230 33.9 (27.8, 40.4)	1.381 (1.148,1.671)
Negative (N=316)	89/148 60.1 (51.8, 68.1)	89/168 53 (45.1, 60.7)	1.135 (0.964,1.337)

Source dataset: ADEF.xpt

Reviewer Comment: In the exploratory subgroup analyses, there is no compelling evidence that the results for any subgroup differ meaningfully from those of the

overall study population.

Sensitivity Analyses

The primary endpoints were analyzed in the full analysis population are summarized in the table below. They are found to be similar to the results presented in the PPS population.

Table 16: Analyses of bpCR in the Full Analysis Population, Study G31

	SB3 n/N % (95% CI)	EU-Herceptin n/N % (95% CI)	pCR Ratio (90% CI)
bpCR (N=834)	214/419 51.1 (46.9,55.2)	174/415 41.9 (37.9,46.1)	1.238 (1.096,1.402)
tpCR (N=795)	180/398 45.2 (41,49.5)	142/397 35.8 (31.8,39.9)	1.29 (1.119,1.491)
ORR (N=819)	394/415 94.9 (92.8,96.6)	368/404 91.1 (88.4,93.3)	1.04 (1.008,1.075)

Source dataset: ADEF.xpt

ORR is based on patients with best overall response during neoadjuvant therapy period in patients without inflammatory breast carcinoma at baseline.

6.7. Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable to this application.

6.8. Discussion of Persistence of Efficacy and/or Tolerance Effects

With the limited number of EFS and OS events observed thus far, there does not appear to be any meaningful difference in conventional early breast cancer time-to-event endpoints between SB3 and EU-Herceptin.

6.9. Additional Efficacy Issues/Analyses

No additional issues.

7. Review of Safety

Safety Summary

Study G31, along with other information in the application, support a determination of no clinically meaningful differences between SB3 and US-Herceptin. The safety analyses in Study G31, which compared SB3 and EU-Herceptin in HER2 positive breast cancer

patients treated in the neoadjuvant and adjuvant settings, did not show any meaningful differences in safety between arms.

7.1. Methods

7.1.1. Studies/Clinical Trials Used to Evaluate Safety

The safety evaluation for this application is based on the neoadjuvant and adjuvant study periods of Study G31. Details of the design for Study G31 are presented in Section 5. Efficacy results for Study G31 are presented in Section 6.

The applicant is seeking approval of SB3 for the same indications as US-Herceptin: 1) adjuvant and metastatic treatment of patients with HER2 positive breast cancer and 2) HER2 positive metastatic gastric adenocarcinoma.

Study G31 is the primary study used for the overall safety assessment of SB3. There is no pooling of safety data.

The clinical and laboratory assessments performed in Study G31 are adequate to evaluate the safety of SB3. There was particular attention to assessment of cardiac adverse events (AEs) due to the known potential for cardiac dysfunction with trastuzumab. Two-dimensional echocardiography or MUGA to assess left ventricular ejection fraction (LVEF) was performed at baseline. During the neoadjuvant period, LVEF assessment was done at baseline, after cycle 4, and at the conclusion of the neoadjuvant period. During the adjuvant period, LVEF was assessed at the end of cycle 6 (i.e., cycle 14 overall) and at the conclusion of adjuvant therapy. Patients also received LVEF assessments if they developed signs and/or symptoms of left ventricular dysfunction.

7.1.2. Categorization of Adverse Events

The applicant defined an adverse event as any untoward medical occurrence in a patient enrolled (i.e. when the ICF was signed) into study G31 regardless of its causal relationship to the study treatment. All reported terms for AEs were coded using the Medical Dictionary for Regulatory Activities, and the grade was reported using NCI-CTCAE v4.0, except CHF which was graded according to both NCI-CTCAE v4.0 and NYHA functional classification; left ventricular dysfunction which was graded according to NCI-CTCAE v3.0; and febrile neutropenia which was graded according to NCI-CTCAE v4.03.

A treatment-emergent AE (TEAE) was defined as any AE with an onset date on or after the date of first dose of study drug until the end of the study. AEs which were already present during the pre-treatment period but worsened in severity during the treatment period were also considered TEAEs.

A serious adverse event (SAE) was defined as any untoward medical occurrence that at any dose resulted in death, is life-threatening, resulted in persistent or significant disability/incapacity, is a congenital anomaly, is an important medical event, or requires inpatient hospitalization or prolongation of existing hospitalization. Progression of breast cancer was not to be reported as an SAE even if it met the seriousness criteria unless the outcome was fatal during the study or within the safety reporting period.

Adverse events were recorded from the time the informed consent form was signed until end of study. End of study was defined as 30 days after the last dose of SB3 or EU-Herceptin. Any SAEs that were considered to be related to study drug were to be collected regardless of planned clinical study length. Unresolved AEs during the study period were followed up until end of study and recorded in the eCRF. Investigators were to monitor AEs and give the appropriate medical care to the subject until the AE had resolved or stabilized. If the subject had an ongoing SAE at the end of the study, the event was to be followed until event resolution or stabilization.

Adverse events of special interest included cardiac dysfunction, infusion reactions, and pregnancy.

7.1.3. Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

There was no pooling of safety data as there was only one comparative clinical study of SB3.

7.2. Adequacy of Safety Assessments

7.2.1. Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The safety population consisted of 875 patients, 437 in the SB3 arm and 438 in the EU-Herceptin arm, and is defined as all patients who received at least 1 dose of study drug in any amount.

Table 17 below lists the exposure to the study drug for the neoadjuvant and adjuvant periods of study G31. The trastuzumab product was given as an 8 mg/kg loading dose and then 6 mg/kg every 3 weeks.

Table 17: Safety Population Study Drug Exposure, Study G31

	EU-Herceptin N=438	SB3 N=437
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Neoadjuvant Period*		
Mean	3424	3424
SD	916	821
Median	3329	3318
Range	441-7518	483-6468
Adjuvant Period*		
Mean	4243	4143
SD	1111	1122
Median	4137	4116
Range	483-9324	525-8022

*All values shown in milligrams.

Source dataset: ADEX.xpt

Reviewer Comments: *The exposure was similar between the two arms in the neoadjuvant and adjuvant periods.*

The safety population consisted of all patients who received at least 1 dose of SB3 or EU-Herceptin in any amount. An overview of the demographics of this population is presented in Table 18 below.

Table 18: Safety Population Demographic Overview, Study G31

	EU-Herceptin N=438		SB3 N=437	
Age (years)				
Mean	49.6		49.5	
SD	9.4		9.5	
Range	22-65		24-65	
<50 yrs	209	48	201	46
≥50 yrs	228	52	236	54
ECOG PS				
0	365	83	366	84
1	73	17	71	17
Race				
Asian	138	31	134	30
White	289	66	294	68
Other	11	3	9	2
ER Status				
ER+	243	55	257	59
ER-	195	46	180	41
PR Status				
PR+	178	41	188	43

	EU-Herceptin N=438		SB3 N=437	
PR-	260	59	249	57
HER2 Status				
HER2+	438	100	437	100
Stage				
IIA	62	14	65	15
IIB	146	33	150	34
IIIA	99	23	85	19
IIIB	86	20	103	24
IIIC	45	10	33	8
IV	0	0	1	<1
Region*				
1	37	8	37	8
2	48	11	42	10
3	86	20	87	20
4	39	9	41	9
5	71	16	72	16
6	52	12	52	12
7	105	24	106	25
EU	110	25	113	26
Non-EU	328	75	324	74

*Geographic regions were defined as follows: Region 1 (Korea), Region 2 (Malaysia, Mexico, Philippines, Vietnam), Region 3 (Bosnia and Herzegovina, Ukraine), Region 4 (Bulgaria, Czech Republic, France, Romania), Region 5 (Poland), Region 6 (India), and Region 7 (Russian Federation)

Source dataset: ADSL.xpt

Reviewer Comments: *The demographics for the safety population are well - balanced. Although no patients from the United States were enrolled in Study G31, the demographic features of the participants are generally consistent with those of US breast cancer clinical trials. African-American patients are not adequately represented, a problem that is unfortunately also common in clinical trials conducted in the US.*

7.2.2. Explorations for Dose Response

Not applicable.

