# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 761100Orig1s000

# NON-CLINICAL REVIEW(S)

# MEMORANDUM

**Date:** December 20, 2018

**From:** Tiffany K. Ricks, PhD

Pharmacology/Toxicology Team Leader (acting)

Division of Hematology Oncology Toxicology (DHOT)

Office of Hematology and Oncology Products (OHOP)

**To:** File for 351 (k) BLA 761100 for SB3

**Re:** Approvability for Pharmacology and Toxicology

The nonclinical data submitted to BLA 761100 were reviewed by C.J. George Chang, PhD. The nonclinical findings are summarized in the “Executive Summary” section of the pharmacology/toxicology BLA review. Based on the determination of similarity of SB3 to US-Herceptin, the nonclinical sections of the labeling should be comparable to the labeling for US-Herceptin.

I concur with Dr. Chang’s conclusion that the submitted pharmacology and toxicology data were adequate to demonstrate similarity in the safety and PK profiles of SB3 and US-Herceptin in cynomolgus monkeys. I concur that the pharmacology and toxicology data support approval of BLA 761100 for SB3 from the pharmacology/toxicology perspective.

---

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

---

/s/

---

TIFFANY RICKS
12/20/2018

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**

# PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION

| | |
|---|---|
| Application number: | 761100 |
| Supporting document/s: | 1 |
| Applicant's letter date: | October 20, 2017 |
| CDER stamp date: | October 20, 2017 |
| Product: | SB3 (proposed biosimilar to trastuzumab |
| Indication: | HER2-overexpressing breast cancer and HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma |
| Applicant: | Samsung Bioepis Co., Ltd.<br>107 Cheomdan-daero, Yeonsu-gu, Incheon<br>Rep of Korea 21987<br>(US Agent: Biologics Consulting Group, Inc.<br>1555 King Street Suite 300, Alexandria, VA<br>22314) |
| Review Division: | Division of Hematology Oncology Toxicology<br>(Division of Oncology Products 1) |
| Reviewer: | C.J. George Chang, DVM, MS, PhD, DABT |
| Supervisor/Team Leader: | Tiffany Ricks, PhD (acting) |
| Division Director: | John K. Leighton, PhD, DABT<br>(Julia Beaver, MD) |
| Project Manager: | Fatima M. Rizvi, RPM |

# TABLE OF CONTENTS

# Table of Tables

# Table of Figures

# 1 Executive Summary

## 1.1 Introduction

Samsung Bioepis Co., Ltd. (Samsung, the applicant) through its agent, Biologics Consulting, Inc., submitted on October 20, 2017 a biologics license application (BLA) under 505(k) biosimilar pathway for SB3 to treat patients with human epidermal growth factor receptor 2 (HER2)-overexpressing breast cancer and HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma. The reference product that the applicant identified is the United States (US)-licensed Herceptin.

The nonclinical efficacy and safety data and the risk assessment for the extractables/leachables in the primary container closure system of SB3 drug product submitted support the approval of this BLA under 505(K) biosimilar pathway from the pharmacology/toxicology perspective.

## 1.2 Brief Discussion of Nonclinical Findings

In a non-GLP mouse xenograft efficacy study, anti-tumor efficacy of SB3/BIIB604 and effects on body weight changes were similar to that of European Union (EU) Herceptin and US Herceptin in an orthotopic BT474 human breast tumor mouse xenograft model.

In a GLP 4-week repeat-dose toxicology study in monkeys, there were no additional drug-related toxicities noted in SB3-treated monkeys when compared with those noted in US-Herceptin (or EU Herceptin)-treated monkeys. Systemic exposure to trastuzumab was similar among monkeys treated with SB3, US Herceptin, or EU Herceptin. No anti-drug antibody was detected in serum samples collected on Days 22 and 29 from monkeys treated with SB3, US Herceptin, or EU Herceptin.

## 1.3 Recommendations

### 1.3.1 Approvability:

Based on the nonclinical pharmacology and toxicology studies and the risk assessment for the extractables/leachables in the primary container closure system of SB3 drug product submitted, this BLA is recommended for approval from the pharmacology/toxicology perspective.

### 1.3.3 Labeling:

Refer to the final approved prescribing Information for the final labeling. Based on the overall determination of similarity of SB3 to US-Licensed Herceptin, the nonclinical sections of the labeling were comparable to those in the label for US-licensed Herceptin.

# 2 Drug Information

## 2.1 Drug

CAS Registry Number: 180288-69-1

Generic Name: Trastuzumab

Code Name: SB3, SAIT103, BIIB604, ED004

Chemical Name: Immunoglobulin G1 (human-mouse monoclonal rhuMAb HER2$\gamma_1$-chain anti-human P185$^{c\text{-}erB2}$ receptor) disulphided with human-mouse monoclonal rhuMAb HER2 light chain, dimer

Molecular Formula/Molecular Weight: $C_{6460}H_{9972}N_{1724}O_{2014}S_{44}$ / 148 kDa (without the N-glycan moiety)

Structure or Biochemical Description:

SB3 (trastuzumab) contains human framework regions with the complementarity-determining regions of a murine antibody (4D5) that binds to HER2. SB3 consists of 1,328 amino acids. The amino acid sequences for the heavy and light chains of SB3 are shown in the figures below.

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

```
  1 EVQLVESGGG LVQPGGSLRL SCAASGFNIK DTYIHWVRQA PGKGLEWVAR
 51 IYPTNGYTRY ADSVKGRFTI SADTSKNTAY LQMNSLRAED TAVYYCSRWG
101 GDGFYAMDYW GQGTLVTVSS ASTKGPSVFP LAPSSKSTSG GTAALGCLVK
151 DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTQT
201 YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP
251 KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN

301 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ
351 VYTLPPSREE MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV
401 LDSDGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK
```

Variable region: Normal letters
Constant region: **Bold underlined letters**
N-linked glycosylation site: *Boxed letter*

(Excerpted from the applicant's submission)

**Figure 2 Amino Acid Sequence of SB3 Light Chain(s)**

```
  1 DIQMTQSPSS LSASVGDRVT ITCRASQDVN TAVAWYQQKP GKAPKLLIYS
 51 ASFLYSGVPS RFSGSRSGTD FTLTISSLQP EDFATYYCQQ HYTTPPTFGQ
101 GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV
151 DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG
201 LSSPVTKSFN RGEC
```

Variable region: Normal letters
Constant region: **Bold underlined letters**

(Excerpted from the applicant's submission)

Pharmacologic Class: HER2/neu receptor antagonist

## 2.2 Relevant INDs, NDAs, BLAs and DMFs

BLA-103792 (Herceptin): Herceptin is the reference product identified by the applicant for this biosimilar BLA.

