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APPLICATION NUMBER:

761100Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology
351(k) Biosimilar Review

351(k) BLA Number	761100
Applicant	Samsung Bioepis Co., Ltd
Submission Date	10/20/2017
Submission Type	*Standard Review*
Link to EDR	\\CDSESUB1\evsprod\BLA761100\
Proprietary Name (Proposed) / Nonproprietary Name	Ontruzant/ trastuzumab-dttb/SB3[1]
Dosage Form and Strength	150 mg lyophilized powder in a single-dose vial for reconstitution
Route of Administration	*Intravenous (IV)*
Proposed Indication(s)	• *Adjuvant Treatment of HER2-Overexpressing Breast Cancer* • *Metastatic HER2-Overexpressing Breast Cancer* • *Metastatic HER2-Overexpressing Gastric or Gastroesophageal Junction adenocarcinoma*
Associated IND	*IND 123158*
Reference Product Information (U.S.-licensed)	
Proprietary (Nonproprietary) Name	Herceptin (trastuzumab)
Dosage Form and Strength	420 mg multiple-dose vial; 150 mg single-dose vial
OCP Review Team Signers	
OCP Review Team	*Sriram Subramaniam, Ph.D.* *Olanrewaju Okusanya, Pharm.D., M.S.*
OCP Final Signatory	*Nam Atiqur Rahman, Ph.D.*

[1] In this document, we generally refer to the applicant's proposed product by the applicant-provided descriptor "SB3", which was the name used to refer to this product in development. Subsequently, the nonproprietary name for this proposed product has been conditionally accepted to be "ONTRUZANT"

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1. EXECUTIVE SUMMARY

This Biologic License Application (BLA) for Ontruzant, referred to as "SB3" by the applicant during development and herein, has been submitted under Section 351(k) of the Public Health Service Act (42 U.S.C. 262(k)). The applicant is seeking approval for SB3 (trastuzumab-dttb) as a proposed biosimilar to US-licensed Herceptin (trastuzumab) licensed under BLA 103792 by Genentech. The applicant is seeking licensure for the treatment of adjuvant or metastatic HER-2 overexpressing breast cancer or metastatic HER2-overexpressing gastric or gastroesophageal junction adenocarcinoma indications for which US-licensed Herceptin is currently approved.

The applicant submitted pharmacokinetic (PK) data from the following studies to support a demonstration of no clinical meaningful difference between SB3 and US-licensed Herceptin:

1) a pivotal PK similarity study, SB3-G11-NHV: a randomized, double-blind, parallel group, single-dose (6 mg/kg) study in 109 healthy subjects to assess PK between SB3, US-licensed Herceptin, and EU-approved Herceptin, and
2) a comparative clinical study, SB3-G31-BC: randomized, double-blind, parallel-arm, multiple dose study in 875 patients with newly diagnosed HER2+ early breast cancer or locally advanced breast cancer in neoadjuvant setting. Trough concentrations were collected to evaluate the potential impact of immunogenicity on the PK of trastuzumab.

The 90% confidence intervals (CI) of the geometric mean ratios for all three pairwise comparisons of $AUC_{0\text{-inf}}$ and C_{max} were within the pre-specified limits of 80 to 125% in Study SB3-G11-NHV. The results of the study established the PK similarity between SB3 and US-licensed Herceptin, provides the PK portion of the scientific bridge between SB3, US-licensed Herceptin, and EU-approved Herceptin, to support the use of EU-approved Herceptin in the comparative clinical Study SB3-G31-BC.

The immunogenicity results in Study SB3-G31-BC indicate similar incidence and titers of anti-drug antibodies (ADA) for SB3 and EU-approved Herceptin. No apparent impact of ADA on safety, efficacy, or PK endpoints was observed. The data indicates that there is no increase in immunogenicity risk for SB3 compared to EU-approved Herceptin.

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

1.1 Recommendations

The Office of Clinical Pharmacology recommends the approval of SB3 based on demonstration of PK similarity and no increase in immunogenicity risk between SB3 and US-licensed Herceptin.

Review Issue	Recommendations and Comments
Pivotal evidence of PK similarity	PK similarity was observed between SB3, US-licensed Herceptin, and EU-approved Herceptin. The PK portion of the scientific bridge between SB3, US-licensed Herceptin, and EU-approved Herceptin was also demonstrated. The 90% CI of the geometric mean ratios for each product pairwise comparison for $AUC_{0\text{-}}$

	$_{inf}$ and C_{max} were within the PK similarity acceptance criteria of 80 to 125% (**Table 1**).
Evidence of immunogenicity comparability	The results of Study SB3-G31-BC indicate similar incidence of anti-drug antibodies (ADA) for SB3 and EU-approved Herceptin.