7.2.3. Special Animal and/or In Vitro Testing

Not applicable.

7.2.4. Routine Clinical Testing

The schedule of safety evaluations is shown in Section 5.3.1 of this review. The frequency of monitoring was considered adequate within the context of the study. Cardiac assessments were adequate

7.2.5. Metabolic, Clearance, and Interaction Workup

Not applicable.

7.2.6. Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Not applicable.

7.3. Major Safety Results

Table 19 below is a summary of the treatment-emergent adverse events (TEAEs). TEAEs occurred in both arms and in both the neoadjuvant and adjuvant periods of the trial. More TEAEs occurred during the neoadjuvant period when trastuzumab was administered with concomitant chemotherapy than during the trastuzumab monotherapy adjuvant period.

Table 19: Summary of TEAEs, Study G31

	Overall		Neoadjuvant		Adjuvant	
	EU-Herceptin N=438 %	SB3 N=437 %	EU-Herceptin N=438 %	SB3 N=437 %	EU-Herceptin N=438 %	SB3 N=437 %
All grade TEAEs	421 (96.1)	426 (97.5)	417 (95.2)	422 (96.6)	241 (55)	246 (56.3)
All TEAEs related to study drug	145 (33.1)	146 (33.4)	117 (26.7)	118 (27)	67 (15.3)	58 (13.3)
Grade 3-5 TEAEs	315 (71.9)	325 (74.4)	307 (70.1)	316 (72.3)	36 (8.2)	27 (6.2)
Study drug discontinuation	14 (3.2)	15 (3.4)	7 (1.6)	4 (0.9)	7 (1.6)	11 (2.5)
Stopped	12 (2.8)	9 (2.1)	12 (2.7)	8 (1.8)	0 (0)	1 (0.2)
Serious TEAEs	58 (13.2)	56 (12.8)	47 (10.7)	46 (10.5)	14 (3.2)	15 (3.4)
Deaths	5 (1.1)	1 (0.2)	3 (0.7)	1 (0.2)	2 (0.5)	0 (0)

Source dataset: ADAE.xpt

Reviewer Comments: More TEAEs were reported during the neoadjuvant period compared to the adjuvant period, presumably due to administration of concomitant chemotherapy. The TEAEs were well-balanced overall between the two arms in each period of the study and throughout the study as a whole, with no meaningful differences between the study groups.

7.3.1. Deaths

There were six on-treatment deaths reported during the study, none of which were attributed by the applicant to the investigational product. Five were in the control arm, and one was in the SB3 arm. Four of the deaths occurred during the neoadjuvant period of the trial, and two during the adjuvant period of the trial. These data are shown in Table 20 below. Deaths that occurred during the post-treatment period are discussed in Section 7.7.

Table 20: On-Treatment Deaths on Study G31

Patient ID	Age	Treatment Arm	Study Period	Cause of Death
(b) (6)	57	SB3	Neoadjuvant	Completed suicide
	49	EU-Herceptin	Neoadjuvant	Pulmonary embolism
	55	EU-Herceptin	Neoadjuvant	Myocardial infarction
	46	EU-Herceptin	Neoadjuvant	Sudden death
	64	EU-Herceptin	Adjuvant	Hemorrhagic stroke
	60	EU-Herceptin	Adjuvant	Pneumonitis

Source datasets: ADAE.xpt, ADSL.xpt

The narratives for these six patients are summarized below:

- (b) (6): 57-year-old Asian female assigned to SB3. She was noted to have a history of insomnia and unspecified psychological disease dating to 2014 and had previously been prescribed alprazolam, zolpidem, quetiapine, and escitalopram. She received her first dose of study drug on January 8, 2015 and received a total of 5 cycles. She did not report to the study site as expected on April 14, 2015 for a complete blood count. Upon contacting the patient's daughter, the applicant learned that the patient (b) (6) and could not be resuscitated. No autopsy was

performed. The cause of death was reported as suicide. The death was reported as unrelated to study drug.

- (b) (6): 49-year-old Asian female assigned to EU-Herceptin. She was noted to have a past medical history of hypertension. She had no past history of thromboembolic events or risk factors for them apart from a cancer diagnosis. She received the first dose of study drug on (b) (6) and received a total of 6 cycles. On cycle 6 day 14, she presented with generalized weakness and dyspnea and suffered two in-hospital cardiopulmonary arrests over the next 24 hours, the second without successful resuscitation. There was no clinical or radiologic evidence of deep venous thrombosis and no evaluation for pulmonary embolism was performed. No autopsy was performed. The cause of death was reported as pulmonary embolism. The death was reported as unrelated to study drug.
- (b) (6): 46-year-old female assigned to EU-Herceptin. She had no past medical history reported. She received the first dose of study drug on (b) (6) and received a total of 6 cycles. Her treatment course was complicated by grade 3 neutropenia for which she was hospitalized without sequelae on cycle 1 day 6. She was seen in the emergency department with complaints of lethargy and vomiting on cycle 6 days 7 and 8. Physical examination was normal, as were laboratories other than a magnesium just below the lower limit of normal at 0.7 mmol/L. The patient was rehydrated and given anti-emetics and sent home. She experienced sudden onset shortness of breath on cycle 6 day 10 and died at home. No autopsy was performed. The cause of death was reported as sudden death not otherwise specified. The death was reported as unrelated to study drug.
- (b) (6): 55-year-old white female assigned to EU-Herceptin. She had a past medical history of hypertension and diabetes. She received her first dose of study drug on (b) (6) and received a total of 1 cycle. She presented with angina on cycle 1 day 4 and was found to have ST elevation and T-wave inversion in leads V1 to V4 consistent with acute ST elevation myocardial infarction. She developed rapid onset of cardiogenic shock unresponsive to inotropes. Autopsy was performed and revealed bilateral acute pulmonary edema and myocardial sclerosis of the posterior left ventricle with coronary soft plaque and aortic atherosclerosis. The cause of death was reported as acute myocardial infarction. The death was reported as unrelated to study drug.
- (b) (6): 64-year-old white female assigned to EU-Herceptin. She had a past medical history of left ventricular hypertrophy, cardiomegaly, left ventricular dysfunction and adhesive pericarditis dating to two days prior to the first dose of study drug. She received her first dose of study drug on (b) (6) and received a total of 13 cycles. She presented with acute onset of abnormal speech, right hemiparesis, and loss of consciousness on cycle 13, day 19 at home per her sister. An ambulance was called, however she stopped breathing and was pronounced dead at home. No autopsy was performed. The cause of death was reported as hemorrhagic stroke without brain imaging performed. The death was reported as unrelated to study drug.

