CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761106Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	351(a) BLA
Application Number(s)	761106
Priority or Standard	Standard
Submit Date(s)	May 1, 2018
Received Date(s)	May 1, 2018
PDUFA Goal Date	March 1, 2019
Division/Office	Division of Oncology Products 1 (DOP1)
Review Completion Date	*Electronic Stamp Date*
Established Name	Trastuzumab and hyaluronidase
(Proposed) Trade Name	Herceptin Hylecta
Pharmacologic Class	Combination of trastuzumab, a humanized IgG1 kappa monoclonal antibody against HER2, and hyaluronidase, an endoglycosidase
Applicant	Genentech, Inc.
Formulation(s)	For injection: 600 mg/5 mL solution for subcutaneous injection in a fixed-dose vial (do not reconstitute or dilute).
Dosing Regimen	600 mg every 3 weeks administered subcutaneously over 2-5 minutes
Applicant Proposed Indication(s)/Population(s)	**Adjuvant Breast Cancer** HERCEPTIN HYLECTA is indicated for adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature breast cancer • as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel • as part of a treatment regimen with docetaxel and carboplatin • as a single agent following multi-modality anthracycline based therapy. Select patients for therapy based on an FDA-approved companion diagnostic for (b) (4). **Metastatic Breast Cancer (MBC)** HERCEPTIN HYLECTA is indicated: • In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer • As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease. Select patients for therapy based on an FDA-approved companion diagnostic for (b) (4).
Recommendation on Regulatory Action	*Approval*

Recommended Indication(s)/Population(s)	**Adjuvant Breast Cancer** HERCEPTIN HYLECTA is indicated for adjuvant treatment of adults with HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature breast cancer • as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel • as part of a treatment regimen with docetaxel and carboplatin • as a single agent following multi-modality anthracycline based therapy. Select patients for therapy based on an FDA-approved companion diagnostic for trastuzumab. **Metastatic Breast Cancer** HERCEPTIN HYLECTA is indicated in adults: • In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer • As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease. Select patients for therapy based on an FDA-approved companion diagnostic for trastuzumab.

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Amy Tilley
Nonclinical Reviewer	Haw-Jyh Chiu, PhD
Nonclinical Team Leader	Tiffany K Ricks, PhD
Office of Clinical Pharmacology Reviewer(s)	Huiming Xia PhD-Clinical Pharmacology Fang Li, PhD-Pharmacometrics
Office of Clinical Pharmacology Team Leader(s)	Pengfei Song, PhD, Jingyu (Jerry) Yu, PhD
Clinical Reviewer	Danielle Krol, MD – Clinical Efficacy Candace Mainor, MD – Safety
Acting Clinical Team Leader	Jennifer Gao, MD
Statistical Reviewer	Laura Fernandes, PhD
Statistical Team Leader	Shenghui Tang, PhD
Associate Director for Labeling	William Pierce, PharmD
Acting Cross-Disciplinary Team Leader	Jennifer Gao, MD
Division Director (DHOT)	John K Leighton, PhD, DABT
Division Director (OCP)	Nam Atiqur Rahman, PhD
Division Director (OB)	Thomas Gwise, PhD
Supervisory Associate Director (DOP1)	Laleh Amiri-Kordestani, MD
Office Director (or designated signatory authority)	Laleh Amiri-Kordestani, MD

Additional Reviewers of Application

OBP	Shadia Zaman / Scott Dallas / Wendy Weinberg / Brian Janelsins / Kathleen Clouse
Microbiology	Madushini Dharmasena / Diane Raccasi / Reyes Candau-Chacon / Patricia Hughes
OPDP	Kevin Wright / Brian Tran
OSI	Lauren Iacono-Connor / Susan Thompson
OSE/DEPI	Carolyn McCloskey / Steven Bird
OSE/DMEPA	Tingting Gao / Alice Tu
OSE/DRISK	Till Olickall / Elizabeth Everhart
Other / Clinical Analyst	Yutao Gong

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report

PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Trastuzumab and hyaluronidase-oysk injection, for subcutaneous use (Herceptin Hylecta, which will be referred to as subcutaneous [SC] trastuzumab throughout this review) is a biological product which contains two active ingredients. Hyaluronidase is an endoglycosidase. 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 a part of the HER family of transmembrane tyrosine kinases that have been shown to play a role in the regulation of cellular survival, proliferation, adhesion, and differentiation.

SC trastuzumab offers patients with breast cancer a different route of administration than Herceptin intravenous (which will be referred to as intravenous [IV] trastuzumab throughout this review). Aside from the different route of administration, other aspects different in comparing SC trastuzumab to IV trastuzumab include: 1) combination with hyaluronidase and flat dose of SC trastuzumab, and 2) SC administration takes place over 2-5 minutes.

The recommended dose of SC trastuzumab is 600 mg/10,000 units (600 mg trastuzumab and 10,000 units hyaluronidase) administered SC over approximately 2-5 minutes once every 3 weeks. No loading dose or dose adjustments for a patient's body weight or for different concomitant chemotherapy regimens are required when used in the adjuvant setting. Patients with adjuvant breast cancer should be treated with SC trastuzumab for 52 weeks or until disease recurrence, whichever occurs first and extending treatment beyond one year is not recommended. Patients with metastatic breast cancer (MBC) should be treated until progression of disease.

The applicant is seeking breast cancer indications that are the same as intravenous trastuzumab. The applicant is not seeking the metastatic gastric or gastroesophageal junction adenocarcinoma indications due to pharmacokinetic differences expected in this patient population.

The applicant's proposed indication at the time of BLA submission were:

Adjuvant Breast Cancer

HERCEPTIN HYLECTA is indicated for adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature breast cancer

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

Select patients for therapy based on an FDA-approved companion diagnostic for (b) (4)

Metastatic Breast Cancer (MBC)

HERCEPTIN HYLECTA is indicated:

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

Select patients for therapy based on an FDA-approved companion diagnostic for (b) (4)

The recommendation for the approval of SC trastuzumab is primarily based on the efficacy and safety from study BO22227 (HannaH), a randomized (1:1), phase III, open-label, multi-center, global, comparability study of SC trastuzumab vs. IV trastuzumab administered in the neoadjuvant and adjuvant settings with chemotherapy for the treatment of early breast cancer. The co-primary endpoints were pathological complete response (pCR) in the breast only at the time of definitive surgery after Cycle 8 and C_{trough} at the end of Cycle 7 (before the Cycle 8 dose). The co-primary endpoints were met, with pCR and C_{trough} at the end of Cycle 7 comparable between the SC trastuzumab and IV trastuzumab study arms. Extrapolation to the proposed MBC indication is based on:

- Comparable PK profiles of IV trastuzumab across the neoadjuvant-adjuvant/adjuvant treatment settings in patients with early breast cancer (EBC) and metastatic breast cancer (EBC)
- Neoadjuvant-adjuvant treatment as used in HannaH is a sensitive setting for establishing clinical similarity of efficacy and immunogenicity
- Mode of action of trastuzumab in the EBC and MBC are the same.