## 2.3 Drug Formulation

### Table 1 Components and Composition of SB3 Drug Product

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

[a] Specification of SB3 DS (trastuzumab) is provided in CTD Section 3.2.S.4.1.
[b] Name following the list of excipients in the prescribing information (PI). In the National Formulary (NF) monograph, trehalose is presented as α-D-Glucopyranosyl α-D-glucopyranoside and thus α,α-trehalose dihydrate is the same as trehalose dihydrate. It should be noted that where applicable, "α,α-Trehalose dihydrate" is also referred as "Trehalose dihydrate" in the relevant CTD Sections.
(b) (4)

(Excerpted from the applicant's submission)

## 2.4 Comments on Novel Excipients

All excipients are compendial.

## 2.5 Comments on Impurities/Degradants of Concern

The primary container closure system of SB3 drug product has the following components:

1. (b) (4) Glass Vials
2. Rubber Stopper
3. Aluminum Seal
4. (b) (4) Seal Cap

On July 26, 2018, the Office of Biological Products review team requested an opinion from the Pharmacology/Toxicology team regarding the applicant's safety assessment for extractables and leachables from the primary container closure system of SB3 drug product. The applicant performed an extractables study, an extractable/leachable correlation study, and a leachables study.

We reviewed the applicant's summary of study procedures and results and related risk assessment and estimated for the leachables their respective Permissible Daily Exposures (PDEs) while considering the recommendations made by the Product Quality Research Institute (PQRI). We briefly summarized the applicant's studies which are followed by our risk assessments for the qualified leachables.

**Extractables Study**

An extractables study was performed by the applicant using the following two types of model solvents following the requirements set in the draft United States Pharmacopoeia (USP) chapter <1663> by applying either an external calibration method or a spiked internal surrogate standard (IS).

1. 100% isopropyl alcohol (IPA): For the worst case scenario to extract potential organic leachables from the samples using reflux technique for 8 hours. The IPA extracts were directly analyzed through gas chromatography/mass spectrometry (GC/MS) and inductively coupled plasma/mass spectroscopy (ICP/MS) after evaporation of the organic solvent, using USP<232>.

2. 5% IPA with 0.016% Polysorbate 20 (adjusted to pH 2.5): This was an aqueous based media for pressurized extraction and sonication of samples for 8 hours. The aqueous extract samples went through solid phase microextraction (SPME) and analyzed through GC/MS (for more volatile organic compounds (VOC) and semi-volatile organic compounds (SVOC)), liquid chromatography/mass spectrometry (LC/MS) (for non-volatile organic compounds (NVOC)), and inductively coupled plasma/mass spectroscopy (ICP/MS, for trace metals; using USP<232>).

The analytical evaluation thresholds (AETs) of extractable compounds (calculations followed the recommendation published by PQRI for parental products) is 1.5 µg/day or 1.5 µg/dose (SB3 is administered as a single daily dose). The extractable compounds detected to be close to or above the AET level of 1.5 µg/day were monitored closely during the leachable study.

A total of 32 VOCs/SVOCs (identified by GC/MS) and 15 NVOCs (identified by LC/MS), but no metallic impurities, were identified above or close to the AET level from the vial, stopper, seal, and cap when they were extracted separately using the two model solvents.

**Extractables/Leachables Correlation**

An extractable/leachable correlation study was conducted on the primary packaging material of SB3 drug product to establish an extractable/leachable correlation to determine which qualified extractables were present as leachable in the finished drug product. (b) (4) were identified

as volatile leachable components in the finished product above the AET of 1.5 µg/dose level. Those three impurities were from the rubber stopper and potentially needed for toxicological assessment if present in the leachable profile. See table below.

**Table 2 Three Leachable Components of Toxicology Concerns**

| Component | Expected Level in the Drug Product (µg/dose) | CAS Number | Retention Time (min) | Molecular Weight |
|---|---|---|---|---|
| (b) (4) | | | | |

(Excerpted from the applicant's submission)

No non-volatile extractables from LC/MS assay results in leachables in the SB3 finish product, nor any metallic impurities analyzed through ICP/MS were above the USP <232> limits. Two (b) (4) peaks observed in the finished product sample were recognized to be associated with the SB3 drug product formulation but not with the primary container closure system.

**Table 3 SB3 Dosage Recommendation**

| Treated Disease | Initial Loading Dose 3-week Interval | Maintenance Dose 3-week Interval | Initial Loading Dose 1-week Interval | Maintenance Dose 1-week Interval |
|---|---|---|---|---|
| Metastatic and early breast cancer | 8 mg/kg BW | 6 mg/kg BW | 4 mg/kg BW | 2 mg/kg BW |
| Gastric cancer | 8 mg/kg BW | 6 mg/kg BW | Not prescribed | Not prescribed |

(Excerpted from the applicant submission)

No publicly available toxicity testing is available for (b) (4). Assessment of the toxicity of (b) (4) can be based on a read-across from the available toxicology data for (b) (4). See table below for the NOAELs of toxicology studies for these (b) (4).

**Table 4 NOAELs for** (b) (4)

| Compound | Study | NOAEL (PPM) | NOAEL (mg/kg/day) |
|---|---|---|---|
| (b) (4) | | | |

(Excerpted from the applicant's submission)

## Leachables Study

The leachables profile of the primary container closure system of SB3 drug product was established by using the samples collected for up to 6 months in a stability study. See table below.

**Table 5 Stability Sampling Points for SB3 Leachables Study**

| Storage Condition | Initial | 1 Month | 3 Month | 6 Month | 12 Month | 18 Month | 24 Month | 36 Month |
|---|---|---|---|---|---|---|---|---|
| Long-term (5 ± 3°C) | X | X | X | X | X | X | X | X |
| Accelerated (25± 2°C, 60 ± 5% RH) | | X | X | X | X | N/P | N/P | N/P |

X: Tests performed or planned to be performed
N/P: Not planned

(Excerpted from the applicant's submission)

### *Volatile Organic Leachables*

All volatile organic leachables analyzed for known extractables with GC/MS, and results showed that the three identified, targeted leachables were either below the TTC limit or less than the limit of quantitation (LOD) for all time points and storage conditions. In addition, no additional leachables were detected to have a response greater than the AET of 1.5 µg/day. Therefore, there is no need to conduct toxicology assessments for those three targeted leachables. See table below.