- (b) (6): 60-year-old Asian female assigned to EU-Herceptin. She had no past medical history reported. She received her first dose of study drug on (b) (6) and received a total of 8 cycles. Her treatment course was complicated by unexplained fever resulting in hospitalization with negative cultures during cycle 2; febrile neutropenia and hemolytic anemia during cycle 5, all of which resolved and study drug was continued. She was hospitalized on study day 216 (postoperative day 18) with a one day history of cough and dyspnea and treated with broad-spectrum antimicrobials. She required intensive care unit admission with mechanical ventilator support 3 days later and experienced a bradycardic arrest the following day. The cause of death was reported as septic shock due to bilateral pneumonitis. The case was queried to confirm whether the event was pneumonia or pneumonitis, and the diagnosis was reconfirmed as pneumonitis. No autopsy was performed. The death was reported as unrelated to study drug.

Reviewer Comments:

The majority of on-treatment deaths (5 out of 6) occurred in patients on the EU-Herceptin arm. The applicant has classified all six on-study deaths as unrelated to study drug. No new safety signals were identified. For patient (b) (6), pneumonitis is a known adverse event associated with trastuzumab, although it is unclear from the clinical history whether the patient who is reported to have had pneumonitis truly had pneumonia or pneumonitis. The records show that patient (b) (6) was given metoclopramide by the emergency department. Administration of metoclopramide in the setting of documented hypomagnesemia may have resulted in a subsequent fatal arrhythmia at home due to QT prolongation.

7.3.2. Serious Adverse Events

Serious TEAEs from Study G31 neoadjuvant and adjuvant periods and the overall study are listed in Table 21, Table 22, and Table 23 below.

Table 21: Serious TEAEs from Study G31 in the Neoadjuvant Period

Adverse Event	SB3 N=437	SB3 %	EU-Herceptin N=438	EU-Herceptin %
Any serious TEAE	46	10.5	47	10.7
Abdominal pain upper	1	0.2	0	0
Anemia	1	0.2	0	0
Anaphylactic reaction	0	0	1	0.2
Asthenia	1	0.2	0	0
Bronchopneumonia	0	0	1	0.2
Cardiac failure congestive	2	0.5	0	0
Carpal tunnel syndrome	0	0	1	0.2

Adverse Event	SB3 N=437	SB3 %	EU-Herceptin N=438	EU-Herceptin %
Cellulitis	1	0.2	0	0
Completed suicide	1	0.2	0	0
Convulsion	0	0	2	0.5
Dengue fever	0	0	1	0.2
Diabetes mellitus	1	0.2	1	0.2
Diarrhea	3	0.7	3	0.7
Erysipelas	0	0	1	0.2
Extravasation	1	0.2	0	0
Fatigue	0	0	1	0.2
Febrile neutropenia	10	2.3	13	3
Furuncle	1	0.2	0	0
Gastritis	0	0	1	0.2
Gastroenteritis	0	0	1	0.2
Gastroesophageal reflux disease	2	0.5	0	0
Hemolytic anemia	0	0	1	0.2
Hemorrhoids	0	0	1	0.2
Hand fracture	0	0	1	0.2
Hepatic function abnormal	1	0.2	0	0
Hypertension	1	0.2	0	0
Hypokalemia	1	0.2	1	0.2
Hyponatremia	1	0.2	1	0.2
Hypotension	0	0	1	0.2
Influenza	0	0	1	0.2
Infusion related reaction	0	0	2	0.5
Intraspinal abscess	0	0	1	0.2
Ischemic stroke	0	0	1	0.2
Leukopenia	0	0	1	0.2
Malnutrition	0	0	1	0.2
Menorrhagia	0	0	1	0.2
Metrorrhagia	1	0.2	0	0
Myalgia	2	0.5	0	0
Myocardial infarction	0	0	1	0.2
Nausea	1	0.2	0	0
Neutropenia	7	1.6	5	1.1
Neutropenic infection	0	0	1	0.2
Neutropenic sepsis	1	0.2	1	0.2
Neutrophil count decreased	8	1.8	4	0.9
Ovarian hyperstimulation syndrome	1	0.2	0	0
Periorbital edema	0	0	1	0.2
Pneumonia	2	0.5	0	0

Adverse Event	SB3 N=437	SB3 %	EU-Herceptin N=438	EU-Herceptin %
Pulmonary embolism	1	0.2	1	0.2
Pyrexia	1	0.2	2	0.5
Renal failure acute	1	0.2	0	0
Retinal hemorrhage	0	0	1	0.2
Soft tissue infection	1	0.2	0	0
Stomatitis	1	0.2	0	0
Sudden death	0	0	1	0.2
Supraventricular tachycardia	1	0.2	0	0
Thrombocytopenia	1	0.2	0	0
Transient ischemic attack	0	0	1	0.2
Upper respiratory tract infection	1	0.2	0	0
Urinary tract infection	1	0.2	0	0
Vomiting	1	0.2	2	0.5
Wheezing	0	0	1	0.2

Source dataset: ADAE.xpt

Table 22: Serious TEAEs in Study G31 in the Adjuvant Period

Adverse Event	SB3 N=437	SB3 %	EU-Herceptin N=438	EU-Herceptin %
Any adverse event	15	3.4	14	3.2
Anemia	1	0.2	0	0
Bronchitis	1	0.2	0	0
Cardiac failure congestive	1	0.2	0	0
Cellulitis	0	0	1	0.2
Chronic obstructive pulmonary disease	1	0.2	0	0
Dengue fever	0	0	1	0.2
Facial bones fracture	1	0.2	0	0
Gastroenteritis	1	0.2	0	0
Hemorrhagic stroke	0	0	1	0.2
Hallucination, auditory	1	0.2	0	0
Influenza	0	0	1	0.2
Lobar pneumonia	0	0	1	0.2
Medical device complication	1	0.2	0	0
Nasal polyps	1	0.2	0	0
Pathological fracture	0	0	1	0.2
Pneumonia	2	0.5	0	0
Pneumonitis	0	0	1	0.2
Polyneuropathy	1	0.2	0	0
Post procedural complication	0	0	1	0.2

Adverse Event	SB3 N=437	SB3 %	EU-Herceptin N=438	EU-Herceptin %
Post procedural hemorrhage	0	0	2	0.5
Postoperative wound infection	0	0	1	0.2
Pulmonary embolism	0	0	1	0.2
Radiation mucositis	0	0	1	0.2
Radiation necrosis	1	0.2	0	0
Radiation pneumonitis	1	0.2	0	0
Tuberculosis	1	0.2	0	0
Urinary tract infection	1	0.2	0	0
Vertigo	1	0.2	0	0
Wound infection	0	0	1	0.2

Source dataset: ADAE.xpt

Table 23: Total Serious TEAEs in Study G31 in the Neoadjuvant and Adjuvant Periods Combined