1.2 Post-Marketing Requirements and Commitments

None

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Clinical Pharmacology and Pharmacokinetics

SB3 is a proposed biosimilar to US-licensed Herceptin (trastuzumab). US-licensed Herceptin is a humanized IgG1 kappa monoclonal antibody that selectively binds with high affinity to the extracellular domain of the human epidermal growth factor receptor 2 protein (HER-2). Trastuzumab is produced by recombinant DNA technology in a mammalian cell (Chinese Hamster Ovary) culture containing the antibiotic gentamicin. Details on the clinical pharmacology of US-licensed Herceptin can be found in the product label (USPI).

The results of the PK similarity assessment in Study SB3-G11-NHV, show that the 90% confidence intervals (CI) for the geometric mean ratios of $AUC_{0\text{-}inf}$ and C_{max} were within the prespecified limits of 80% to 125% in the pairwise comparisons between SB3, US-licensed Herceptin, and EU-approved Herceptin, as summarized in **Table 1**.

Table 1. Summary of statistical analyses for PK similarity (SB3-G11-NHV)

Comparision	Geometric Mean Ratio (90% CI)	
	C_{max} (N = 34)*	**$AUC_{0\text{-}inf}$ (N = 34)***
SB3 vs US-licensed Herceptin	99.8 (93.5, 106.6)	94.5 (88.8, 100.5)
SB3 vs EU-approved Herceptin	99.5 (93.2, 106.3)	97.0 (91.2, 103.1)
EU-approved Herceptin vs US-licensed Herceptin	100.3 (93.9, 107.1)	97.4 (91.6 – 103.6)

*n=33 for SB3 and US-Herceptin

Overall, the submitted clinical pharmacology study is adequate to demonstrate PK similarity between SB3 and US-licensed Herceptin. Study SB3-G11-NHV, conducted in healthy subjects, is considered sufficiently sensitive to detect clinically significant differences in PK among the products. The PK results support a demonstration of no clinically meaningful differences between SB3 and US-licensed Herceptin, and add to the totality of the evidence to support a demonstration of biosimilarity of SB3 and US-licensed Herceptin.

The incidence of immunogenicity for SB3 and EU-approved Herceptin was compared in a multiple-dose, parallel-arm study in 875 patients with HER2+ early breast cancer (EBC) or locally advanced breast cancer (LABC) in neoadjuvant setting (Study SB3-G31-BC). The results indicate similar incidence and titers of anti-drug antibodies (ADA) for both products.

Overall, the clinical studies adequately demonstrated PK similarity and showed no increase in immunogenicity risk between SB3 and US-licensed Herceptin. These results support a demonstration of no clinically meaningful differences between SB3 and US-licensed Herceptin and add to the totality of the evidence to support the biosimilarity demonstration of SB3 and US-licensed Herceptin.

2.2 Outstanding Issues

None

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Regulatory Background

3.1.1 If applicable, describe (in tabular format) relevant regulatory history for the review of this 351(k) BLA.

SB3 is a proposed biosimilar to US-licensed Herceptin. The applicant is seeking licensure for the the same indications for which US-licensed Herceptin is currently approved.

3.2 Clinical Pharmacology Review Questions

3.2.1 What are the design features of the clinical pharmacology and/or clinical studies to support biosimilarity?

The applicant conducted one clinical pharmacology study and one comparative clinical study, as described in **Table 2**.

Table 2: Summary of relevant clinical studies

Protocol	Study Design	Subjects	Objectives	Route/Dose/Duration
PK Similairty Study				
SB3-G11-NHV	Randomized, double-blind, single-Dose, 3-Arm, parallel group in healthy male subjects	Healthy (n=109) (SB3: 36; US Herceptin = 36; EU Herceptin = 36)	PK similarity	Single dose 6 mg/kg via 90 min IV infusion
Comparative Clinical Study				
SB3-G31-BC	Randomised, double-blind, parallel group, multicenter study in women with HER2 positive EBC or LABC in neoadjuvant setting.	Women with newly diagnosed HER2+ EBC or LABC; N= 875 (SB3: 437; EU Herceptin: 438)	To compare the efficacy, safety, PK and immunogenicity between SB3 and EU-Herceptin.	- IV infusion of SB3 8 mg/kg (loading dose), then 6 mg/kg (maintenance dose) - SB3 or Herceptin in neoadjuvant setting for 8 cycles concurrently with 8 cycles of chemotherapy (4 cycles of docetaxel followed by 4 cycles of 5-fluorouracil/epirubicin/ cyclophosphamide). After surgery, patients received further 10 cycles of adjuvant SB3 or Herceptin as per

				randomisation to complete one year of therapy.