**Table 6 Volatile Organic Leachables Assessed through GC/MS Evaluation**

(b) (4)

(Excerpted from the applicant's submission)

***Non-Volatile Leachables***

Stability samples collected up to 6 months were also analyzed for non-volatile leachable organic compounds using LC with ultra-violet (UV) and MS detectors (evaluated against the AET standard of 1.5 µg/day). The following four peak responses were observed to be >1.5 µg/day with values below qualification threshold (QT, at 5 µg/day) which is the threshold at which it is necessary to develop and validate a full quantitative method for monitoring the leachables.

(b) (4)

**Table 7 Non-Volatile Organic Leachables Assessed through LC/UV/MS**

(b) (4)

(Excerpted from the applicant's submission)

***Trace Metal Leachables***

All values of trace metal leachables detected by ICP/MS were below the LOD (2.5 ng/mL) or the PDE listed in USP <232>, except for (b) (4) of which the values ranged from (b) (4)

Therefore, the following four compounds were identified from leachables study with their concentrations above the AET of 1.5 µg/mL recommended by the PQRI:

(b) (4)

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

(b) (4)

**Conclusion**

As the margins of life-time exposure (MoE) are reasonably high for all leachables (b) (4) the components of the leachables in the primary container closure system of SB3 drug product are relatively safe for storage and transport (up to room temperature) and pose negligible risk of adverse health effects with a reasonable margin of safety.

### 2.7 Regulatory Background

None

# 3 Studies Submitted

### 3.1 Studies Reviewed

| Code | Pharmacology | Location |
|---|---|---|
| BIOEP-CP-Y001 | Evaluation of efficacy of SB3/BIIB604 and Herceptin in the treatment of orthotopic BT474 human breast tumor xenograft model + addendum | 4.2.1.1 |
| | **Toxicology** | |
| 523870 | A 4 week repeat dose toxicity study of SB3/BIIB604 by intravenous infusion in Cynomolgus monkeys | 4.2.3.2 |

### 3.2 Studies Not Reviewed

| Code | Pharmacokinetics | Location |
|---|---|---|
| 20041814 | Validation of an enzyme-linked immunosorbent assay (ELISA) method for the determination of SB3/BIIB604, EU Herceptin and US Herceptin in Cynomolgus monkey serum | 4.2.2.1 |
| RD_17820 | Validation of ECL methodology to determine the presence of antibodies to transtuzumab in Cynomolgus monkey serum + amendment | 4.2.2.1 |
| RD_17821 | Validation of methodologies for the formulation and analysis of SB3BIIB604, US Herceptin and EU Herceptin in intravenous dosing solutions + amendment | 4.2.2.1 |

### 3.3 Previous Reviews Referenced

None

# 4 Pharmacology

## 4.1 Primary Pharmacology

**Study title: Evaluation of efficacy of SB3/BIIB604 and Herceptin in the treatment of orthotopic BT474 human breast tumor xenograft model**

| | |
|---|---|
| Study no.: | BIOEP-CP-Y001 |
| Study report location: | 4.2.1.1 |
| Conducting laboratory and location: | (b) (4) |
| Date of study initiation: | May 17, 2013 |
| GLP compliance: | No |
| QA statement: | N/A |
| Drug, lot #, and % purity: | SB3/BIIB604; (b) (4)-002175; 99.0% purity<br>EU Herceptin; Lot #H4115; 99.7% purity<br>US Herceptin: Lot #488865; 99.7% purity |

**Key Study Findings**

- Anti-tumor efficacy of SB3/BIIB604 and effects on body weight changes were similar to that of EU Herceptin and US Herceptin in an orthotopic BT474 human breast tumor mouse xenograft model.

Methods

| | |
|---|---|
| Doses: | 0, 1, 5, and 15 mg/kg |
| Frequency of dosing: | Once weekly for 4 consecutive weeks |
| Route of administration: | Intravenously |
| Dose volume: | Based on actual concentration measured by NanoDrop |
| Formulation/Vehicle: | Formulation buffer and Bacteriostatic Water for Injection (BWFI) |
| Species/Strain: | NOD/SCID mice |
| Number/Sex/Group: | 12 Females/sex/group |
| Age: | 9 weeks old at inoculation |
| Weight: | 16.8 – 24.7 g |
| Satellite groups: | None |
| Unique study design: | See table below |
| Deviation from study protocol: | Not reported |

**Table 10 Design of Efficacy Study in NOD/SCID Mice**

| Group | Treatment | Dose (mg/kg) | *n* | Dosing Route | Schedule |
|---|---|---|---|---|---|
| 1 | Vehicle control | - | 12 | *i.v.* | 1/week x 4 wks |
| 2 | SB3/BIIB604 | 1 | 12 | *i.v.* | 1/week x 4 wks |
| 3 | | 5 | 12 | *i.v.* | 1/week x 4 wks |
| 4 | | 15 | 12 | *i.v.* | 1/week x 4 wks |
| 5 | EU Herceptin® | 1 | 12 | *i.v.* | 1/week x 4 wks |
| 6 | | 5 | 12 | *i.v.* | 1/week x 4 wks |
| 7 | | 15 | 12 | *i.v.* | 1/week x 4 wks |
| 8 | US Herceptin® | 1 | 12 | *i.v.* | 1/week x 4 wks |
| 9 | | 5 | 12 | *i.v.* | 1/week x 4 wks |
| 10 | | 15 | 12 | *i.v.* | 1/week x 4 wks |

Note:

1. *n*: animal number;
2. Dosing volume: adjust dosing volume based on actual concentration measured by NanoDrop, one syringe per each mouse;

The mice were implanted with estrogen pellets (17-estradiol, 0.36 mg/60 days).
The treatment started when the mean BT474 tumor volume (at the fat pad of right mammary gland #3) reached 153 $mm^3$.
(Excerpted from the applicant's submission)