Adverse Event	SB3 N=437	SB3 %	EU-Herceptin N=438	EU-Herceptin %
Any adverse event	56	12.8	58	13.2
Anemia	2	0.5	0	0
Anaphylactic reaction	0	0	1	0.2
Asthenia	1	0.2	0	0
Bronchitis	1	0.2	0	0
Bronchopneumonia	0	0	1	0.2
Cardiac failure congestive	3	0.7	0	0
Carpal tunnel syndrome	0	0	1	0.2
Cellulitis	1	0.2	1	0.2
Chronic obstructive pulmonary disease	1	0.2	0	0
Completed suicide	1	0.2	0	0
Convulsion	0	0	2	0.5
Dengue fever	0	0	2	0.5
Diabetes mellitus	1	0.2	1	0.2
Diarrhea	3	0.7	3	0.7
Erysipelas	0	0	1	0.2
Extravasation	1	0.2	0	0
Facial bones fracture	1	0.2	0	0
Fatigue	0	0	1	0.2
Febrile neutropenia	10	2.3	13	3
Furuncle	1	0.2	0	0
Gastritis	0	0	1	0.2
Gastroenteritis	1	0.2	1	0.2

Adverse Event	SB3 N=437	SB3 %	EU-Herceptin N=438	EU-Herceptin %
Gastroesophageal reflux disease	2	0.5	0	0
Hemolytic anaemia	0	0	1	0.2
Hemorrhagic stroke	0	0	1	0.2
Hemorrhoids	0	0	1	0.2
Hallucination, auditory	1	0.2	0	0
Hand fracture	0	0	1	0.2
Hepatic function abnormal	1	0.2	0	0
Hypertension	1	0.2	0	0
Hypokalemia	1	0.2	1	0.2
Hyponatremia	1	0.2	1	0.2
Hypotension	0	0	1	0.2
Influenza	0	0	2	0.5
Infusion related reaction	0	0	2	0.5
Intraspinal abscess	0	0	1	0.2
Ischemic stroke	0	0	1	0.2
Leukopenia	0	0	1	0.2
Lobar pneumonia	0	0	1	0.2
Malnutrition	0	0	1	0.2
Medical device complication	1	0.2	0	0
Menorrhagia	0	0	1	0.2
Metrorrhagia	1	0.2	0	0
Myalgia	2	0.5	0	0
Myocardial infarction	0	0	1	0.2
Nasal polyps	1	0.2	0	0
Nausea	1	0.2	0	0
Neutropenia	7	1.6	5	1.1
Neutropenic infection	0	0	1	0.2
Neutropenic sepsis	1	0.2	1	0.2
Neutrophil count decreased	8	1.8	4	0.9
Ovarian hyperstimulation syndrome	1	0.2	0	0
Pathological fracture	0	0	1	0.2
Periorbital edema	0	0	1	0.2
Pneumonia	4	0.9	0	0
Pneumonitis	0	0	1	0.2
Polyneuropathy	1	0.2	0	0
Post procedural complication	0	0	1	0.2
Post procedural hemorrhage	0	0	2	0.5
Postoperative wound infection	0	0	1	0.2
Pulmonary embolism	1	0.2	2	0.5
Pyrexia	1	0.2	2	0.5

Adverse Event	SB3 N=437	SB3 %	EU-Herceptin N=438	EU-Herceptin %
Radiation mucositis	0	0	1	0.2
Radiation necrosis	1	0.2	0	0
Radiation pneumonitis	1	0.2	0	0
Renal failure acute	1	0.2	0	0
Retinal hemorrhage	0	0	1	0.2
Soft tissue infection	1	0.2	0	0
Stomatitis	1	0.2	0	0
Sudden death	0	0	1	0.2
Supraventricular tachycardia	1	0.2	0	0
Thrombocytopenia	1	0.2	0	0
Transient ischemic attack	0	0	1	0.2
Tuberculosis	1	0.2	0	0
Upper respiratory tract infection	1	0.2	0	0
Urinary tract infection	2	0.5	0	0
Vertigo	1	0.2	0	0
Vomiting	1	0.2	2	0.5
Wheezing	0	0	1	0.2
Wound infection	0	0	1	0.2

Source dataset: ADAE.xpt

Reviewer Comments: *Serious TEAEs were relatively infrequent in Study G31, approximately 13% in each arm, and primarily occurred during the neoadjuvant period when chemotherapy was administered concomitantly with HER2-directed therapy. Approximately 3% of patients in each arm experienced a serious TEAE during the adjuvant period of the study when trastuzumab product alone was being administered. These results were similar between arms and consistent with the safety profile of US-Herceptin.*

7.3.3. Dropouts and/or Discontinuations

The investigator could discontinue study treatment or study participation for any participant in the event of progressive disease, unacceptable toxicity, withdrawal of consent, protocol violation that could affect patient safety, pregnancy, study treatment delays or greater than 6 weeks from last study drug administration during the neoadjuvant period or 5 weeks from last administration during the adjuvant period. Patients with symptomatic CHF also permanently discontinued trastuzumab.

Table 24 below lists patients on each treatment arm and during the neoadjuvant and adjuvant study periods who had TEAEs leading to permanent discontinuation from the study and the associated MedDRA term and grade.

Table 24: TEAEs Leading to Permanent Discontinuation From Study G31

Patient ID	Study Period	Treatment Arm	Adverse Event	Grade
(b) (6)	Neoadjuvant	EU-Herceptin	Hypotension	3
	Neoadjuvant	EU-Herceptin	Alanine aminotransferase increased	2
	Neoadjuvant	EU-Herceptin	Left ventricular dysfunction	2
	Neoadjuvant	SB3	Diarrhea	3
	Neoadjuvant	SB3	Renal failure acute	3
	Neoadjuvant	SB3	Cardiac failure congestive	3
	Neoadjuvant	SB3	Left ventricular dysfunction	1
	Neoadjuvant	SB3	Left ventricular dysfunction	2
	Neoadjuvant	EU-Herceptin	Neutropenia	1
	Neoadjuvant	SB3	Supraventricular tachycardia	3
	Neoadjuvant	EU-Herceptin	Fatigue	2
	Neoadjuvant	EU-Herceptin	Left ventricular dysfunction	2
	Neoadjuvant	EU-Herceptin	Infusion related reaction	4
	Neoadjuvant	EU-Herceptin	Anaphylactic reaction	4
	Adjuvant	EU-Herceptin	Left ventricular dysfunction	2
	Adjuvant	SB3	Left ventricular dysfunction	2
	Adjuvant	SB3	Left ventricular dysfunction	2
	Adjuvant	SB3	Alanine aminotransferase increased	2
	Adjuvant	SB3	Aspartate aminotransferase increased	2
	Adjuvant	SB3	Thrombocytopenia	3

(b) (6)	Adjuvant	SB3	Left ventricular dysfunction	3
	Adjuvant	SB3	Left ventricular dysfunction	2
	Adjuvant	EU-Herceptin	Left ventricular dysfunction	2
	Adjuvant	SB3	Cardiac failure congestive	3
	Adjuvant	EU-Herceptin	Cardiac failure congestive	3
	Adjuvant	SB3	Left ventricular dysfunction	2
	Adjuvant	SB3	Local swelling	2
	Adjuvant	EU-Herceptin	Headache	2
	Adjuvant	EU-Herceptin	Hemorrhagic stroke	5
	Adjuvant	SB3	Left ventricular dysfunction	1
	Adjuvant	EU-Herceptin	Pathological fracture	3
	Adjuvant	SB3	Left ventricular dysfunction	2
	Adjuvant	EU-Herceptin	Left ventricular dysfunction	3
	Adjuvant	EU-Herceptin	Left ventricular dysfunction	3

Source dataset: ADAE.xpt

Reviewer Comments: *The TEAEs leading to permanent discontinuation were similarly distributed between the two arms. Please refer to Section 7.3.1 for details regarding the patients with grade 5 TEAEs. Overall there were no new safety signals identified.*

7.3.4. Submission Specific Primary Safety Concerns

7.3.4.1 Treatment-Related TEAEs

Table 25 below lists a summary of treatment-related TEAEs by grade, which were similar in the two treatment arms. The majority of treatment-related TEAEs occurred during the neoadjuvant period and were grade 1-2 in severity.