PK similarity was determenied based on data from Study SB3-G11-NHV. This study was a single-dose, randomized, single-blind, 3-arm, parallel-group study designed to compare the PK of SB3 (n = 36), US-licensed Herceptin (n = 36), and EU-approved Herceptin (n = 39) administered as a single 6 mg/kg IV infusion over 90 minutes to healthy male subjects (N=109).

The study design of Study SB3-G11-NHV is considered adequate due to the following reasons:

1. 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.
2. 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.
3. Considering PK assay sensitivity, dose-exposure linearity, and tolerability, a single IV dose of 6 mg/kg trastuzumab is considered appropriate for a PK similarity study.

Study SB3-G31-BC was a comparative clinical study in patients with HER2-positive EBC or LABC. Refer to Clinical review for further details.

3.2.2 What are the endpoints in the clinical pharmacology and/or clinical studies to support biosimilarity?

The pre-specified PK endpoints evaluated in Study SB3-G11-NHV were $AUC_{0\text{-inf}}$, AUC_{last}, and C_{max}. PK similarity was concluded if the 90% CI of the geometric mean ratios of PK parameters for each pairwise comparison between SB3, US-licensed Herceptin, and EU-approved Herceptin were within the pre-specified limits of 80% to 125%. Blood samples for PK analysis were collected prior to start of infusion, and at 0.75, 1.5 (end of infusion), 3, 6, 12, 24, 48, 72, 96, 168, 336, 672, 1008 and 1344 hours after start of infusion. This provided sufficient data for the determination of $AUC_{0\text{-inf}}$. Blood samples were collected for determination of anti-drug antibodies (ADA) to trastuzumab and neutralising antibodies (NAbs) at Day 1 (pre-dose), Day 29 and Day 57.

Refer to Clinical review for the primary efficacy endpoint for Study SB3-G31-BC. The secondary objectives included evaluation of PK and immunogenicity between SB3 and EU-approved Herceptin. Blood samples for PK were collected at predose of Cycle 1, 3, 5, 7, and 8, and for ADA and NAb were collected at predose of Cycles 1, 5, 9, & 14, and 30 days after the last dose.

3.2.3 Are the pharmacogicallyactive moieties of the proposed biosimilar and the reference product in plasma (or other biological matrix) appropriately identified and measured to assess the PK parameters?

Yes. See **Section 4.1** for details. Trastuzumab levels were measured in serum by a validated ELISA assay.