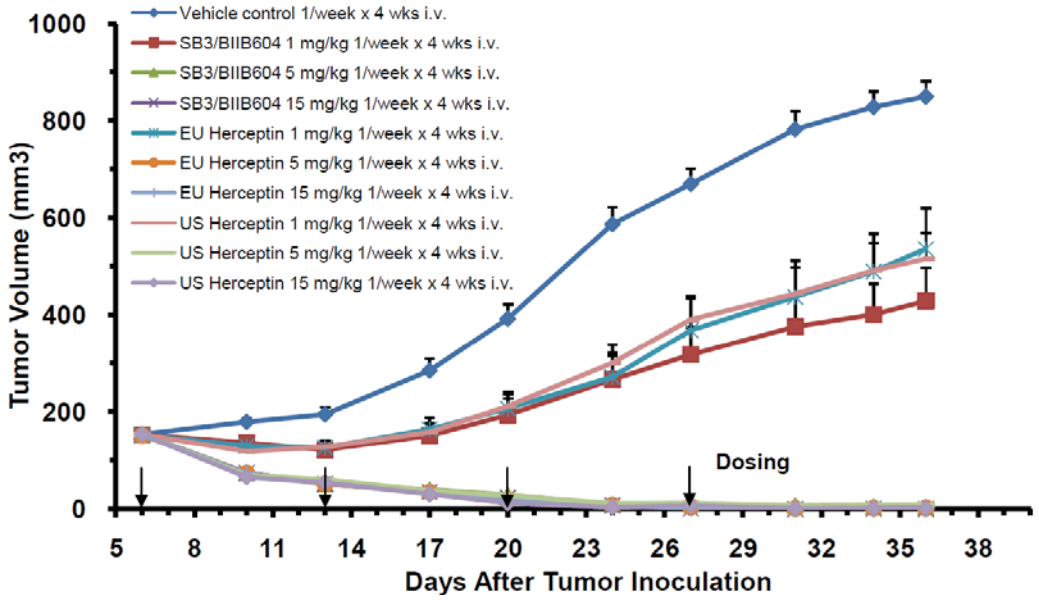
**Observations and Results**

| **Measurements** | **Frequency** |
|---|---|
| Morbidity and Mortality | Daily |
| Clinical Observation | Daily |
| Tumor Growth (Volume) | Twice weekly |

| | |
|---|---|
| Body Weights | Twice weekly |

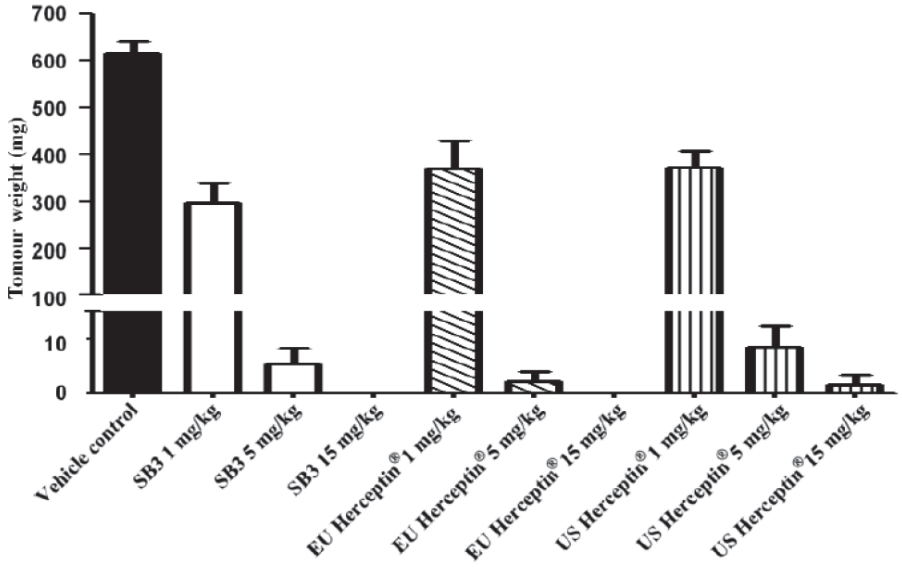
There were no significant differences in tumor volumes and tumor weights of xenografted BT474 human breast tumor at each dose level of SB3/BIIB604, EU Herceptin, and US Herceptin. The anti-tumor effects of B3/BIIB604, EU Herceptin, and US Herceptin were similar, when compared with vehicle controls. Body weight changes during the dosing phase were similar among B3/BIIB604-, EU Herceptin-, or US Herceptin-treated mice. See figures and tables below.

**Figure 3 Antitumor Activity of SB3/BIIB604 and Herceptin in Treating Orthotopic BT474 Human Breast Tumor Xenograft Model – Tumor Volume Measured Twice Weekly**



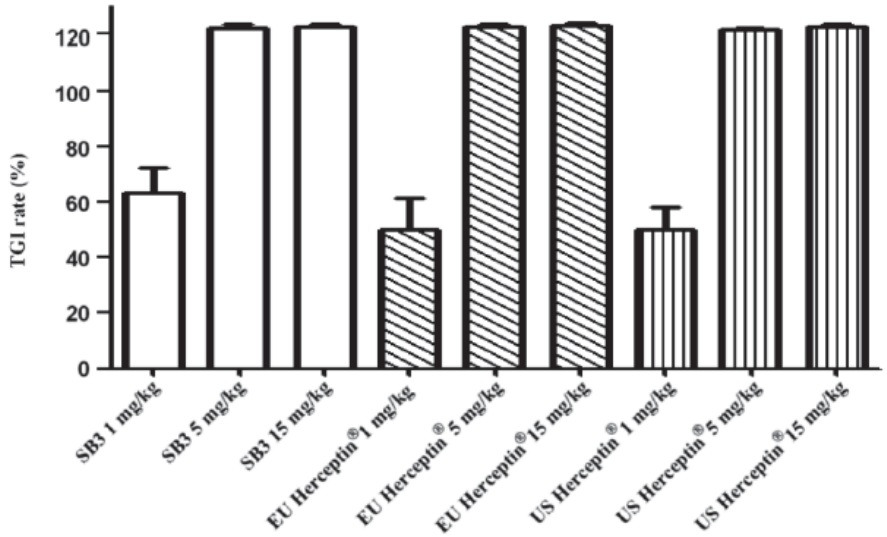

The error bars are standard errors of mean (SEM).
Mice were implanted with estrogen pellets (17-estradiol, 0.36 mg/60 days) at the right flank one day before the tumor inoculation.
(Excerpted from the applicant's submission)

**Figure 4 Group Mean Tumor Weights of Orthotopic BT474 Human Breast Tumor in SB3/BIIB604-, EU Herceptin-, or US Herceptin-Treated Mouse in the Xenograft Model – Tumor Weight Measured at the End of Dosing Phase (Day 36)**




The error bars are SEM.
(Excerpted from the applicant's submission)

**Figure 5 Tumor Growth Inhibition (TGI) Effects of SB3/BIIB604 and Herceptin in Treating Orthotopic BT474 Human Breast Tumor in the Mouse Xenograft Model – Tumor Growth Inhibition (TGI) Rate at the End of Dosing Phase (Day 36)**




TGI: Tumor Growth Inhibition = $[1-(T_{final}-T_{inital})/(C_{final}-C_{initial}))] \times 100\%$
The error bars are SEM.
(Excerpted from the applicant's submission)

For both 1 mg/kg and 5 mg/kg dose groups, there were no significant differences in tumor volume or tumor weight among SB3-, EU Herceptin-, and US Herceptin-treated mice when compared with that of vehicle control. See table below.