Table 25: Summary of Treatment-Related TEAEs for Study G31

AE Grade	Neoadjuvant Period		Adjuvant Period	
	SB3 N=437 n (%)	EU-Herceptin N=438 n (%)	SB3 N=437 n (%)	EU-Herceptin N=438 n (%)
1	42 (9.6)	55 (12.6)	32 (7.3)	43 (9.8)
2	42 (9.6)	36 (8.2)	20 (4.6)	19 (4.3)
3	15 (3.4)	13 (3)	6 (1.4)	5 (1.1)
4	19 (4.3)	13 (3)	0	0
5	0	0	0	0

Source dataset: ADAE.xpt

Reviewer comments: *The treatment-related TEAEs were well-balanced between the two arms. The majority occurred during the neoadjuvant period when multidrug chemotherapy is co-administered with trastuzumab products. The majority of treatment-related AEs were grade 1-2 in severity. In the adjuvant period, when trastuzumab products were administered as monotherapy, there were only 11 treatment-related grade 3 AEs, 6 in the SB3 arm and 5 in the EU-Herceptin arm. No treatment-related grade 4 or 5 AEs were reported in either arm during the adjuvant period.*

7.3.4.2 Adverse Events of Special Interest

Adverse events of special interest in the G31 trial include cardiac dysfunction, infusion reactions, and embryo-fetal toxicity. There were no cases of pregnancy or embryo-fetal toxicity reported on Study G31. Cardiac dysfunction and infusion reactions are discussed below.

7.3.4.2.1 Cardiac Toxicity

In Study G31, the incidence of cardiac AEs was similar between the two arms: 47 patients (10.8%) on the SB3 arm and 54 patients (12.3%) on the EU-Herceptin arm experienced at least one cardiac AE of any grade. The majority of these (90.1%) were grade 1/2 in severity. Cardiac AEs occurred more commonly during the neoadjuvant period (7.3% and 8.4% of participants in the SB3 and EU-Herceptin arms, respectively) when chemotherapy and trastuzumab were concurrently administered than in the adjuvant period (4.3 and 6% of participants in the SB3 and EU-Herceptin arms, respectively) when trastuzumab products were administered as monotherapy.

There were ten grade ≥ 3 cardiac TEAEs reported in Study G31, 5 (1.1%) in each arm. Most of these were grade 3; there was one grade 5 fatal myocardial infarction in the EU-Herceptin arm.

There were 16 patients (3.7%) on the SB3 arm and 12 patients (2.8%) on the EU-Herceptin arm who experienced a decline in left ventricular ejection fraction (LVEF) of ≥ 10 percentage points from baseline to less than 50%. The majority of these were grade 1-2 decreases in LVEF. There were three cases of grade ≥ 3 left ventricular systolic dysfunction reported, one in the SB3 arm and two in the EU-Herceptin arm. There were no cases of grade 4 or 5 left ventricular dysfunction reported in either arm. For the overall study period, including the day 120 safety update, a total of 7 patients in each arm (1.6%) experienced a LVEF $< 45\%$. These data are consistent with the known cardiac safety profile for US-Herceptin.

There were 4 cases of symptomatic congestive heart failure (CHF) reported in the overall study period, 3 (0.7%) in the SB3 arm and 1 in the EU-Herceptin arm (0.2%), evenly divided between the neoadjuvant and adjuvant study periods. This included two cases of NYHA Class II CHF in the SB3 arm, one case of NYHA Class IV CHF in the SB3 arm, and one case of NYHA Class II CHF in the EU-Herceptin arm. The case report forms of these patients were reviewed. All four patients with symptomatic CHF on Study G31 had additional cardiac risk factors, including hypertension and/or diabetes. Two of four cases were deemed unrelated to study drug. Two of the four cases of symptomatic CHF were deemed to be resolved by the time of the 120 day safety update, and two were ongoing.

The CRFs and narratives for patients with grade ≥ 3 cardiac TEAEs or cardiac SAEs have been reviewed and are summarized below.

Patient (b) (6) (CHF): 51 year-old Asian female randomized to receive SB3 and received first dose of study drug on (b) (6). Received a total of 6 cycles. Course complicated by several hospitalizations for febrile neutropenia, urinary tract infection, diarrhea, mucositis, myelosuppression, hyponatremia, and hypokalemia during the neoadjuvant period when chemotherapy was being co-administered with trastuzumab product. On study day 133, she was hospitalized with grade 3 diarrhea and vomiting and had a creatinine elevated to 2.0 mg/dL. On study day 139, she developed shortness of breath. A MUGA scan revealed a LVEF of 54%. Two days later, she had further shortness of breath and was found to be in acute renal failure (ARF). Her creatinine was 3.9 mg/dL. An echocardiogram showed an LVEF of 36%. She was treated for both ARF and CHF in the ICU and withdrawn from the study due to the event. The last cardiac function assessment approximately 3 weeks later showed a LVEF of 48%.

Patient (b) (6) (CHF): 48 year-old white female randomized to receive SB3 and received first dose of study drug on July 23, 2014. Received a total of 8 cycles. Course complicated by a hospitalization for urinary tract infection in the setting of a kidney stone. On study day 293, she reported decreased exercise tolerance and on echo was found to have a LVEF of 35%. She was withdrawn from the study due to the event. The last cardiac function assessment approximately 2 months later showed a LVEF of 45%.

Patient (b) (6) (CHF): 65 year-old white female randomized to receive SB3 and received first dose of study drug on (b) (6). Received a total of 6 cycles. On study day 106, she was hospitalized with dyspnea and diagnosed with NYHA Class II CHF. Cardiac function was “relatively normal” despite the clinical diagnosis, but no exact LVEF was available during that hospitalization. Study drug was delayed, and the patient ultimately withdrew from the study due to the event. A follow-up LVEF approximately 2 weeks later was normal at 55%, and the last cardiac function assessment on LVEF on February 11, 2015 was also normal at 59%.

Patient (b) (6) (Left ventricular systolic dysfunction): 55 year-old Asian female randomized to receive SB3 and received first dose of study drug on May 14, 2015. Received a total of 12 cycles. She presented on study day 302 with an echo that showed a LVEF of 30%. She was withdrawn from the study due to the event. The outcome of the event was reported by the applicant to be unknown.

Patient (b) (6) (Supraventricular tachycardia): 65 year-old white female randomized to receive SB3 and received first dose of study drug on April 24, 2015. Received a total of 4 cycles. She presented on study day 85 with a grade 3 event of supraventricular tachycardia. Tachycardia was terminated pharmacologically. She permanently discontinued study drug due to the event. She presented with another episode of supraventricular tachycardia on study day 110 that was again treated pharmacologically with resolution. She was withdrawn from the study due to the event.