The recommended indications are:

Adjuvant Breast Cancer

HERCEPTIN HYLECTA is indicated for adjuvant treatment of adults with HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature breast cancer

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

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

Metastatic Breast Cancer

HERCEPTIN HYLECTA is indicated in adults:

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

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

1.2. Conclusions on the Substantial Evidence of Effectiveness

This recommendation for the regular approval of HERCEPTIN HYLECTA, according to 21 Code of Federal Regulations (CFR) 314.126(a)(b), is based on efficacy and safety data from the HannaH study. This study's co-primary endpoints were pathological complete response (pCR) in the breast only at the time of definitive surgery after Cycle 8 and C_{trough} at the end of Cycle 7 (before the Cycle 8 dose). In the primary analysis in the efficacy per-protocol population (EPP), pCR rates were 40.7% (95% CI: 34.7%, 46.9%) in the IV trastuzumab arm and 45.4% (95% CI: 39.2%, 51.7%) in the SC trastuzumab arm, resulting in an absolute difference of 4.7% in favor of the SC trastuzumab arm. Subgroup analyses suggest efficacy of SC trastuzumab was not worse when compared to IV trastuzumab in different body weight groups under the flat dosing schedule. The SC trastuzumab arm achieved equal or higher C_{trough} across treatment cycles compared to the IV trastuzumab arm, with geometric mean ratio of 1.3 (90% CI: 1.2-1.4). The safety profile of SC trastuzumab was compared with IV trastuzumab with special attention to cardiac, pulmonary, administration-related reactions, and embryo-fetal toxicities. Administration-related reactions for SC trastuzumab were the only newly identified safety signals. Safety was also evaluated across different body weight subgroups with no new safety signals identified other than administration-related reactions.

Even though at the EOP2 meeting in 2010, FDA stated DFS is the preferred primary endpoint for HannaH and the proposed pharmacokinetic endpoint of C_{trough} at the end of cycle 7 would be exploratory, the development approach of SC trastuzumab is consistent with FDA Guidance on "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products", which states the following: "In certain cases, effectiveness of an approved drug product for a new indication, or effectiveness of a new product, may be adequately demonstrated without additional adequate and well-controlled clinical efficacy trials. Ordinarily, this will be because other types of data provide a way to apply the known effectiveness to a new population or a different dose, regimen or dosage form." When being applied to different doses, regimens, or dosage forms, the above FDA Guidance states that "it may be possible to conclude that a new dose, regimen, or dosage form is effective on the basis of PK data without an additional clinical efficacy trial". In the current application, PK data, together with comparable pCR rates from HannaH study can bridge to establish safety and efficacy results between IV trastuzumab to SC trastuzumab in all breast cancer indications.

Two additional studies were submitted by the applicant in support of the BLA. Study MO28048 (SafeHER) is an ongoing phase III, prospective, two-cohort, non-randomized, multicenter, open-label study looking at the safety and tolerability of SC trastuzumab in the early breast cancer setting. Study MO22982 (PrefHER) is a completed phase II, international, randomized, multicenter, open-label, two-cohort and two-arm cross-over study in the early breast cancer setting designed to look at patient preference.

All disciplines reviewing this BLA agreed with approval of SC trastuzumab or did not identify any outstanding issues that precluded approval. In summary SC trastuzumab demonstrated a favorable benefit-risk profile with enough evidence to recommend approval.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

In the United States (US), breast cancer is the most common cancer in women, with more than 260000 new cases and 40000 deaths annually. Approximately 20% of breast cancers strongly overexpress human epidermal growth factor receptor 2 (HER2) which is a protein that belongs to the HER family. HER2 overexpression in breast cancer is associated with more aggressive disease and an increased recurrence and despite advances in treatment of patients with HER2-positive early breast cancer with anti-HER2 therapies, there remain a proportion of patients who go on to develop distant recurrences which can be associated with significant morbidity and decline in function. Once HER2-positive breast cancer recurs distantly, it is no longer curable, and these patients will eventually die due to metastatic disease.

In the adjuvant treatment setting, FDA approved therapies for patients with HER2+ breast cancer currently include intravenous trastuzumab (improvement in disease free survival and overall survival with addition of intravenous trastuzumab to chemotherapy), pertuzumab (improvement in invasive disease free survival when pertuzumab added to intravenous trastuzumab and chemotherapy), neratinib (improvement in invasive disease free survival in the extended adjuvant treatment setting following trastuzumab-based therapy), and 3 intravenous trastuzumab biosimilars (trastuzumab-dkst, trastuzumab-pkrb, and trastuzumab-dttb). In the metastatic treatment setting, FDA approved therapies for patients with HER2+ breast cancer currently include intravenous trastuzumab (improvement in time to progression and overall response rate), lapatinib (improvement in time to progression with the addition of lapatinib to capecitabine compared to capecitabine alone), pertuzumab (improvement in progression free survival and overall survival), and 3 intravenous trastuzumab biosimilars (trastuzumab-dkst, trastuzumab-pkrb, and trastuzumab-dttb).

Trastuzumab and hyaluronidase-oysk is a subcutaneous (SC) formulation of trastuzumab and provides patients with a different dosing regimen and route of administration compare to intravenous (IV) trastuzumab. The HannaH study met its co-primary endpoints of pCR in the breast only at the time of definitive surgery and C_{trough} at cycle 7. The pCR rates were 40.7% (95% CI: 34.7%, 46.9%) in the IV trastuzumab arm and 45.4% (95% CI: 39.2%, 51.7%) in the SC trastuzumab arm in the efficacy per protocol population. Subgroup analyses suggest efficacy of SC trastuzumab was not worse when compared to IV trastuzumab in different body weight groups under the flat dosing schedule. The SC trastuzumab arm achieved equal or higher C_{trough} across treatment cycles compared to the IV trastuzumab arm, with geometric mean ratio of 1.3 (90% CI: 1.2-1.4).

The safety profile in the HannaH and SafeHER (safety and tolerability study) of SC trastuzumab was similar with IV trastuzumab,

aside from an increase in administration-related reactions. Safety was also evaluated across different body weight subgroups with similar findings. Results from the patient preference study (PrefHER) suggest patients preferred the SC route due to time.

In conclusion, the efficacy and safety of SC trastuzumab was comparable to IV trastuzumab and offers a new route of administration for patients with HER2-positive breast cancer. The safety profile is acceptable in the intended population. Appropriate labeling was included in labeling for Dosage and Administration, for the route of administration of SC trastuzumab and in Warnings and Precautions for cardiomyopathy, hypersensitivity and administration-related reactions, embryo-fetal toxicity, pulmonary toxicity, and exacerbation of chemotherapy induced neutropenia.