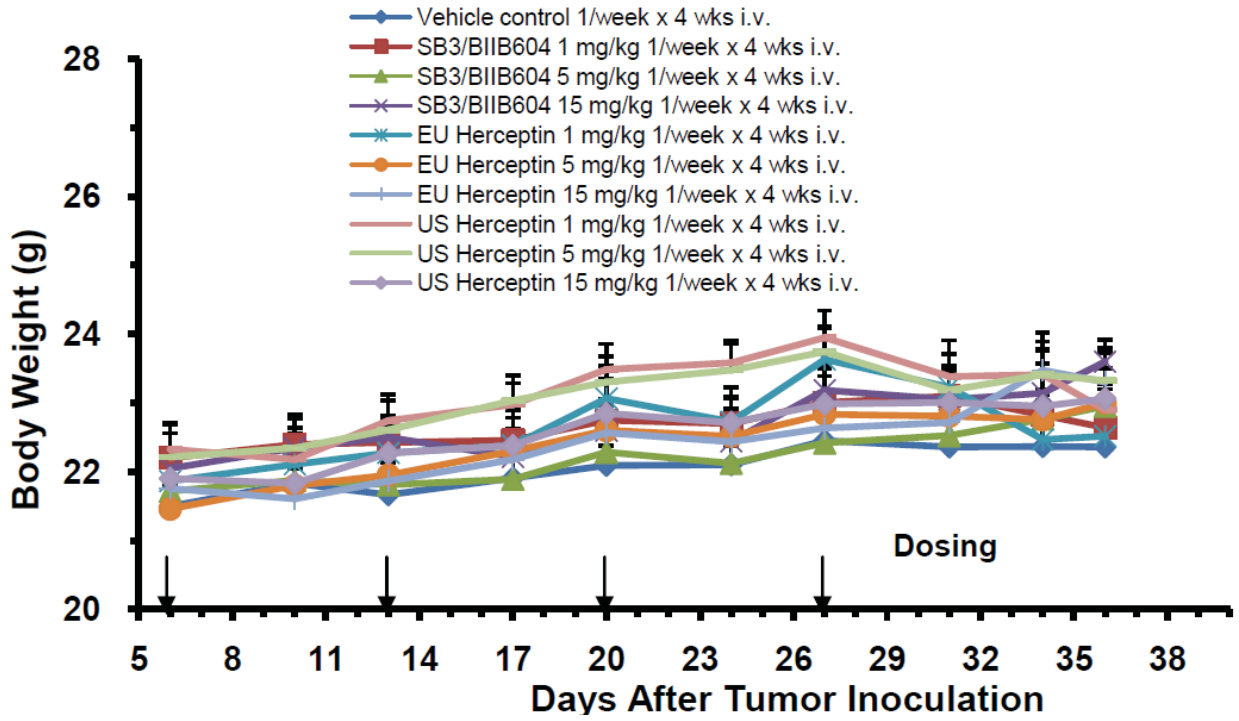
**Table 11 Summary of Statistical Results for BT474 Human Breast Tumor Volume and Tumor Weight at the End of the Dosing Phase (Day 36)**

| Measurement | | Dose: 1 mg/kg | | | Dose: 5 mg/kg | | |
|---|---|---|---|---|---|---|---|
| | | SB3/BIIB604 | EU Herceptin® | US Herceptin® | SB3/BIIB604 | EU Herceptin® | US Herceptin® |
| Tumor volume at study termination | Mean ($mm^3$) | 429 | 536 | 515 | 4 | 2 | 9 |
| | SD | 67 | 85 | 54 | 2 | 2 | 4 |
| | Normality[a] | 0.381 | 0.536 | 0.976 | <0.005 | <0.005 | <0.005 |
| | *p*-value | 0.524[b] | | | 0.669[c] | | |
| Tumor weight at study termination | Mean (mg) | 296.6 | 369.4 | 372.1 | 5.4 | 2.1 | 8.6 |
| | SD | 43.1 | 58.5 | 34.6 | 2.9 | 1.8 | 3.9 |
| | Normality[a] | 0.157 | 0.745 | 0.607 | <0.005 | <0.005 | <0.005 |
| | *p*-value | 0.436[b] | | | 0.679[c] | | |

[a] Result from Anderson-darling test (if the *p*-value is less than 0.05, the data were considered as non-normal distribution.)
[b] Result from one-way ANOVA followed by normality test using Minitab statistical software (normal distribution assumed)
[c] Result from Kruskal-Wallis test followed by normality test using Minitab statistical software (non-normal distribution assumed)

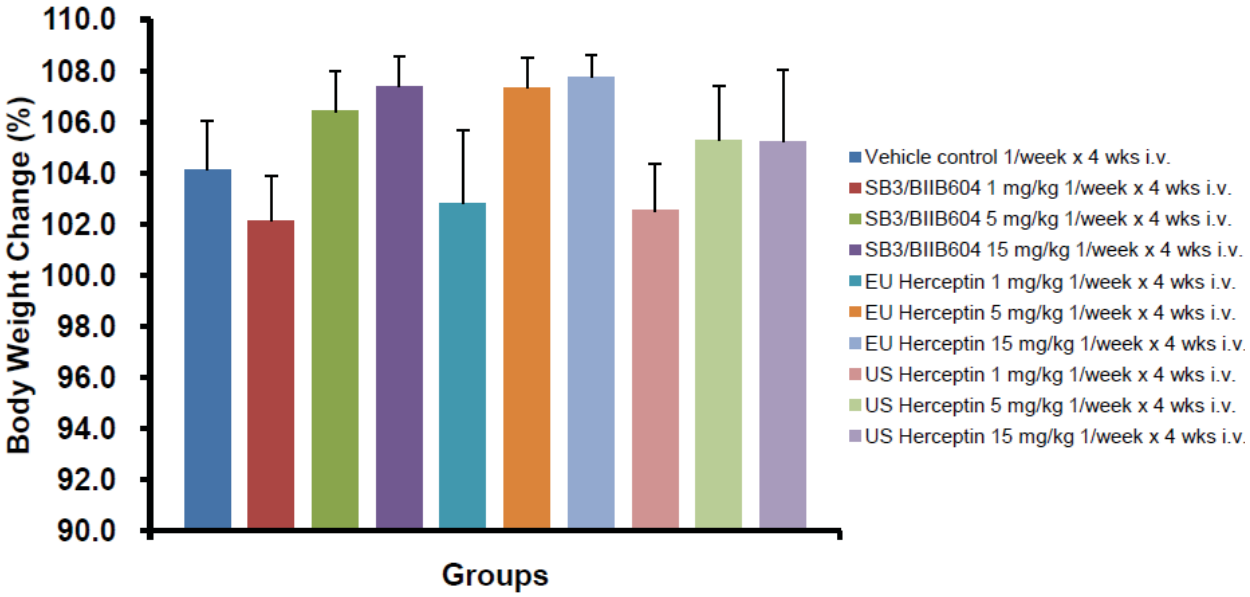
(Excerpted from the applicant's submission)