3.2.4 Is PK similarity met?

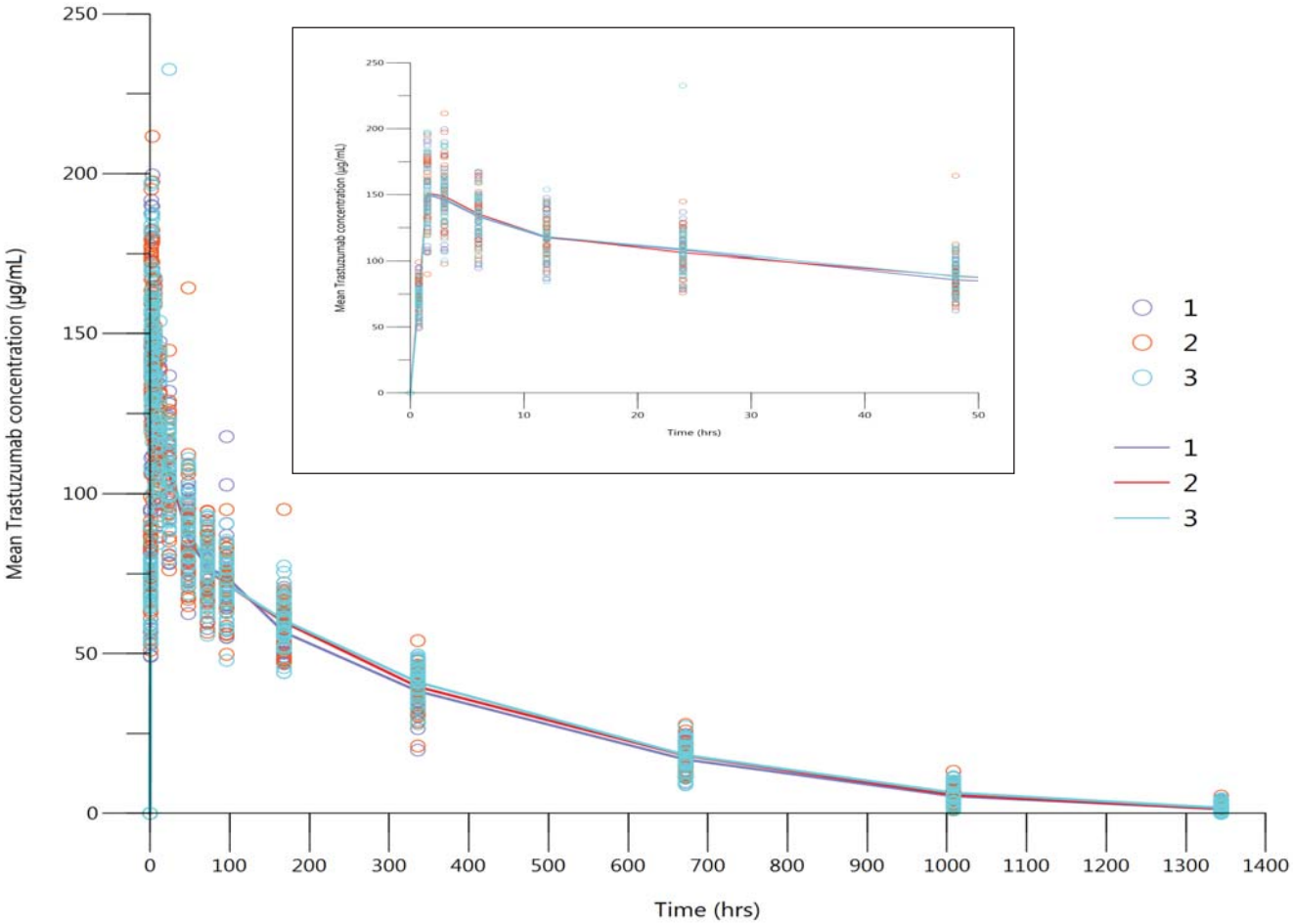
Yes, PK similarity between SB3, US-licensed Herceptin, and EU-approved Herceptin was demonstrated. The 90% CI of geometric mean ratios of the PK endpoints for each product pairwise comparison were

contained within pre-defined criteria of 80 to 125% (**Table 3**). The mean PK profiles of SB3, US-licensed Herceptin, and EU-approved Herceptin overlay each other (**Figure 1**). A summary of the PK parameters after the administration of 6 mg/kg IV single dose of SB3, US-licensed Herceptin, and EU-approved Herceptin® to healthy subjects in Study SB3-G11-NHV is provided in **Table 4**.

Table 3: Summary of statistical analyses for PK similarity (SB3-G11-NHV)

Parameter	Geometric Mean Ratio (90% CI, %)		
	SB3 vs US-Herceptin	SB3 vs EU-Herceptin	EU-Herceptin vs US-Herceptin
$AUC_{0\text{-last}}$ (µg•h/mL)	95.1 (89.5, 101.0)	97.2 (91.5, 103.2)	97.8 (92.1, 103.9)
AUC_{inf} (µg•h/mL)	94.5 (88.8, 100.5)	97.0 (91.2, 103.1)	97.4 (91.6, 103.6)
C_{max} (µg /mL)	99.8 (93.5, 106.6)	99.5 (93.2, 106.3)	100.3 (93.9, 107.1)
n=33 for SB3 & US-Herceptin; and n=34 for EU-Herceptin 3 subjects each in SB3 and US-Herceptin arms, and 2 subjects in EU-Herceptin arm were excluded from PK analysis due for bioanalytical reasons (see Section 4.1.1.1) *Source: Reviewer's analysis*			

Figure 1: Mean serum concentrations versus nominal time profiles of SB3, EU-approved Herceptin and US-licensed Herceptin in Study SB3-G11-NHV (inset: concentration profiles at times 0 to 50 hours)