HERCEPTIN HYLECTA is recommended for approval for the following indications:

Adjuvant Breast Cancer

HERCEPTIN HYLECTA is indicated for adjuvant treatment of adults with HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature breast cancer

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

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

Metastatic Breast Cancer

HERCEPTIN HYLECTA is indicated in adults:

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

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

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• In 2018, it is estimated that there will be over 260000 new cases of breast cancer. • HER2-positive breast cancer accounts for ~20% of breast cancer diagnoses.	HER2-positive breast cancer is a serious and life- threatening disease.
Current Treatment Options	• Adjuvant setting: o Intravenous trastuzumab o Pertuzumab o Neratinib o 3 intravenous trastuzumab biosimilars • Metastatic setting: o Intravenous trastuzumab o Lapatinib o Pertuzumab o 3 intravenous trastuzumab biosimilars: trastuzumab-dkst, trastuzumab-pkrb, and trastuzumab-dttb	Treatment options for HER2-positive breast cancer depends on the stage. SC trastuzumab provides patients with an option for an alternative route of administration in the adjuvant and metastatic settings.
Benefit	• The HannaH study met its co-primary endpoints of pCR in the breast only at the time of definitive surgery and Ctrough at cycle 7. The pCR rates were 40.7% (95% CI: 34.7%, 46.9%) in the IV trastuzumab arm and 45.4% (95% CI: 39.2%, 51.7%) in the SC trastuzumab arm in the efficacy per protocol population. Subgroup analyses suggest efficacy of SC trastuzumab was not worse when compared to IV trastuzumab in different body weight groups under the flat dosing schedule. The SC trastuzumab arm achieved equal or higher C_{trough} across treatment cycles compared to the IV trastuzumab arm, with geometric mean ratio of 1.3 (90% CI: 1.2-1.4). • In the PrefHER study, patients reported preferring the SC route of administration over IV, primarily due to time.	The efficacy of SC trastuzumab is comparable to IV trastuzumab. Results from the PrefHER study show patients prefer the SC route of administration due to time.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• Safety data from the HannaH and SafeHER studies show the safety profile of SC trastuzumab was comparable to IV trastuzumab, except for increased administration-related reactions. • Safety was evaluated across different body weight subgroups with no new safety signals identified.	The safety profile of SC trastuzumab is acceptable for the intended population. There were higher administration-related reaction adverse events with SC trastuzumab and this is included in the USPI Warnings and Precautions. SC trastuzumab should not be given intravenously and this is included in the USPI Dosage and Administrations. SC trastuzumab is not indicated for use used in patients with metastatic gastric or gastroesophageal junction adenocarcinoma. The safe use of SC trastuzumab can be managed through accurate labeling and routine oncology care. No REMS is indicated.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application

□	The patient experience data that was submitted as part of the application, include:				Section where discussed, if applicable
	x	Clinical outcome assessment (COA) data, such as			
			x	Patient reported outcome (PRO)	Section 8.3
			□	Observer reported outcome (ObsRO)	
			□	Clinician reported outcome (ClinRO)	
			□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			
	□	Patient-focused drug development or other stakeholder meeting summary reports			
	□	Observational survey studies designed to capture patient experience data			
	□	Natural history studies			
	x	Patient preference studies (e.g., submitted studies or scientific publications)			Sections 7.3.3 and 8.3
	□	Other: (Please specify)			
□	Patient experience data that was not submitted in the application, but was considered in this review.				

X

Jennifer Gao, MD
Acting Cross-Disciplinary Team Leader

2. Therapeutic Context

In the United States (US), breast cancer is the most common cancer in women, with an estimated 266,120 cases expected in 2018[1]. It is the second most common cause of cancer-related death in women in the US, with an estimated 40, 920 deaths expected for 2018[1].

Human epidermal growth factor receptor 2 protein (HER2/neu) receptor overexpressed breast cancer accounts for ~20% of breast cancer diagnoses. HER2 overexpression in breast cancer is associated with more aggressive disease and an increased recurrence rate. Historically, HER2/neu receptor over-expressed was associated with a poor prognosis, but with the advent of trastuzumab based therapy for the treatment of breast cancer, the prognosis of HER2/neu overexpressed breast cancer has improved. Despite advances in treatment of patients with HER2-positive EBC, patient still develop metastatic disease.

2.1. Analysis of Current Treatment Options

The FDA approved HER2-targeted therapies are listed below in Table 1.

Table 1: Summary of FDA Approved HER2-Targeted Therapies

Product Name	Relevant Indication	Year of Approval	Dosing and Administration	Efficacy Information	Important Safety and Tolerability Issues
Trastuzumab (IV, Herceptin)	HER2 overexpressing breast cancer HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma	1998	Adjuvant breast cancer (52 weeks total): -4mg/kg load, then 2mg/kg weekly with taxane, then 6mg/kg every 3 weeks -After anthracycline based chemotherapy 8mg/kg load, then 6mg/kg every 3 weeks Metastatic breast cancer: 4mg/kg load, then 2mg/kg weekly	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

[1] National Cancer Institute, Surveillance, Epidemiology, and End Result Program (2018, May). Cancer Stat Facts: Female Breast Cancer. Retrieved from: https://seer.cancer.gov/statfacts/html/breast.html
[2] Mitri Z, Constantine T, O'Regan R. The HER2 Receptor in Breast Cancer: Pathophysiology, Clinical Use, and New Advances in Therapy. *Chemother Res Pract*. 2012;2012:743193.

			Metastatic gastric cancer: 8mg/kg load, then 6mg/kg every 3 weeks		
Lapatinib (PO, Tykerb)	In combination with: - capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress human epidermal growth factor receptor 2 (HER2) and who have received prior therapy including an anthracycline, a taxane, and trastuzumab. Limitations of Use: Patients should have disease progression on trastuzumab prior to initiation of treatment with TYKERB in combination with capecitabine. - letrozole for the treatment of postmenopausal women with hormone receptor-positive metastatic breast cancer that overexpresses the HER2 receptor for whom hormonal therapy is indicated.	2007	HER2+ MBC: 1,250 mg PO once daily on Days 1-21 continuously in combination with capecitabine 2,000 mg/m2 per day on Days 1-14 in a repeating 21-day cycle. HR+, HER2+ MBC: 1,500 mg PO once daily continuously in combination with letrozole (2.5 mg once daily).	HER2+ MBC: 1 study with improvement in time to progression (TTP), defined as time from randomized to tumor progression or death related to breast cancer, with the addition of lapatinib to capecitabine compared to capecitabine alone (HR 0.57, 95% CI 0.43-0.77) HR+, HER2+ MBC: 1 study with improvement in PFS with addition of lapatinib to letrozole (HR 0.71, 95% CI 0.53-0.96)	Left ventricular ejection fraction decrease, hepatotoxicity, diarrhea, interstitial lung disease and pneumonitis, QT prolongation, severe cutaneous reactions, embryo-fetal toxicity
Pertuzumab (IV, Perjeta)	In combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease	2012	840 mg loading dose, followed by 420 mg every 3 weeks	CLEOPATRA: PFS improvement (HR 0.62, 95% CI 0.51-0.75, p<0.0001) and OS improvement (HR 0.68, 95% CI 0.56-0.84, p 0.0002)	Left Ventricular Dysfunction, embryo-fetal toxicity, infusion related reactions, hypersensitivity reactions/anaphylaxis
Pertuzumab	In combination with	2013	840 mg initial	NeoSphere:	Left Ventricular