**Figure 6 Body Weight Changes in the BT474 Human Breast Tumor-Bearing Mice Treated with Vehicle, SB3, EU Herceptin, or US Herceptin**




(Excerpted from the applicant's submission)

**Figure 7 Mouse Body Weight Changes (%) on Day 36 Post Tumor Inoculation**




(Excerpted from the applicant's submission)

# 6 General Toxicology

## 6.2 Repeat-Dose Toxicity

**Study title: A 4 week repeat dose toxicity study of SB3/BIIB604 by intravenous infusion in Cynomolgus monkeys (Report Amendment 1)**

| | |
|---|---|
| Study no.: | 523870 |
| Study report location: | 4.2.3.2 |
| Conducting laboratory and location: | (b) (4) |
| Date of study initiation: | May 30, 2013 |
| GLP compliance: | Yes |
| QA statement: | Provided |
| Drug, lot #, and % purity: | SB3/BIIB604; Batch # (b) (4)-002175; 99.0% purity<br>EU Herceptin; Batch #H0783; 99.7% purity<br>US Herceptin; Lot #488865; 99.7% purity |

**Key Study Findings**

- No additional SB3/BIIB604-related toxicity in monkeys was noted when findings from SB3/BIIB604-treated monkeys were compared to that of US Herceptin- or EU Herceptin-treated monkeys.

- No apparent differences in systemic exposure in monkeys to SB3/BIIB604 existed when exposure values of SB3/BIIB604-treated monkeys are compared with those of US Herceptin- or EU Herceptin-treated monkeys.
- No anti-drug antibody was detected in any of the serum samples collected at pretrial and on Days 22 and 29.

Methods

| | |
|---|---|
| Doses: | SB3/BIIB604: 0 or 25 mg/kg<br>EU Herceptin: 25 mg/kg<br>US Herceptin: 25 mg/kg |
| Frequency of dosing: | Once weekly |
| Route of administration: | Intravenous infusion (in 60 minutes) |
| Dose volume: | 5 mL/kg |
| Formulation/Vehicle: | Formulation buffer |
| Species/Strain: | Cynomolgus monkeys |
| Number/Sex/Group: | 3/sex/group |
| Age: | Not specified |
| Weight: | Males: 2.9-3.4 kg<br>Females: 2.7-3.2 kg |
| Satellite groups: | None |
| Unique study design: | See table below |
| Deviation from study protocol: | None reported were significant. |

**Table 12 Design of Repeat-Dose Toxicology Study**

| Group No. | No. of Animals | | Test Item | Dose Level (mg/kg) | Dose Volume (mL/kg) | Dose Concentration (mg/mL) | Infusion Time (Min) |
|---|---|---|---|---|---|---|---|
| | Male | Female | | | | | |
| 1 | 3 | 3 | Control (Vehicle) | 0 | 5 | 0 | 60 |
| 2 | 3 | 3 | SB3/BIIB604 | 25 | 5 | 5 | 60 |
| 3 | 3 | 3 | EU Herceptin® | 25 | 5 | 5 | 60 |
| 4 | 3 | 3 | US Herceptin® | 25 | 5 | 5 | 60 |

(Excerpted from the applicant's submission)

**Observations and Results**

**Table 13 Measurements Made in the Repeat-Dose Toxicology Study in Monkeys**

| Measurements | Schedule |
|---|---|
| Mortality/Moribundity | Twice daily |
| Clinical observations:<br>Cageside<br>Detailed<br>Postdose | <br>At least once daily<br>At least once weekly<br>During and for the first hour after dosing |
| Body Weight | Weekly |
| Food Consumption | Daily |

<table>
<tr><td>(visual check)</td><td></td></tr>
<tr><td>Ophthalmic Examination</td><td>Pretrial and in Week 4</td></tr>
<tr><td>Electrocardiology: I, II, III, aVR, aVL, aVF leads; P-R, QRS, and Q-T intervals; heart rate</td><td>Pretrial and approximately 24 hours after the last dosing in Week 4</td></tr>
<tr><td>Clinical Pathology: Hematology, coagulation, clinical chemistry, urinalysis</td><td>
<table>
<tr><th>Group Nos.</th><th>Time Point</th><th>Haematology</th><th>Coagulation</th><th>Clinical Chemistry</th><th>Urinalysis</th></tr>
<tr><td>All animals</td><td>Week -1</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>All animals</td><td>Week 4 (Day 27)</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
</table>
X = Sample collected;
</td></tr>
<tr><td>Toxicokinetics</td><td>Days 1 and 22: Predose and 1, 2, 4, 8, 12, 24, 96, and 168 hours postdose</td></tr>
<tr><td>Immunogenicity</td><td>Days 22 and 29</td></tr>
<tr><td>Terminal Sacrifice</td><td>Day 29</td></tr>
<tr><td>Organ Weight</td><td>
<table>
<tr><td>Brain<br>Epididymis[a]<br>Gland, adrenal[a]<br>Gland, pituitary<br>Gland, prostate<br>Gland, thyroid[a]<br>Heart<br>Kidney[a]</td><td>Liver<br>Lung<br>Ovary[a]<br>Spleen<br>Testis[a]<br>Thymus<br>Uterus</td></tr>
</table>
[a] Paired organ weight.
</td></tr>
<tr><td>Pathology</td><td>
<table>
<tr><td>Administration site<br>Animal identification<br>Artery, aorta<br>Bone marrow, femur<br>Bone marrow, sternum<br>Bone, femur<br>Bone, sternum<br>Brain<br>Cervix<br>Epididymis<br>Eye[a]<br>Gallbladder<br>Gland, adrenal<br>Gland, lacrimal<br>Gland, mammary<br>Gland, parathyroid<br>Gland, pituitary<br>Gland, prostate<br>Gland, salivary<br>Gland, thyroid<br>Gross lesions/masses<br>Gut-associated lymphoid tissue<br>Heart<br>Kidney<br>Large intestine, caecum<br>Large intestine, colon<br>Large intestine, rectum</td><td>Liver<br>Lung<br>Lymph node, lumbar<br>Lymph node, mandibular<br>Lymph node, mesenteric<br>Muscle, skeletal<br>Nerve, optic[a]<br>Nerve, sciatic<br>Oesophagus<br>Ovary<br>Oviduct<br>Pancreas<br>Skin<br>Small intestine, duodenum<br>Small intestine, ileum<br>Small intestine, jejunum<br>Spinal cord<br>Spleen<br>Stomach<br>Testis[b]<br>Thymus<br>Tongue<br>Trachea<br>Ureter<br>Urinary bladder<br>Uterus<br>Vagina</td></tr>
</table>
[a] Preserved in Davidson's fixative.<br>[b] Preserved in Modified Davidson's fixative.
</td></tr>
<tr><td>Bone Marrow Smear Analysis</td><td>Day 29; smears prepared but not evaluated</td></tr>
</table>