1 = SB3, 2 = EU-approved Herceptin, and 3 = US-licensed Herceptin

Table 4: Summary of single dose PK parameter results (Study SB3-G11-NHV)

	Geometric mean (Geometric %CV)		
Treatment (N)	**$AUC_{0\text{-}inf}$ (µg*h/mL)**	**$AUC_{0\text{-}last}$ (µg*h/mL)**	**C_{max} (µg/mL)**
SB3 (N=33)	35958 (15)	35518 (14)	152 (17)
US-Herceptin (N=33)	38057 (16)	37357 (15)	153 (16)
EU-Herceptin (N=34)	37080 (15)	36543 (15)	153 (16)
Source: Reviewer's analysis			

Immunogenicity

3.2.5 Is the immunogenicity assay capable of detecting the antidrug antibodies (ADA) in the presence of concentration of product in the study samples?

Detection, confirmation, and titration of ADAs were determined utilizing a Meso Scale Discovery (MSD) assay.The screening assay sensitivity was 2.88 ng/mL (Study SB3-G11-NHV) and 5.34 ng/mL (Study SB3-G31-BC) and the confirmatory assay sensitivity was 25 ng/mL (Study SB3-G31-BC). The low positive controls (LPC) were 6.5 ng/mL (study SB3-G11-NHV) and 4 ng/mL (Study SB3-G31-BC) and the hight positive controls (HPC) were 10000 ng/mL in both studies. The drug tolerance limit was 250 ng/mL anti-trastuzumab antibody in the presence of 50 mg/mL (Study SB3-G11-NHV) or 150 mg/mL (Study SB3-G31-BC) of SB3, EU-approved Herceptin, and US-licensed Herceptin.

The neutralizing anti-trastuzumab antibodies were analysed by the MSD platform assay in Study SB3-G31-BC. The relative sensitivity of the assay was 214.69 ng/mL, and LPC at 275 ng/mL and HPC at 2000 ng/mL. The drug tolerance limit was 275.00 ng/mL in the presence of 150.00 µg/mL of SB3 and EU-approved Herceptin.

Refer to the immunogenicity assay review by the Office of Biological Products review for details regarding the assays.

3.2.6 Is the sampling plan adequate to capture baseline, early onset, and dynamic profile (transient or persistent) of anti-drug antibodies (ADA) formation?

The sampling schedules in the studies were adequate to minimize interference from the presence of the drug product in the samples, if the ADA assay is not drug-tolerant. The sampling schedules for the studies were as follows:

- Study SB3-G11-NHV: Day 1 (pre-dose), Day 29, and Day 57.
- Study SB3-G31-BC: Pre-dose of Cycle 1, 5, 9, & 14, and 30 days after the last dose.

3.2.7 What is the incidence of anti-drug antibodies (ADA)?

No subject developed ADA to trastuzumab in Study SB3-G11-NHV.

In Study SB3-G31-BC, the overall incidence of ADA to trastuzumab was low in both SB3 and EU-approved Herceptin treatmemt groups. At end of study (EOS), the number of patients with an overall ADA positive result was 3 (0.7%) each in the SB3 and EU-approved Herceptin treatment groups (**Table 5**).

The data indicate that there is no increase in immunogenicity risk for SB3 compared to EU-approved Herceptin, and supports the demonstration that there are no clinically meaningful differences between SB3 and US-licensed Herceptin.

Of note, a scientific bridge was established between SB3, US-licensed Herceptin, and EU-approved Herceptin, supporting the relevance of comparative data, including immunogenicity data, generated using EU-approved Herceptin to support a demonstration of no clinically meaningful differences between SB3 and US-licensed Herceptin.

Table 5: Incidence of anti-drug antibody (ADA) and neutralising antibodies (NAb) positive results by visit (Study SB3-G31-BC)

Time Point	Immunogenicity	SB3 (%)*	EU-Herceptin (%)*
Cycle 1 (baseline)	ADA	4 (0.9%)	4 (0.9%)
	NAb	0	0
Cycle 5	ADA	3 (0.7%)	1 (0.2%)
	NAb	2	0
Cycle 9	ADA	0	1 (0.2%)
	NAb	0	0
Cycle 14	ADA	1 (0.3)	0
	NAb	0	0
End of Study (EOS)	ADA	2 (0.5%)	3 (0.8%)
	NAb	0	2
Cycle 9 Overall	ADA	3 (0.7%)	0
EOS Overall	ADA	3 (0.7%)	3 (0.7%)

*percent of number of patients with available assessment results at each time point.
NAb results only presented for those patients who were ADA positive.
Source: Table 12-22, CSR

3.2.8 Do the anti-drug antibodies (ADA) have neutralizing activity?

No neutralizing ADA was detected in the data obtained from Study SB3-G11-NHV.