Patient (b) (6) (Atrial fibrillation): 63 year-old white female randomized to receive SB3 and received first dose of study drug on January 28, 2015. She presented on study day 126 with a grade 3 event of atrial fibrillation. She continued on study drug, and the event was reported to have resolved on study day 127. Received a total of 11 cycles with discontinuation of study drug due to diagnosis of a brain metastasis.

Patient (b) (6) (CHF): 63 year-old white female randomized to receive EU-Herceptin and received first dose of study drug on April 29, 2015. Received a total of 11 cycles. She presented with a grade 3 event of NYHA class II CHF on study day 262. She withdrew from the study due to the event. The last cardiac function assessment on Mar 17, 2016 showed LVEF of 38%.

Patient (b) (6) (LVSD): 60 year-old white female randomized to receive EU-Herceptin and received first dose of study drug on January 13, 2015. Received a total of 18 cycles. Presented on study day 416 for her end of study visit and was found to have an LVEF of 35%. The study treatment had concluded, so no action was taken with the study drug. The event was reported to be resolving on study day 417, but no follow-up LVEF was available.

Patient (b) (6) (LVSD): 60 year-old white female randomized to receive EU-Herceptin and received first dose of study drug on April 3, 2015. Received a total of 13

cycles. On study day 287, was found to have a LVEF of 42%. She withdrew from the study due to the event. The last LVEF from February 4, 2016 revealed a LVEF of 45%.

Patient (b) (6) (Cardiac valvular disease): 55 year-old Asian female randomized to receive EU-Herceptin and received first dose of study drug on April 16, 2015. Received a total of 8 cycles. On study day 89, was found to have a LVEF of 51%. Trastuzumab product was permanently discontinued, but no action was taken with chemotherapy. On study day 152, the patient was diagnosed with a grade 3 event of cardiac valvular disease and LVEF was 37%. The AE was reported to be resolving, and last cardiac function assessment on October 22, 2015 revealed a LVEF of 45%.

Patient (b) (6) (Myocardial infarction): 55 year-old white female with history of diabetes randomized to receive EU-Herceptin and received first dose of study drug on (b) (6). Received a total of 1 cycle. Presented on study day 4 with angina and was found to have ST elevation and T-wave inversion in leads V1 to V4. Developed cardiogenic shock unresponsive to inotropes and died the same day. An autopsy revealed a flabby heart with myocardial sclerosis, a 2 cm plaque in the coronary artery, aortic atherosclerosis, and acute pulmonary edema.

Reviewer Comment: *The incidence of cardiac AEs of any type was higher on the EU-Herceptin arm than on the SB3 arm. The majority of all cardiac TEAEs reported in Study G31 were grade 1-2. A few more patients on the SB3 arm experienced a decrease in left ventricular ejection fraction or symptomatic congestive heart failure, but the percentages in both arms are within the expected incidence of cardiac dysfunction based on the US-Herceptin label. Overall the differences do not impact our conclusion that Study G31 supports a finding of no clinically meaningful differences.*

7.3.4.2.2 Infusion Reactions and Pulmonary Toxicity

Infusion reactions were reported in a similar percentage of patients in the two arms and were more common during the neoadjuvant period when cytotoxic agents were co-administered with trastuzumab products. During the neoadjuvant period, there were 36 patients (8.2%) in the SB3 arm who experienced infusion-related reactions compared with 44 patients (10%) in the EU-Herceptin arm. The incidence of infusion reactions was highest during the first 2 cycles in the neoadjuvant period. During the adjuvant period, when trastuzumab products are administered as monotherapy, there were only 2 patients who experienced infusion-reactions, both in the SB3 arm (0.5%). Almost all infusion reactions observed in Study G31 were grade 1 or 2. There were no grade ≥ 3 infusion reactions observed in the SB3 arm. Three patients (0.7%) in the EU-Herceptin arm experienced a grade 3 infusion reaction, and one patient (0.2%) in the EU-Herceptin arm experienced a grade 4 infusion reaction during docetaxel administration. All AEs of infusion reaction resolved, but two of the four patients discontinued the study due to the AEs.

The incidence of pulmonary adverse events of all types and grades was similar between the two arms, 33.6% and 34.9% for SB3 and EU-Herceptin, respectively. The majority of these general pulmonary AEs occurred during the neoadjuvant period when chemotherapy was co-administered with trastuzumab products. In addition to infusion reactions discussed above, there was 1 (0.2%) case of radiation fibrosis of the lung in the SB3 arm, which was reported following breast radiation in the adjuvant period. There were three cases of pulmonary fibrosis, 2 (0.5%) in the SB3 arm and 1 (0.2%) in the EU-Herceptin arm, both reported during the adjuvant period. There was also 1 (0.2%) case of pneumonitis in the EU-Herceptin arm, which was reported in the adjuvant period.

Reviewer Comments: *There are no new safety concerns noted for infusion reactions or pulmonary toxicity for SB3.*

7.4. Supportive Safety Results

7.4.1. Common Adverse Events

Common TEAEs seen in $\geq 5\%$ of patients in any group during both the neoadjuvant and adjuvant periods of the study are shown in the table below. Adverse events of special interest were discussed in Section 7.3.4.2 above.

Table 26: TEAEs in $\geq 5\%$ of Patients in Study G31

All grade adverse events	SB3 N=437	SB3 %	EU- Herceptin N=438	EU- Herceptin %
Any adverse event	426	97.5	421	96.1
Alanine aminotransferase increased	84	19.2	83	18.9
Alopecia	299	68.4	283	64.6
Anemia	96	22	95	21.7
Arthralgia	48	11	47	10.7
Aspartate aminotransferase increased	68	15.6	63	14.4
Asthenia	59	13.5	55	12.6
Blood alkaline phosphatase increased	22	5	29	6.6
Bone pain	23	5.3	24	5.5
Cough	44	10.1	27	6.2
Decreased appetite	40	9.2	41	9.4
Diarrhea	92	21.1	67	15.3
Dyspepsia	27	6.2	23	5.3

All grade adverse events	SB3 N=437	SB3 %	EU- Herceptin N=438	EU- Herceptin %
Fatigue	88	20.1	80	18.3
Febrile neutropenia	28	6.4	34	7.8
Headache	33	7.6	35	8
Infusion related reaction	37	8.5	44	10
Insomnia	22	5	22	5
Joint range of motion decreased	27	6.2	20	4.6
Leukopenia	125	28.6	114	26
Lymphorrhea	32	7.3	30	6.8
Myalgia	63	14.4	66	15.1
Nail disorder	22	5	23	5.3
Nausea	144	33	135	30.8
Neuropathy peripheral	22	5	12	2.7
Neutropenia	294	67.3	282	64.4
Neutrophil count decreased	56	12.8	57	13
Edema peripheral	18	4.1	31	7.1
Oropharyngeal pain	25	5.7	19	4.3
Pain in extremity	22	5	20	4.6
Peripheral sensory neuropathy	30	6.9	23	5.3
Postoperative wound complication	27	6.2	21	4.8
Procedural pain	39	8.9	53	12.1
Pruritus	20	4.6	22	5
Pyrexia	41	9.4	44	10
Radiation skin injury	48	11	38	8.7
Rash	48	11	50	11.4
Stomatitis	61	14	51	11.6
Upper respiratory tract infection	44	10.1	40	9.1
Vomiting	62	14.2	52	11.9
White blood cell count decreased	25	5.7	32	7.3

Source dataset: ADAE.xpt

Reviewer Comments: TEAEs seen in $\geq 5\%$ in any arm during the study are well balanced with no meaningful differences. The most common TEAEs observed in Study G31--alopecia, myelosuppression, fatigue, and gastrointestinal symptoms--are well-described toxicities of chemotherapy.