(IV, Perjeta)	trastuzumab and chemotherapy for the neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer		dose followed by 420 mg every 3 weeks, with trastuzumab and docetaxel every 3 weeks for 3 to 6 cycles	improvement in pCR in patients who received pertuzumab added to trastuzumab and docetaxel (39.3% vs. 21.5%, p 0.0063) TRYPHAENA and BERENICE provided additional supportive evidence.	Dysfunction, Embryo-fetal toxicity, infusion-related reactions, hypersensitivity reactions/anaphylaxis
Trastuzumab-dkst (IV, Ogivri, biosimilar)	Same as Herceptin	2017	Same as Herceptin	Studies conducted to support finding a finding of biosimilarity	Studies conducted to support a finding of biosimilarity
Pertuzumab (IV, Perjeta)	In combination with trastuzumab and chemotherapy for the adjuvant treatment of patients with HER2 positive early breast cancer at high risk or recurrence	2017	840 mg initial dose followed by 420 mg every 3 weeks, for total 1 year	Improvement in IDFS based on APHINITY trial, HR 0.82 (p 0.047) when pertuzumab added to chemotherapy and trastuzumab	Left Ventricular Dysfunction, Embryo-fetal toxicity, infusion-related reactions, hypersensitivity reactions/anaphylaxis
Neratinib (PO, Nerlyx)	The extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer, to follow adjuvant trastuzumab-based therapy	2017	Oral administration of 240 mg (6 tablets) given once daily with food continuously for one year	Estimated iDFS at 24 months 94.2% in the neratinib arm vs. 91.9% in the placebo arm with a HR of 0.66 (95% CI 0.49, 0.90, p=0.008)	Diarrhea, including 40% of patients experiencing Grade 3 diarrhea, nausea, abdominal pain, vomiting, fatigue
Trastuzumab-pkrb (IV, Herzuma, biosimilar)	HER2 over-expressing BC	2018	Adjuvant Breast Cancer (52 weeks total) -Initial dose of 4mg/kg, then	Studies conducted to support finding a finding of biosimilarity	Studies conducted to support a finding of biosimilarity

			2mg/kg weekly for 12 weeks (with paclitaxel or docetaxel) or 18 weeks (with docetaxel and carboplatin). One week after last dose of HERZUMA, administer 6mg/kg as an IV infusion over 30-90min every 3 weeks to complete a total of 52 weeks Metastatic -Initial dose of 4mgkg followed by weekly doses of 2mg/kg		
Trastuzumab-dttb (IV, Ontruzant, biosimilar)	Same as Herceptin	2019	Same as Herceptin	Studies conducted to support finding a finding of biosimilarity	Studies conducted to support a finding of biosimilarity

Important Safety Issues with Consideration to Related Drugs

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

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

SC trastuzumab was approved by EMA/EU in 8/26/13 for early breast cancer (EBC) and metastatic breast cancer (MBC), and Australia 3/13/15 for EBC, Locally Advanced Breast Cancer, and MBC. Per the applicant, Herceptin SC has been approved in over 80 countries and marketing applications are ongoing in: Pakistan, Turkey, Taiwan, Indonesia, and Egypt.

3.2. Summary of Presubmission/Submission Regulatory Activity

Type B Face-to-Face End-of-Phase 2 meeting (EOP2) on 6/21/10:

- FDA and the applicant agreed to the following:
    - The clinical development of this product should be conducted under a new IND application due to the differences between this product and Herceptin, and the request for marketing approval would be submitted under an original BLA.
    - FDA agreed with the proposed non-clinical toxicology submission.
    - FDA did not agree with Genentech's proposed clinical program (design, patient population, strategy to investigate immunogenicity, endpoints and planned analyses of pivotal trial BO2227), and stated that the appropriate primary endpoint would be DFS not pCR (which is primary endpoint in BO22227). The proposed pharmacokinetic endpoint of observed trough concentration at cycle 7 would be exploratory.
    - FDA advised Genentech that a sufficient justification for proposed effect size must be submitted, along with a revised margin for Non-Inferiority (NI) and resizing based on a more conservative NI margin. Genentech proposed a margin of 12.5%, and the agency did not agree.
    - FDA and Genentech agreed on definition of DFS and EFS.
    - Genentech stated that they will submit the results of Study BO22227-a non-inferior study based on co-primary endpoints of pCR and EFS.
    - FDA recommended that the statistical plan for BO2227 be revised to support an approval and include analysis plan for primary endpoint in both the PPP and ITT population

Type B Face-to-Face pre-BLA Meeting 10/17/17:

- FDA and the applicant agree to the following:
    - Trastuzumab and hyaluronidase solution for subcutaneous injection would not be considered a combination product, but rather a co-formulation of trastuzumab and rHuPH20.
    - The trastuzumab drug substance in trastuzumab and hyaluronidase solution for subcutaneous injection is the same as that in Herceptin for intravenous infusion and is not considered a new molecular entity or associated with a new mode of action.

Type C Face-to-Face CMC meeting 11/17/17:

- FDA and the applicant discussed and agreed upon the following:
    - PK and clinical data from BO22227 and MO28048 supported the use of Herceptin SC 600mg Q3w fixed dose, although the adequacy of PK data would be a review issue.
    - A higher ratio of trastuzumab to rHuPH20 for stability study would be warranted.
    - FDA did not agree with the molecular integrity of trastuzumab and the absence of detrimental interactions between rHuPH20 and trastuzumab in Herceptin SC has been shown.
    - FDA agreed that the available data and planned activities by the applicant were sufficient to demonstrate that there was no product quality or patient safety impact due to polysorbate 20 (b) (4) in Herceptin SC.
    - FDA agreed with the proposal to cross-reference specific drug substance dossier sections of Herceptin IV license in trastuzumab SC DS dossier.

FDA comments: Even though at the EOP2 meeting in 2010, FDA stated DFS is the preferred primary endpoint for HannaH and the proposed pharmacokinetic endpoint of C_{trough} at the end of cycle 7 would be exploratory, the development approach of SC trastuzumab is consistent with FDA Guidance on "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products", which states the following: "In certain cases, effectiveness of an approved drug product for a new indication, or effectiveness of a new product, may be adequately demonstrated without additional adequate and well-controlled clinical efficacy trials. Ordinarily, this will be because other types of data provide a way to apply the known effectiveness to a new population or a different dose, regimen or dosage form." When being applied to different doses, regimens, or dosage forms, the above FDA Guidance states that "it may be possible to conclude that a new dose, regimen, or dosage form is effective on the basis of PK data without an additional clinical efficacy trial". In the current application, PK data, together with comparable pCR rates from HannaH study can bridge to establish safety and efficacy results between IV trastuzumab to SC trastuzumab in all breast cancer indications.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Three clinical sites and investigators, Dr. Robert Hegg, MD (site 163927), Dr. Bozena Kukielka-Budny, MD (site 163863), and Dr. Renata Sienkiewicz, MD (site 163861), were selected for clinical inspections from the HannaH study. There were no significant inspectional findings for these clinical investigators and the data submitted for the HannaH study for BLA 761106 appear reliable. Refer to the review dated January 2, 2019 from Drs. Lauren Iacono-Connors, Susan Thompson, and Kassa Ayalew for full details.