Up to EOS, 4 patients had an incidence of neutralising ADA positive results (2 patients in each SB3 and EU-approved Herceptin group) in Study SB3-G31-BC (**Table 5**).

3.2.9 What is the impact of anti-drug antibodies (ADA) on the PK, PD, safety, and clinical outcomes of the therapeutic protein?

No subject developed ADA to trastuzumab in Study SB3-G11-NHV. Due to the low incidence of positive ADA results in both treatment groups, the impact analysis of ADA up to Cycle 9 on the PK was not applicable.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

4.1.1 Pharmacokinetic Assay

4.1.1.1 How are the concentrations of the pharmacologically active moieties (parent and/or any relevant catabolites) measured in the plasma and other matrices in the clinical pharmacology studies? If applicable, which catabolites have been selected for analysis and why?

Trastuzumab concentrations in human serum were determined using a validated enzyme-linked immunosorbent assay (ELISA). The method for the quantification of SB3, US-licensed Herceptin, and EU-approved Herceptin in human serum was validated at (b) (4).

Briefly, the assay involved 96-well plates coated with monoclonal anti-idiotypic antibody to trastuzumab and blocked using a non-specific protein. Following minimum required dilution, calibration standard and quality controls (QC) samples were added to the designated wells, followed by the addition of peroxidase-conjugated mouse anti-human IgG (Fcγ fragment specific) and then a chromogenic substrate (TMB). The resulting color development was halted using a stop solution and detected with a spectrophotometer. The concentrations of SB3, EU-approved Herceptin, or US-licensed Herceptin in samples were back-calculated from the calibration curve.

Calibration range was initially for 100 to 3000 ng/mL, with quality control (QC) samples at 100, 300, 700, 2100 and 3000 ng/mL. However, selectivity met acceptance criteria only at 250 & 300 ng/mL. Therefore, the assay range was revised (**Table 6**). Calibration curves with less than 6 non-zero standards were rejected.

A summary results of the validation parameters for the trastuzumb assay are shown in **Table 6**.

Table 6: Summary of trastuzumab assay validation

Analyte	SB3	EU-approved Herceptin®	US-licensed Herceptin®
Assay	ELISA		
Matrix	Human Serum		
Reference Standard	Lot P51702A, 150 mg/vial Lot P51715A, 1.07 mg/vial	Lot H4259B01, 150 mg/vial Lot H4792H01, 1.03 mg/ vial	Lot 554761, 440 mg/vial Lot 3202692, 0.97 mg/vial
Minimum required dilution (MRD)	1:50		
Standard Curve	250, 450, 750, 1250, 2250, 3000 ng/mL Anchor points: 100 and 5000 ng/mL	--	--
Standard performance	Accuracy 0.1 to 1.8%, and Precision 3.1 to 5.2 % CV		
QC levels	300, 700, 2100, and 3000 ng/mL		
QC performance: Intra-assay accuracy Intra-assay (%CV) Total Error	 2.2% to 17.2% 0.6% to 17.5% 7.6% to 27.4%	 0.6% to 15.4% 0.8% to 17.3% 8.6% to 28.7%	 5.1% to 17.2% 1.7% to 17.1% 3.9% to 28.4%
Inter-assay accuracy Inter-assay (%CV)	3% to 11.2% 3.7% to 10%	6.4% to 12.2% 4.6% to 12.4%	8.9% to 12.3% 4.5% to 11.3%

Total Error	12.7% to 18.4%	11% to 20%	13.6% to 21.4%
Hook Effect	No hook effect		
Selectivity	Met acceptance criteria at 250 & 300.00 ng/mL		
Interference	No matrix effect		
Dilution linearity	1:100 to 1:400 with 220 µg/mL QC (at the expected Cmax range)		
Matrix Stability:			
Analyte Room Temperature	24 hours at room temperature		
Accuracy	91% to 93%	93% to 94%	85% to 97%
Freeze/Thaw Stability	Up to 6 cycles at ≤ −50°C		
Accuracy	86% to 89%	89% to 100%	88% to 100%
Long-term Stability	At -10ºC: up to 3 months		
Accuracy	89% to 102%	89% to 105%	83% to 94%
	At <-50ºC: up to 18 months		
Accuracy	85% to 115%	80% to 119%	88% to 109%