**Mortality**

No early mortalities occurred.

**Clinical Signs**

No drug-related clinical signs of toxicity were noted.

**Body Weights**

No drug-related changes in body weight or body weight gain were noted.

**Feed Consumption**

No food consumption results were presented in the report.

**Ophthalmoscopy**

No drug-related ocular changes were noted.

**ECG**

No drug-related changes in electrocardiography were noted.

**Hematology and Coagulation**

No drug-related changes in hematology and coagulation parameters were noted.

**Clinical Chemistry**

No significant drug-related changes in clinical chemistry parameters were noted.

**Urinalysis**

No drug-related changes in urinalysis parameters were noted.

**Gross Pathology**

No drug-related gross pathology findings were noted.

**Organ Weights**

No drug-related changes in organ weight were noted.

**Histopathology**

Adequate Battery: Sufficient

Peer Review: Performed

Histological Findings

No drug-related microscopic findings were noted.

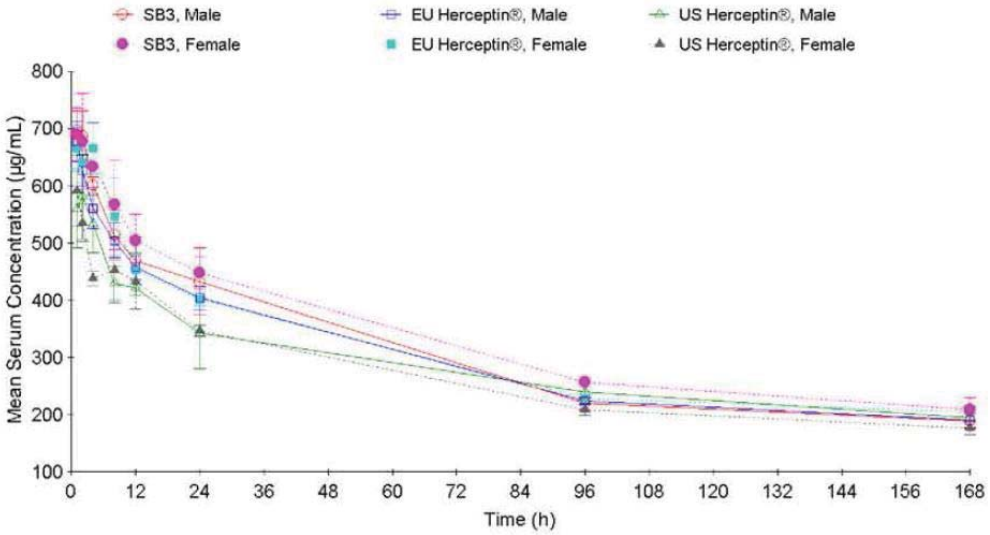
**Special Evaluation - Immunogenicity**

No anti-drug antibodies (ADA) were detected from any of the serum samples collected at pretrial and on Days 22 and 29.

**Toxicokinetics**

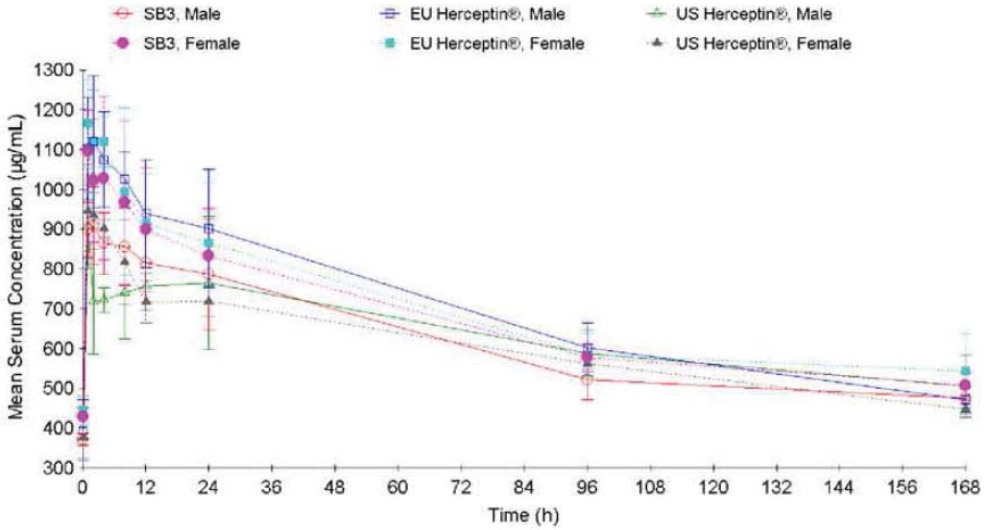
Systemic exposure to trastuzumab, in terms of $AUC_{0-t}$ and $C_{max}$, was comparable between males and females for both Days 1 and 21. See figures and table below.