4.2. Product Quality

The Office of Pharmaceutical Quality (OPQ) recommends approval of trastuzumab and hyaluronidase-oysk/solution for injection manufactured by Genentech, Inc. The data submitted support the conclusion that the manufacture of the product is well-controlled and leads to a product that is pure and potent. Refer to the OPQ Executive Summary dated February 1, 2019 for full details. OPQ recommended the core name of "trastuzumab and hyaluronidase", thereby not including "human" in the proposed core name. Information regarding the source and origin can be communicated within Section 11 of the USPI. Refer to the memo dated February 27, 2019 for full details.

The Office of Biotechnology Products (OBP) reviewed the immunogenicity assay and the reviewers found the information and data provided with the BLA sufficient to support the suitability of the anti-trastuzumab immunogenicity assays to generate meaningful clinical immunogenicity data in support of the BLA. Refer to the Immunogenicity Assay Review dated January 30, 2019 for full details.

4.3. Clinical Microbiology

The reviewers recommended approval of the BLA from a microbiology product quality perspective for drug product and drug substance. Refer to the Product Quality Microbiology Review and Evaluation reviews dated January 23, 2019 (drug substance) and February 5, 2019 (drug product) for full details.

4.4. Devices and Companion Diagnostic Issues

Center for Devices and Radiologic Health (CDRH) was consulted for input on the USPI for BLA 761106 regarding the proposed statement for the companion diagnostic. It was decided that the wording for the companion diagnostic would be "Select patients for therapy based on an FDA-approved companion diagnostic for trastuzumab" in section 1 of the USPI. This was agreed upon by the applicant. Refer to the review dated January 30, 2019 from Drs. Soma Ghosh and Reena Philip for full details.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Herceptin Hylecta is a combination of trastuzumab, a HER2/neu receptor antagonist, and hyaluronidase, an endoglycosidase. Trastuzumab administered via the intravenous route of administration and hyaluronidase are FDA-approved products. Hyaluronidase increases permeability of the subcutaneous tissue by locally and transiently depolymerizing hyaluronan, allowing local subcutaneous administration of trastuzumab.

In this BLA submission, the applicant provided the results from pharmacology, pharmacokinetic, and toxicology studies conducted with the co-formulation containing trastuzumab and recombinant hyaluronidase (rHuPH20) to support this BLA. Additional supporting data from studies conducted with recombinant hyaluronidase and trastuzumab administered by the intravenous route of administration were provided by cross-reference to NDA 21859 for Hylenex, BLA 103792 for Herceptin and BLA 761064 for Rituxan Hycela, and were previously reviewed in support of these BLA and NDA applications.

Subcutaneous formulation of trastuzumab containing rHuPH20 showed similar anti-tumor activity when compared to the intravenous formulation of trastuzumab at similar trough levels of trastuzumab in a mouse xenograft model of HER2-positive cancer.

In a pharmacokinetic study in Gottingen minipigs, subcutaneously administered trastuzumab was absorbed significantly faster when administered with rHuPH20 (mean T_{max} = 24 – 29 h) compared to trastuzumab alone (mean T_{max} = 67 h). However, co-administration with rHuPH20 had no significant effects on other exposure parameters (C_{max} and $AUC_{0\text{-}inf}$) or bioavailability for trastuzumab following a single subcutaneous administration.

Trastuzumab administered with rHuPH20 was evaluated in a GLP-compliant, repeat-dose toxicology study in cynomolgus monkeys. In the study, male and female animals were administered vehicle control (containing 12000 U/mL rHuPH20) or 30 mg/kg/dose trastuzumab with 12000 U/mL rHuPH20 subcutaneously, once weekly for 13 weeks. The purpose of the study was to compare the toxicity profile of trastuzumab after subcutaneous administration with rHuPH20 and intravenous administration (from previously conducted 6-month study to support BLA 103792) at similar exposure levels of trastuzumab. Weekly administration of 30 mg/kg/dose trastuzumab with 12000 U/mL rHuPH20 was well tolerated and did not result in any test article-related findings. This is consistent with previously conducted toxicology studies with trastuzumab administered intravenously.

To evaluate the local tolerance of subcutaneous administration of trastuzumab, the applicant conducted a GLP-compliant, local tolerance study in which male New Zealand White rabbits were administered a single dose of vehicle control (0.9% NaCl) or 60 mg trastuzumab subcutaneously. No clinical signs, local reactions, or macroscopic and microscopic findings were observed.

The applicant did not conduct additional genetic toxicology or reproductive and developmental toxicology studies to support this BLA. Previously conducted studies with trastuzumab IV and

hyaluronidase were reviewed under the cross-referenced NDA 21859 for Hylenex, BLA 103792 for Herceptin and BLA 761064 for Rituxan Hycela and were considered adequate to support this BLA. Results from these studies from labels for Herceptin and Hylenex were collated into the Herceptin Hylecta label, with no major changes from the most recent labels except for updating animal-to-human exposure margins for rHuPH20. These were calculated using the potency of rHuPH20 provided by the applicant (100970 – 120201 U/mg in animal studies and ≥ 75000 U/mg in patients).

The submitted nonclinical data support the approval of Herceptin Hylecta for the proposed indication.

5.2. Referenced NDAs, BLAs, DMFs

NDA 21859 for Hylenex, BLA 103792 for Herceptin, BLA 761064 for Rituxan Hycela

5.3. Pharmacology

Primary Pharmacology

In this BLA submission, the applicant submitted a pharmacology study in a xenograft model with HER2-positive Calu-3 cell line in female Balb/c nude mice to compare the anti-tumor activity of the subcutaneous formulation of trastuzumab containing rHuPH20 to the intravenous formulation of trastuzumab. In the study, mice were administered 0, 1, 3, or 10 mg/kg of either formulation, once weekly, 29 days after cell transplantation. Overall, no statistically significant differences in trough levels of trastuzumab or tumor growth inhibition were observed at any dose levels following 5 weekly administrations of either formulation. (Study # NC1032485)

5.4. ADME/PK

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>Absorption</td><td></td></tr>
<tr><td>RO0452317 (Herceptin, trastuzumab): SC bioavailability study of trastuzumab/rHuPH20 co-formulations in Gottingen minipigs (Study # NC 1029906)</td><td>Mean PK parameters after a single administration of 10 mg/kg trastuzumab IV (G1), 120 mg trastuzumab SC (G2), 120 mg trastuzumab+2000 U rHuPH20 SC (G3), 120 mg trastuzumab+6000 U rHuPH20 SC (G4), 240 mg trastzumab+4000 U rHuPH20 SC (G5):
<table>
<tr><th>Parameters</th><th>G1</th><th>G2</th><th>G3</th><th>G4</th><th>G5</th></tr>
<tr><td>C_{max} (mcg/mL)</td><td>164</td><td>101</td><td>126</td><td>129</td><td>266</td></tr>
<tr><td>T_{max} (h)</td><td>0.08</td><td>67.2</td><td>28.8</td><td>24</td><td>24</td></tr>
<tr><td>$AUC_{(0\text{-}inf)}$ (mcg·h/mL)</td><td>24900</td><td>36700</td><td>31300</td><td>33400</td><td>87200</td></tr>
<tr><td>$T_{1/2}$ (h)</td><td>136</td><td>206</td><td>148</td><td>156</td><td>256</td></tr>
<tr><td>F (%)</td><td></td><td>90.2</td><td>81.8</td><td>87.2</td><td>NC</td></tr>
</table>
NC: not calculated</td></tr>
</table>