Common TEAEs seen in $\geq 5\%$ of patients in any group during the neoadjuvant period of study G31 are shown in the table below. Adverse events of special interest were discussed in Section 7.3.4.2 above.

Table 27: TEAEs in ≥5% of Patients During the Neoadjuvant Period of Study G31

Adverse Event	SB3 N=437	SB3 %	EU- Herceptin N=438	EU- Herceptin %
Any adverse event	422	96.6	417	95.2
Alopecia	294	67.3	277	63.2
Anemia	81	18.5	89	20.3
Arthralgia	30	6.9	32	7.3
Aspartate aminotransferase increased	61	14	57	13
Asthenia	52	11.9	48	11
Bone pain	20	4.6	24	5.5
Cough	32	7.3	19	4.3
Decreased appetite	39	8.9	37	8.4
Diarrhea	89	20.4	66	15.1
Dyspepsia	25	5.7	20	4.6
Fatigue	63	14.4	67	15.3
Febrile neutropenia	28	6.4	34	7.8
Headache	27	6.2	25	5.7
Infusion related reaction	36	8.2	44	10
Leukopenia	122	27.9	108	24.7
Myalgia	63	14.4	64	14.6
Nail disorder	19	4.3	22	5
Nausea	137	31.4	133	30.4
Neutropenia	293	67	279	63.7
Neutrophil count decreased	55	12.6	56	12.8
Edema peripheral	16	3.7	25	5.7
Peripheral sensory neuropathy	28	6.4	22	5
Pyrexia	29	6.6	39	8.9
Rash	42	9.6	46	10.5
Stomatitis	60	13.7	49	11.2
Upper respiratory tract infection	28	6.4	28	6.4
Vomiting	59	13.5	49	11.2
White blood cell count decreased	24	5.5	31	7.1

Source dataset: ADAE.xpt

Reviewer Comments: TEAEs seen in ≥5% in any arm during the neoadjuvant period are balanced with no meaningful differences between SB3 and EU-Herceptin. The most common TEAEs observed during the neoadjuvant period--alopecia, myelosuppression, nausea/vomiting, and diarrhea--are well-described toxicities of chemotherapy.

Common TEAEs seen in $\geq 5\%$ of patients in any group during the adjuvant period of the study are shown in Table table below.

Table 28: TEAEs in $\geq 5\%$ of Patients During the Adjuvant Period of Study G31

Adverse Event	SB3 N=437	SB3 %	EU- Herceptin N=438	EU- Herceptin %
Any adverse event	246	56.3	241	55
Anemia	28	6.4	20	4.6
Fatigue	37	8.5	31	7.1
Joint range of motion decreased	26	5.9	20	4.6
Lymphorrhea	32	7.3	30	6.8
Postoperative wound complication	26	5.9	21	4.8
Procedural pain	38	8.7	53	12.1
Radiation skin injury	48	11	36	8.2
Upper respiratory tract infection	25	5.7	21	4.8

Source dataset: ADAE.xpt

Reviewer Comments: TEAEs seen in $\geq 5\%$ in any arm during the adjuvant period are well-balanced without meaningful differences between arms. Adverse events during the adjuvant period, when chemotherapy was no longer being administered, were much less common and attributable in large part to surgery and/or radiotherapy. No concerning findings are identified.

7.4.2. Laboratory Findings

Trastuzumab products are not known to cause significant laboratory abnormalities, but chemotherapy is. The reported changes in laboratory values for Study G31 were reviewed and overall well balanced between the treatment arms in hematology labs and chemistries for the safety population in the neoadjuvant and adjuvant periods.

Reviewer Comments: No safety concerns noted. Trastuzumab products are not known to cause significant laboratory findings.

7.4.3. Vital Signs

Changes in vital signs for the safety population reported were reviewed and overall well balanced between the treatment arms for temperature, blood pressure, heart rate, and

respiratory rate for the neoadjuvant and adjuvant periods of Study G31.

Reviewer Comments: No safety concerns noted.

7.4.4. Electrocardiograms (ECGs)

Trastuzumab products are not known to cause clinically significant ECG changes. The reported ECG findings for Study G31 were reviewed. Patients with a history of serious cardiac conditions that would preclude the use of trastuzumab products and those with evidence of prior transmural infarction or clinically significant arrhythmia were excluded. ECGs were performed at baseline, after cycle 4, at the conclusion of the neoadjuvant period, after cycle 6 in the adjuvant setting (cycle 10 overall), and at end of study, as well as at additional time points if clinically indicated. Overall there were only six patients (0.7%) throughout Study G31 with abnormal, clinically significant ECG results post-baseline (2 in the SB3 arm and 4 in the EU-Herceptin arm).

Reviewer Comments: Very few patients had abnormal, clinically significant ECG results post-baseline during the neoadjuvant and adjuvant periods. No new safety concerns were identified.

7.4.5. Special Safety Studies/Clinical Trials

No special safety studies were conducted.

7.4.6. Immunogenicity

The incidence of anti-drug antibodies (ADAs) and neutralizing antibodies (Nabs) was assessed at pre-dose of cycles 1, 5, 9, 14, and 30 days after the final dose of study drug. At baseline, 4 patients in each arm (0.9%) had a positive ADA, and no patients in either arm had a positive Nab (0%).

For patients with a negative ADA at baseline, a positive ADA result was defined as any positive result after at least one dose of study drug. For patients with a positive ADA at baseline, a positive ADA result was defined as at least one positive result following administration of trastuzumab product with a higher titer level than at baseline. Using these definitions, only 6 patients, 3 (0.7%) in each arm, had positive ADA results at any point from first administration of study drug through end of study. A total of 4 patients had a positive Nab result, 2 patients (0.4%) in each arm.

Due to the low incidence of positive ADAs, the impact of ADA on efficacy (bpCR rate) and pharmacokinetics could not be assessed. None of the six patients with a positive ADA experienced an infusion-related reaction.

Reviewer Comments: No safety concerns.

7.5. Other Safety Explorations

None

7.6. Additional Safety Evaluations

7.6.1. Human Carcinogenicity

Not applicable.

7.6.2. Human Reproduction and Pregnancy Data

A pregnancy test was required within 2 weeks prior to randomization for all women of childbearing potential including women with onset of menopause within the past 2 years. Women of childbearing potential were required to agree to use contraception during the study and for 7 months after last dose of study drug. Any pregnancy from the time of first dose of study drug until safety follow-up was required to be reported to the study sponsor within 24 hours, and all pregnancies were required to be followed until 6-8 weeks after the estimated date of delivery. No pregnancies were reported on Study G31.

Reviewer comment: Trastuzumab products are known to cause embryo-fetal toxicity. No pregnancies were reported on Study G31.