**Figure 8 Group Mean Serum Concentrations of Trastuzumab in Monkeys following Weekly Intravenous Infusion Administration of 25 mg/kg SB3, EU Herceptin or US Herceptin (Day 1)**




(Excerpted from the applicant's submission)

**Table 14 Group Mean Serum Concentrations of Trastuzumab in Monkeys following Weekly Intravenous Infusion Administration of 25 mg/kg SB3, EU Herceptin or US Herceptin (Day 22)**




(Excerpted from the applicant's submission)

**Table 15 Toxicokinetic Parameters in Monkeys Following Intravenous Administration of SB3, EU Herceptin, or US Herceptin**

| Dose (mg/kg) | Day | Sex | $AUC_{(0-t)}$ (µg•h/mL) | | | $C_{max}$ (µg/mL) | | |
|---|---|---|---|---|---|---|---|---|
| | | | SB3 | EU Herceptin® | US Herceptin® | SB3 | EU Herceptin® | US Herceptin® |
| 25 | 1 | Female | 54,700 | 50,100 | 43,900 | 698 | 694 | 591 |
| | | Male | 50,100 | 48,900 | 46,800 | 702 | 678 | 616 |
| | 22 | Female | 112,000 | 116,000 | 101,000 | 1,110 | 1,170 | 987 |
| | | Male | 103,000 | 116,000 | 106,000 | 919 | 1,160 | 952 |

(Excepted from the applicant's submission)

Exposure to trastuzumab, in terms of AUC/dose, increased by 2.1 to 2.3 folds after repeated doses when comparing Day 22 to Day 1 values for SB3 (2.1:1), EU Herceptin (2.3:1), and US Herceptin (2.3:1). See table below.

**Table 16 Toxicokinetic Parameters of Trastuzumab in Monkey Serum Samples (Sex-Combined) following Weekly Intravenous Doses of 25 mg/kg of SB3, EU Herceptin, or US Herceptin for 4 Consecutive Weeks**

| Sample Day | Test Item | Cmax (µg/mL) | Cmax/D (µg/mL)/(mg/kg) | Tmax (h) | AUC(0-t) (µg.h/mL) | AUC(0-t)/D (µg.h/mL)/(mg/kg) | CL (mL/h/kg) | Vd (mL/kg) | T1/2 (h) |
|---|---|---|---|---|---|---|---|---|---|
| Day 1 | SB3 | 700 (41.4) | 28.0 (1.65) | 1.00 | 52400 (4190) | 2090 (168) | NR | NR | NR |
| | EU Herceptin® | 686 (31.0) | 27.4 (1.24) | 1.00 | 49500 (1890) | 1980 (75.5) | NR | NR | NR |
| | US Herceptin® | 604 (54.6) | 24.2 (2.18) | 1.00 | 45300 (3520) | 1810 (141) | NR | NR | NR |
| Day 22 | SB3 | 1020 (147) | 40.6 (5.89) | 1.50 | 107000 (10300) | 4290 (413) | 0.235 (0.0229) | NR | NR |
| | EU Herceptin® | 1170 (94.7) | 46.8 (3.79) | 2.00 | 116000 (13200) | 4630 (527) | 0.218 (0.0258) | NR | NR |
| | US Herceptin® | 970 (42.2) | 38.8 (1.69) | 1.00 | 103000 (9210) | 4140 (368) | 0.243 (0.0193) | NR | NR |

N = 6 for males and females combined.
Arithmetic mean (SD) reported for all parameters except for Tmax where median only is reported.
NR = Not reported, in all cases the extrapolation of the AUC to infinity represented more than 20% of the total area.
Note: On Day 22 CL and Vd estimates calculated using AUC(0-tau) where tau was the dosing interval (168 h).

(Excerpted from the applicant's submission)

The exposure ratios (in terms of $AUC_{0-t}$) of SB3 vs US Herceptin were 1.1 for Day 1 and 1.0 for Day 22 in male monkeys and were 1.2 for Day 1 and 1.1 for Day 22 in female monkeys. The exposure ratios (in terms of $AUC_{0-t}$) of SB3 vs EU Herceptin were 1.0 for Day 1 and 0.9 for Day 22 in male monkeys and were 1.1 for Day 1 and 1.0 for Day 22 in female monkeys. See table below.

**Table 17 Comparative Ratios of Exposure Parameters of Trastuzumab in Monkey Serum following Weekly Intravenous Doses of 25 mg/kg for 4 Consecutive Weeks**

| Comparison | Sample Day | Male | | Female | |
|---|---|---|---|---|---|
| | | Ratio Cmax | Ratio AUC(0-t) | Ratio Cmax | Ratio AUC(0-t) |
| SB3 vs EU Herceptin® | Day 1 | 1.0 | 1.0 | 1.0 | 1.1 |
| | Day 22 | 0.8 | 0.9 | 0.9 | 1.0 |
| SB3 vs US Herceptin® | Day 1 | 1.1 | 1.1 | 1.2 | 1.2 |
| | Day 22 | 1.0 | 1.0 | 1.1 | 1.1 |

Ratios based on mean parameter estimates for the comparisons SB3/EU or SB3/US Herceptin® on each sample day.

(Excerpted from the applicant's submission)

**Dosing Solution Analysis**

Analytical results showed that the concentrations of all dosing formulations were within 95% to 104% to targets. See table below.

**Table 18 Analytical Results of Dose Formulations**

| Treatment Group | Theoretical Concentration (mg/mL) | Week | Found Concentrations (mg/mL) | | Mean Found Concentration (mg/mL) | % Difference from Theoretical Concentration |
|---|---|---|---|---|---|---|
| 1 | 0 | 1 | 0 | 0 | 0 | 0 |
| | | 2 | 0 | 0 | 0 | 0 |
| | | 3 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 |
| 2 | 5.0 | 1 | 5.04 | 5.25 | 5.15 | 3.0 |
| | | 2 | 5.21 | 5.10 | 5.16 | 3.2 |
| | | 3 | 5.15 | 5.25 | 5.20 | 4.0 |
| | | 4 | 5.06 | 5.19 | 5.13 | 2.6 |
| 3 | 5.0 | 1 | 5.06 | 5.06 | 5.06 | 1.2 |
| | | 2 | 4.80 | 4.88 | 4.84 | -3.2 |
| | | 3 | 4.92 | 4.97 | 4.95 | -1.0 |
| | | 4 | 4.94 | 4.92 | 4.93 | -1.4 |
| 4 | 5.0 | 1 | 4.86 | 4.86 | 4.86 | -2.8 |
| | | 2 | 4.85 | 4.68 | 4.77 | -4.6 |
| | | 3 | 4.81 | 4.86 | 4.84 | -3.2 |
| | | 4 | 4.79 | 4.70 | 4.75 | -5.0 |

(Excerpted from the applicant's 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.**

---

/s/
---

CHING-JEY G CHANG
12/20/2018

TIFFANY RICKS
12/20/2018