Type of Study	Major Findings
Trastuzumab (RO0452317): pharmacokinetics of trastuzumab after subcutaneous administration of trastuzumab/rHuPH20 to cynomolgus monkey (Study # NC 1031088)	Single dose level: 25 mg/kg SC C_{max} = 307 mcg/mL $AUC_{(0\text{-}inf)}$ = 116000 mcg·h/mL T_{max} = 24 h $T_{1/2}$ = 295 h
Distribution	
No new studies were conducted	
Metabolism	
Not conducted	
Excretion	
Not conducted	
TK data from general toxicology studies 13-Week SC study in monkeys (Study # NC 1027259)	Monkey *$T_{1/2}$: Not available* *Accumulation: Yes; 2.9- and 3.5-fold for C_{max} and $AUC_{(0\text{-}168h)}$, respectively (Day 78/Day 1)*
TK data from reproductive toxicology studies No new reproductive toxicology studies were conducted	
TK data from Carcinogenicity studies No carcinogenicity studies were conducted	

5.5. Toxicology

5.5.1. General Toxicology

Study title/ number: Ro 045-2317/F03-01: A 13-week subcutaneous injection toxicity and toxicokinetic study in cynomolgus monkeys with a 17-week recovery phase / NC 1027259

Key Study Findings

- No significant test article-related findings were observed.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 30 mg/kg/dose
Route of administration: Subcutaneous injection
Formulation/Vehicle: (b) (4) U/mL rHuPH20 (RO5221651) in (b) (4)

	histidine, (b) (4), (b) (4) methionine, 0.04% polysorbate 20, (b) (4)
Species/Strain:	Cynomolgus monkeys/Macaca fascicularis
Number/Sex/Group:	5 (main), 2 (recovery)
Age:	3 – 5 years old
Satellite groups/ unique design:	No
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: Changes from Control

Parameters	**Major findings**
Mortality	None
Clinical Signs	Unremarkable
Body Weights	Unremarkable
Ophthalmoscopy	Unremarkable
ECG	Unremarkable
Blood Pressure Measurements	Unremarkable
Hematology	Unremarkable
Clinical Chemistry	Unremarkable
Urinalysis	Unremarkable
Gross Pathology	Unremarkable
Organ Weights	Unremarkable
Histopathology **Adequate battery:** Yes	Unremarkable

The applicant did not conduct any new genetic toxicology studies in support of this BLA submission. Genetic toxicology studies with trastuzumab were submitted in support of the BLA submission for trastuzumab IV and have been reviewed by FDA and incorporated into labeling for Herceptin. Results from these studies were collated into the Herceptin Hylecta label, with no major changes from the most recent label. No genetic toxicology studies with rHuPH20 have been conducted and are not required since it is an endogenous human enzyme.

5.5.2. Carcinogenicity

Not conducted and not required to support this BLA submission.

5.5.3. Reproductive and Developmental Toxicology

The applicant submitted reproductive and developmental toxicology studies that had previously been reviewed by FDA and incorporated into labeling for Herceptin and Hylenex. Results from these studies from both labels were collated into the Herceptin Hylecta label, with no major changes from the most recent labels except for updating animal-to-human exposure margins for rHuPH20 and language to comply with PLLR.

5.5.4. Other Toxicology Studies

The applicant conducted a GLP-compliant, local tolerance study after a single subcutaneous administration of trastuzumab in male New Zealand White rabbits. Animals were administered vehicle control (0.9% NaCl) or 60 mg trastuzumab subcutaneously to the left and right flanks, respectively. Animals were observed for up to 4 days, and local reactions and macroscopic and microscopic evaluations of injection sites and lymph nodes (axillary and inguinal) were performed on Days 1 and 5. All animals survived until their scheduled necropsy. No clinical signs, local reactions, or macroscopic and microscopic findings were observed. (Study # NC 1030364).

X	X
Haw-Jyh Chiu Primary Reviewer	Tiffany K Ricks Team Leader

6. Clinical Pharmacology

6.1. Executive Summary

Recommendations
The Office of Clinical Pharmacology has reviewed the information contained in BLA 761106 and recommends approval. Key review issues are summarized below.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness[†]	The proposed dosing regimen is supported by non-inferiority established with efficacy and PK co-primary endpoints in Study HannaH. The difference in pCR rate (SC-IV arm) is 4.7% (95% CI: -4.0%, 13.3%). The geometric mean ratio for C_{trough} at pre-dose cycle 8 is 1.3 (90% CI: 1.2-1.4).
General dosing instructions	600 mg trastuzumab and 10,000 Units hyaluronidase (rHuPH20) over 2-5 min every 3 weeks. Dose reduction is not allowed.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No dose individualization is recommended based on intrinsic and extrinsic factors. Body-size based dosing is not required as SC trastuzumab achieved equal or higher C_{trough} at pre-dose cycle 8 and no worse efficacy across body weight groups, as compared to IV trastuzumab. There is no clear trend identified between safety and trastuzumab exposure or patient's body weight.
Immunogenicity	Numerically higher rate of treatment-induced ADA was observed in the SC trastuzumab arm relative to IV trastuzumab. However, the increased ADA rate does not affect PK and efficacy comparability. Safety profiles are comparable between ADA positive and negative cohorts.
Labeling	Generally acceptable upon the applicant's agreement to the FDA revisions to the label with specific content and formatting change recommendations. Clinical pharmacology labeling recommendations are detailed in section 11.

Post-Marketing Requirements and Commitments
None

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

SC trastuzumab is a co-formulation of trastuzumab and hyaluronidase rHuPH20. Trastuzumab is a HER2 monoclonal antibody. Intravenous trastuzumab has been approved for the treatment of $HER2^+$ breast cancer and gastric cancer under BLA 103792. The excipient in SC trastuzumab formulation, rHuPH20, is a recombinant hyaluronidase approved as a tissue permeability modifier under NDA 021859.

In current submission, a non-inferiority approach, with pre-surgery C_{trough} at pre-dose Cycle 8 and rate of pCR being co-primary endpoints for PK and efficacy, was adopted to demonstrate comparability of both formulations. The main differences between the SC trastuzumab and IV trastuzumab are shown in Table 2 .

Table 2: Comparison Between IV Trastuzumab and SC Trastuzumab

Characteristics	SC Trastuzumab	IV Trastuzumab
Administration	SC injection over 5 minutes	IV infusion over 30-90 hours
Dosing regimen	600 mg trastuzumab+ 10,000 Units rHuPH20	• Loading Dose 4 mg/kg + Maintain Dose 2 mg/kg Q1W • Loading Dose 8 mg/kg + Maintain Dose 6 mg/kg Q3W
Dosage Forms and Strengths	600 mg/5 mL solution in a fixe dose vial	150/420 mg lyophilized powder in single/multiple dose vial
Co-formulation	hyaluronidase (rHuPH20)	None

Source: Reviewer's summary

The trastuzumab PK of in patients with early breast cancer was described by using a two-compartment model with parallel linear and nonlinear elimination. The subcutaneous absorption was characterized using a first-order absorption process. A summary of the clinical pharmacokinetics of SC Trastuzumab is provided in Table 3.