Study SB3-G11-NHV

In Study SB3-G11-NHV, serum trastuzumab levels were determined using an ELISA as described above at (b) (4). A summary of the assay performance is listed in **Table 7**. Study samples were analyzed in 66 analytical runs. Calibration curves with less than 6 non-zero standards were rejected. Nine analytical runs (14%) were rejected, mainly for not meeting calibration or QC acceptance criteria, affecting PK data from 8 subjects that were excluded from the PK similarity analysis (see Section 3.2.4). All study samples, except predose samples, were diluted. Approximately 91% of observed concentrations (without correcting for dilution) were ≥ 700 ng/mL, with majority ≥ 900 ng/mL. Incurred sample reanalyses of study samples showed that 97% of the reanalyzed samples had differences less than 30% compared to their original values, indicating incurred sample reproducibility. The maximum duration of frozen storage of study samples (85 days) was within the validated long-term storage duration for SB3, EU-approved Herceptin, or US-licensed Herceptin.

Table 7: Summary of in-study assay parameters and performance (Study SB3-G11-HNV)

Analyte	
Matrix	Human Serum
Reference standard	SB3, 147 mg/vial
Minimum required dilution	1:50
Standard curve concentrations (ng/mL)	250, 450, 750, 1250, 2250, and 3000 (ULOQ) ng/mL Anchor Points: 100 ng/mL and, 5000 ng/mL
Standard Performance	Accuracy 0 to 4%, and Precision 2.2 to 3.8 % CV
QCs	300, 700, & 2100 ng/mL
QC Performance:	
Inter-assay accuracy	300 ng/ml: 3.3% 700 ng/ml: 1.4% 2100 ng/ml: 0.5%
Inter-assay precision (%CV)	300 ng/ml: 6.5% 700 ng/ml: 5.8% 2100 ng/ml: 7.2 %

4.2 Sensivity Analyses

4.2.1 Study SB3-G11-NHV

A sensitivity analysis was performed to evaluate the robustness of the study results if the LLOQ was increased to 450 ng/mL. To this effect, calibration range was revised to 450 to 3000 ng/mL, and QC results and study concentrations were restimated. The revised range did not affect did not affect the outcome of the PK biosimilarity analysis (**Table 8**), and the performance of the QCs at 700 and 2100 ng/mL in the analytical runs in the study. Also, the PK parameters (**Table 9**) were similar to the original analysis. Majority of the observed concentrations (without correcting for dilution) were in the 900 ng/mL range or greater.

Table 8: Statisitical analyses for assessment of PK similarity (Study SB3-G11-NHV)

Parameter	Geometric Mean Ratio (90% CI, %)		
	SB3 vs US-Herceptin	**SB3 vs EU-Herceptin**	**EU-Herceptin vs US-Herceptin**
$AUC_{0\text{-last}}$ (µg•h/mL)	93.7 (87.8, 99.9)	97.3 (91.2, 103.8)	96.3 (90.3, 102.6)
AUC_{inf} (µg•h/mL)	93.9 (88.5, 99.7)	97.6 (92.0, 103.6)	96.2 (90.7, 102.1)
C_{max} (µg /mL)	97.9 (91.8, 104.3)	98.9 (92.7, 105.4)	99.0 (92.9, 105.5)
n=34 for SB3 & n=35 for US-Herceptin and EU-Herceptin 2 subjects in SB3 and 1 subject each in US-Herceptin and EU-Herceptin arms were excluded from PK analysis as the analytical runs failed to meet calibration acceptance criteria.. *Source: Reviewer's analysis*			

Table 9: Summary of Single Dose PK Parameter Results (Study SB3-G11-NHV)

	Geometric mean (Geometric %CV)		
Treatment (N)	**$AUC_{0\text{-inf}}$ (µg*h/mL)**	**$AUC_{0\text{-last}}$ (µg*h/mL)**	**C_{max} (µg/mL)**
SB3 (N=34)	36325 (15)	35102 (16)	151 (17)
US-Herceptin (N=35)	38675 (15)	37477 (16)	154 (16)
EU-Herceptin (N=35)	37204 (15)	36072 (17)	153 (16)
Source: Reviewer's analysis			

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/s/

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12/13/2018

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