7.6.3. Pediatrics and Assessment of Effects on Growth

Pediatric patients were not eligible to enroll in Study G31 and have not been treated with SB3.

7.6.4. Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no reported cases of overdose of SB3 in Study G31 or throughout the SB3 clinical development program. There is no known potential for drug abuse, withdrawal, or rebound from trastuzumab products.

7.7. Additional Submissions / Safety Issues

The Day 120 Safety Update for Study G31 was submitted on February 14, 2018. No patients were treated with SB3 or EU-Herceptin as part of the clinical development of SB3 since the original BLA submission. At the time of clinical data cut-off for the 120 day safety update, participants had been followed up for a median of 916 days (range: 560-1264) in the SB3 arm and 918 days (range: 711-1248) in the control arm.

Among the 764 patients who completed treatment in Study G31, 367 patients enrolled in the 5-year follow-up extension study (SB3-G31-BC-E), 186 in the SB3 arm and 181 in the EU-Herceptin arm. At the time of the October 19, 2017 data cut-off for the safety update, 4 patients enrolled in the extension study had died, 1 in the SB3 arm and 3 in the EU-Herceptin arm. Three of the deaths were due to breast cancer. The other cause of death was unknown.

Cardiac Safety

In the 120 day safety update, there were 3 patients with asymptomatic LVEF decreases reported (asymptomatic decline of $\geq 10\%$ from baseline at entry to Study G31 to $\leq 50\%$, 1 (0.5%) of whom had received SB3 and 2 (1.1%) of whom had received EU-Herceptin. All had recovered to within normal limits by the next scheduled assessment of cardiac function. There were no cases of symptomatic CHF, other cardiac AEs, or cardiac deaths reported during the extension study. Brief narrative summaries for these patients are provided below:

- Patient (b) (6): 58 year-old white female randomized to receive SB3. Baseline LVEF at screening was 69%. An asymptomatic LVEF decrease to 47% was detected on scheduled echo on study day 572. Follow-up LVEF assessment on study day 755 revealed improvement in LVEF to 55%, and the AE was considered to have resolved.
- Patient (b) (6): 55 year-old white female randomized to receive EU-Herceptin. Baseline LVEF at screening was 61%. An asymptomatic LVEF decrease to 49% was detected on scheduled echo on study day 601. Follow-up LVEF assessment on study day 799 revealed improvement in LVEF to 54%, and the AE was considered to have resolved.
- Patient (b) (6): 49 year-old white female randomized to receive EU-Herceptin. Baseline LVEF at screening was 58%. An asymptomatic LVEF decrease to 48% was detected on scheduled echo on study day 617. Follow-up LVEF assessment on study day 795 revealed improvement in LVEF to 61%, and the AE was considered to have resolved.

Reviewer Comments: There were no new clinically significant cardiac safety findings in the Day 120 Safety Update. Asymptomatic LVEF decrease was rare in patients following completion of treatment with the trastuzumab product, and all affected patients had recovery of cardiac function by the next follow-up LVEF assessment a few months later. No new cases of symptomatic CHF or cardiac death were reported in patients following completion of treatment with the trastuzumab product.

Deaths

The 120 day safety update submission included four case report forms of patients who died during the follow-up period.

Deaths that occurred during the neoadjuvant and adjuvant periods of the study are discussed in Section 7.3.1 above. Narratives for deaths that occurred during the follow-up period included in the 120 day safety update are summarized below:

- Patient (b) (6): 57 year-old white female randomized to receive SB3 on Study G31. Documented to have recurrent breast cancer by biopsy on study day 693. Died on study day 758 with cause of death listed as breast cancer.
- Patient (b) (6): 55 year-old white female randomized to receive EU-Herceptin on Study G31. Died on study day 701. Cause of death was unknown at time of data cutoff for 120 day safety update.
- Patient (b) (6): 35 year-old white female randomized to receive EU-Herceptin on Study G31. Documented to have recurrent breast cancer by CT scan on study day 822. Died on study day 845 with cause of death listed as breast cancer.
- Patient (b) (6): 39 year-old white female randomized to receive EU-Herceptin on Study G31. Documented to have recurrent breast cancer by CT scan on study day 694. Died on study day 824 with cause of death listed as breast cancer.

Reviewer Comments: Narratives for deaths reported in the follow-up period were reviewed for all patients and discussed above. Overall, 2 patients who received SB3 and 1 who received EU-Herceptin died of recurrent breast cancer. These values are within the expected survival rate for patients with early-stage HER2+ breast cancer treated in the adjuvant setting.

8. Postmarketing Experience

SB3 is not yet marketed in the United States.

9. Appendices

9.1. Literature Review

1. NCI: SEER, Cancer Stat Facts: Breast Cancer, <https://seer.cancer.gov/statfacts/html/breast.html>, Accessed November 13, 2017.
2. NCI: SEER, Cancer Stat Facts: Stomach Cancer, <https://seer.cancer.gov/statfacts/html/stomach.html>, Accessed November 13, 2017.
3. Bang, et al., Lancet 2010, 376: 687-697
4. Nahta, et al., Oncogene 2007, 26: 3637-3643
5. Pupa, et al., Oncogene 1993, 8: 2917-2923
6. Hayes, et al., Clinical Cancer Research 2001, 7: 2701-2711
7. Arnould, et al., British Journal of Cancer 2006, 94: 2559-2267
8. Wen, et al., Oncogene 2006, 25: 6986-6996
9. Gasparini, et al., Breast Cancer Research and Treatment 2007, 101: 355-365
10. Marty, et al., Journal of Clinical Oncology 2005, 4265-4274
11. Slamon, et al., New England Journal of Medicine 2001, 365: 783-792
12. Buzdar, et al. Journal of Clinical Oncology 2005; 23 (16): 3676-3685
13. Chang, et al. Journal of Clinical Oncology 2008; 26 (15S, May 20 Supplement): 604.
14. Cortazar, et al. Lancet 2014; 384: 164-172.
15. Gianni, et al. Lancet 2010; 375 (9712): 377-384.

9.2. Labeling Recommendations

The following changes were made to the Ontruzant label:

1. Per guidance for biosimilars, throughout the label:
 - a. “trastuzumab” refers to US-Herceptin
 - b. “trastuzumab product(s)” refers to US-Herceptin and biosimilars
 - c. “Ontruzant” refers to SB3
2. Highlights of Prescribing Information

- a. Product name changed to “ONTRUZANT”
 - b. Full product title changed to “ONTRUZANT (trastuzumab-dttb)”
 - c. Added description of biosimilar and biosimilarity of Ontruzant
3. Section 1 Indications and Usage: Wording changed to: *“Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.”*
4. Section 2.4 Preparation for Administration: Added language to clarify that the vial contains the lyophilized powder of Ontruzant, which has a cake-like appearance, and that the stream of diluent should be directed into the cake to reconstitute the product for administration
5. Section 6.3 Postmarketing Experience: Added risk of tumor lysis syndrome for consistency with update to US-Herceptin label dated September 20, 2018
6. Section 8 Use in Specific Populations
 - a. “Pregnancy Exposure Registry and Pharmacovigilance Program” section removed.

9.3. Advisory Committee Meeting

No Oncology Advisory Committee Meeting (ODAC) was deemed necessary for this BLA submission.

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.

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