Table 3: Trastuzumab PK parameters following Subcutaneous Administration of SC Trastuzumab[a]

Absorption	
Absolute Bioavailability	0.77 (13)
First-order absorption rate, ka (day^{-1})	0.4 (2.92 [b])
T_{max} (day)	3 (1-14) [c]
Distribution	
Volume of Central Compartment (L)	2.9 (19.1)
Elimination	
Linear Elimination Clearance (L/day)	0.11 (30)
Non-linear Elimination V_{max} (mg/day)	11.9 (19.9 [b])
Non-linear Elimination K_m (mg/L)	33.9 (38.6 [b])

[a]Parameters represented as geometric mean (%CV) unless otherwise specified
[b]Residual standard error
[c]Median (range)

Source: Reviewer's summary. PK parameter values have been verified by the reviewer.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The applicant has proposed trastuzumab SC dose of 600 mg with 10,000 Units hyaluronidase for both adjuvant breast cancer or metastatic breast cancer. The dose regimen was selected to achieve equal or higher trastuzumab C_{trough} compared to the approved IV trastuzumab doses. This dose was evaluated in the pivotal trial HannaH for neoadjuvant-adjuvant setting, which confirmed the PK and efficacy comparability. The extrapolation to metastatic breast cancer is based on the following justifications (refer to the applicant's response to IR on 12/17/2018):

- Comparable PK profiles of Herceptin IV across the neoadjuvant-adjuvant/adjuvant treatment settings in patients with EBC and in patients with MBC
- Neoadjuvant-adjuvant treatment as used in HannaH is a sensitive setting for establishing clinical similarity of efficacy and immunogenicity
- Mode of action of trastuzumab in the EBC and MBC are the same

Therapeutic Individualization

No dose individualization is required for adult patients. Body weight showed a statistically significant influence on PK. In patients with a body weight < 51 kg, mean steady state AUC of trastuzumab was about 80% higher after SC trastuzumab than after intravenous trastuzumab treatment, whereas in the highest BW group (> 90 kg) AUC was 20% lower after SC trastuzumab than after intravenous trastuzumab treatment. However, no body-weight based dose adjustments are needed in EBC patients, as the exposure changes are not considered clinically relevant, as SC trastuzumab achieved equal or higher C_{trough} at pre-dose cycle 8 and no worse efficacy across body weight groups, as compared to IV trastuzumab. There is lack of sufficient evidence to support exposure-response relationship for efficacy or safety.

Outstanding Issues

None.

6.3 Comprehensive Clinical Pharmacology Review

Overview of the Product and Regulatory Background

SC trastuzumab is provided as single-dose vials containing 600 mg trastuzumab and 10,000 units of hyaluronidase rHuPH20 per 5 mL. The proposed indications are for the treatment of adult patients with $HER2^+$ breast cancer. This is the same indications which IV trastuzumab has been approved for, except that the applicant is not seeking $HER2^+$ gastric cancer in current submission, given the lower trastuzumab exposure in gastric cancer patients (refer to the applicant's response to IR on 10/30/2018).

Hyaluronidase-based SC formulation has also been adopted in the Rituximab SC formulation submission (RITUXAN HYCELA, BLA 761064). The approval suggestion was made based on a comparative PK non-inferiority paradigm, in which the applicant used a PK bridging strategy and by leveraging the known and established efficacy of rituximab IV.

In current application, the applicant used both PK and efficacy based bridging strategy, based on pathological complete response (pCR) and serum trough concentration (C_{trough}) data from pivotal study HannaH.

6.3.1 General Pharmacology and Pharmacokinetic Characteristics

A population PK model with two-compartment model with parallel linear and nonlinear elimination was constructed to describe the observed trastuzumab PK concentrations following SC administration and administration (Table 4).

Following subcutaneous administration of SC trastuzumab, trastuzumab concentrations were approximately at steady-state after the Cycle 7 dose with < 15% increase in concentration up to Cycle 13. The mean C_{trough} at the pre-dose Cycle 18 in trastuzumab arm is similar to that of Cycle 13, suggesting no further increase after Cycle 13. The mean C_{max} was 32% lower, and the mean $AUC_{0\text{-}21\ days}$ following the Cycle 7 dose and Cycle 12 dose was approximately 10% and 20% higher, respectively, in the trastuzumab arm than in the intravenous trastuzumab arm.

Table 4: Trastuzumab Exposure Following Subcutaneous Administration of SC Trastuzumab or IV Trastuzumab

Trastuzumab Exposure		SC Trastuzumab	IV Trastuzumab
C_{trough} (mcg/mL)	Cycle 1	28.2 (14.8 – 40.9)	29.4 (5.8 – 59.5)
	Cycle 7	75.0 (35.1 – 123)	47.4 (5 – 114.7)
C_{max} (mcg/mL)	Cycle 1	79.3 (56.1 – 109)	178 (117 – 291)
	Cycle 7	149 (86.1 – 214)	179 (107 – 309)
$AUC_{0\text{-}21\ days}$ (mcg/mL•day)	Cycle 1	1065 (718 – 1504)	1373 (736 – 2245)
	Cycle 7	2337 (1258 – 3478)	1794 (673 – 3618)

Source: Applicant's report during labeling negotiation. Values for the exposure parameters verified by the reviewer.

A summary of general pharmacology and PK characteristics of SC trastuzumab is shown in Table 5.

Table 5: Summary of General Pharmacology and Pharmacokinetic Characteristics of Trastuzumab

Pharmacology	
Mechanism of Action	Trastuzumab is an anti-HER2 monoclonal antibody. Trastuzumab is a mediator of antibody-dependent cellular cytotoxicity (ADCC). In vitro, trastuzumab-mediated ADCC has been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2.
	Hyaluronidase is a dispersion agent, which modifies the permeability of connective tissue through the hydrolysis of hyaluronic acid, a polysaccharide found in the intercellular ground substance of

<table>
<tr><td></td><td>connective tissue. Hyaluronidase hydrolyzes hyaluronic acid by splitting the glucosaminidic bond between C1 of an N-acetylglucosamine moiety and C4 of a glucuronic acid moiety. This temporarily decreases the viscosity of the cellular cement and promotes dispersion of injected fluids or of localized transudates or exudates, thus facilitating their absorption.</td></tr>
<tr><td colspan="2">General Information</td></tr>
<tr><td rowspan="2">Bioanalysis</td><td>A validated enzyme-linked immunosorbent assay (ELISA) was used to measure trastuzumab concentrations in serum samples. Recombinant p185 human epidermal growth factor receptor 2 (HER2) and goat anti-human IgG Fc conjugated to horseradish peroxidase were used to capture and detect trastuzumab in samples, respectively. The assay performance parameters and associated clinical studies are summarized in the following table.
<table>
<tr><th></th><th>Trastuzumab</th></tr>
<tr><td>Validation Report No.</td><td>HH2.13.AVR_2-A1</td></tr>
<tr><td>Validation and Sample Analysis Site</td><td>(b) (4)</td></tr>
<tr><td>Standard Curve Range</td><td>0.750 to 200 ng/mL</td></tr>
<tr><td>MQC</td><td>156 ng/mL</td></tr>
<tr><td>Intra-assay Precision (%CV)</td><td>4 to 10</td></tr>
<tr><td>Inter-assay Precision (%CV)</td><td>6 to 17</td></tr>
<tr><td>Inter-assay Accuracy (%Recovery)</td><td>100 to 104</td></tr>
<tr><td>Studies</td><td>BP22023, BO22227</td></tr>
</table>
MQC: minimum quantifiable concentration in neat plasma samples; %CV: percent coefficient of variation; %DEV: percent deviation of a value from theoretical; %RE: percent relative error</td></tr>
<tr><td>Two methods were used to measure rHuPH20 enzymatic activity in plasma in clinical study BP22023. The US Pharmacopoeia (USP) turbidimetric assay did not achieve the desired sensitivity; therefore, a more sensitive colorimetric method was developed and validated (rHuPH20 microplate-based colorimetric assay). An even more sensitive method (total immunoreactive electrochemiluminescence assay [ECLA]) was developed upon request by the EMA following the approval of Herceptin SC. See the following table for more details.</td></tr>
</table>

<table>
<tr><td></td><td>
<table>
<tr><th></th><th>rHuPH20 Turbidimetric Assay</th><th>rHuPH20 Hyaluronidase Activity Assay</th><th>Total Immuno-reactive rHuPH20 Assay</th></tr>
<tr><td>Validation Report Nos.</td><td>HALO R05013 (b) (4) 05313]
HALO R06041
HALO 10167</td><td>HALO 10165 (b) (4) 09B-0187]
HALO 11025
HALO 14106</td><td>HALO 15032
HALO 18040</td></tr>
<tr><td>Validation and Sample Analysis Site</td><td colspan="2">(b) (4)</td><td>Halozyme, Inc.</td></tr>
<tr><td>Standard Curve Range</td><td>10 to 100 U/mL</td><td>0.3125 to 10 U/mL</td><td>0.06144 to 76.80 ng/mL</td></tr>
<tr><td>MQC</td><td>10 U/mL</td><td>0.3125 U/mL</td><td>0.06144 ng/mL</td></tr>
<tr><td>Intra-assay Precision (%CV)</td><td>2 to 7</td><td>2 to 9</td><td>4.1 to 13.2</td></tr>
<tr><td>Inter-assay Precision (%CV)</td><td>N/A</td><td>7 to 9</td><td>4.3 to 16.2</td></tr>
<tr><td>Inter-assay Accuracy</td><td>%DEV: -4.4 to 2.0</td><td>%DEV: -7.63 to 11.0</td><td>%RE: -8.8 to 8.2</td></tr>
<tr><td>Studies</td><td>BP22023</td><td>BP22023, HALO-104-104</td><td>HALO-104-104</td></tr>
</table>
</td></tr>
<tr><td>Healthy Subjects vs Patients</td><td>Trastuzumab PK was similar in healthy male subjects and female patients who received 8 mg/kg SC trastuzumab.</td></tr>
<tr><td>Drug exposure at steady state following the therapeutic dosing regimen</td><td>The mean (CV%) trastuzumab C_{trough} at pre-dose on cycle 8 before surgery was 77.6 (55.3). The estimated mean (CV%) is 166 (35.4) mcg/mL for trastuzumab C_{max} at steady state and 2610 (36.2) mcg/mL•day for trastuzumab $AUC_{0\text{-}21\ days}$ at steady state.</td></tr>
<tr><td colspan="2">ADME of Trastuzumab</td></tr>
<tr><td>Absorption</td><td>The mean (CV%) relative bioavailability of trastuzumab SC was estimated to be 0.77 (13). The mean (RSE%) first order absorption rate was estimated to be 0.4 day^{-1} (2.92). The median T_{max} was approximately 3 days (range 1-14 days).</td></tr>
<tr><td>Distribution</td><td>The estimated mean (%RSE) for volume of distribution for the central compartment was 2.9 (19.1) L, and 0.445 (10.5) L/day for distribution clearance.</td></tr>
<tr><td>Metabolism</td><td>Not studied. In general, antibodies are expected to be metabolized into peptides and amino acids via catabolic pathway.</td></tr>
<tr><td>Elimination</td><td>The mean (%CV) linear elimination clearance was 0.11 (30) L/day. The mean (%RSE) was 11.9 (19.9) for maximum rate for non-linear clearance(V_{max}), and 33.9 (38.6) for concentration at which the non-linear clearance rate is half of Vmax (K_M), respectively.</td></tr>
<tr><td colspan="2">Immunogenicity</td></tr>
<tr><td>Immunogenicity</td><td>Numerically higher incidence of ADA in SC Trastuzumab arm was observed as compared to the IV trastuzumab (15.9% [47/295] vs 10.1% [30/296]). However, patients of anti-trastuzumab antibody in the SC trastuzumab arm still achieve C_{trough} equal or higher than that in the IV trastuzumab arm regardless of ADA status. ADA positive patient cohort has no worse rate of pCR as compared to the ADA negative cohort within each arm. No dramatic changes in serious AEs or dose adjustment were noticed in ADA positive cohort as</td></tr>
</table>

	compared to the ADA negative cohort within each arm. ADA status was evaluated by bridging immunogenicity assay. This assay will be affected by the present of trastuzumab in plasma. Drug tolerance study were conducted with anti-trastuzumab antibody positive controls at 11 to 4000 ng/mL in the presence of 100 to 50000 ng/mL of trastuzumab (refer to section 19.4 and CMC memo by Dr. Shadia Zaman).

6.3.2 Clinical Pharmacology Questions

Does the proposed flat dose of 600 mg SC trastuzumab provide adequate exposure?

Yes. The selected flat dose of 600 mg Q3W through subcutaneous injection was selected based modeling and simulation. This dose was confirmed in the pivotal study to provide adequate trastuzumab exposure as suggested by the achievement of PK non-inferiority criteria with the co-primary PK endpoint of C_{trough} at pre-dose Cycle 8.

Dose finding for the pivotal study

Prior to the pivotal Phase III HannaH study (BO22227), SC trastuzumab fixed dose of 600 mg every weeks (q3w) was never tested in any clinical studies. The fixed dose was derived from one Phase I study BP22023 with modeling and simulation approach.

The dose-finding and dose-confirmation phase I study (BP22023) incorporated a SC trastuzumab dose-finding part in male healthy subjects and female HER2-positive early breast cancer (EBC) patients, and a dose-confirmation part in female HER2-positive EBC patients. PK results of study BP22023 were used to construct a population PK model, which was used to perform simulations to determine the non-weight-based fixed dosing regimen of Herceptin SC to be used for the Phase III pivotal HannaH study (BO22227). PK modeling and evaluation of a range of doses (400 to 700 mg) in Study BP22023 showed that a fixed Herceptin SC dose of 600 mg Q3W provided C_{trough} levels at Cycle 1 as well as at steady-state (pre-dose Cycle 8) that were at least as high as those achieved by the weight-based dosing of Herceptin IV q3w, without the need for a loading dose. The Herceptin SC 600 mg every 3 weeks was then selected for the pivotal Phase 3 studies.

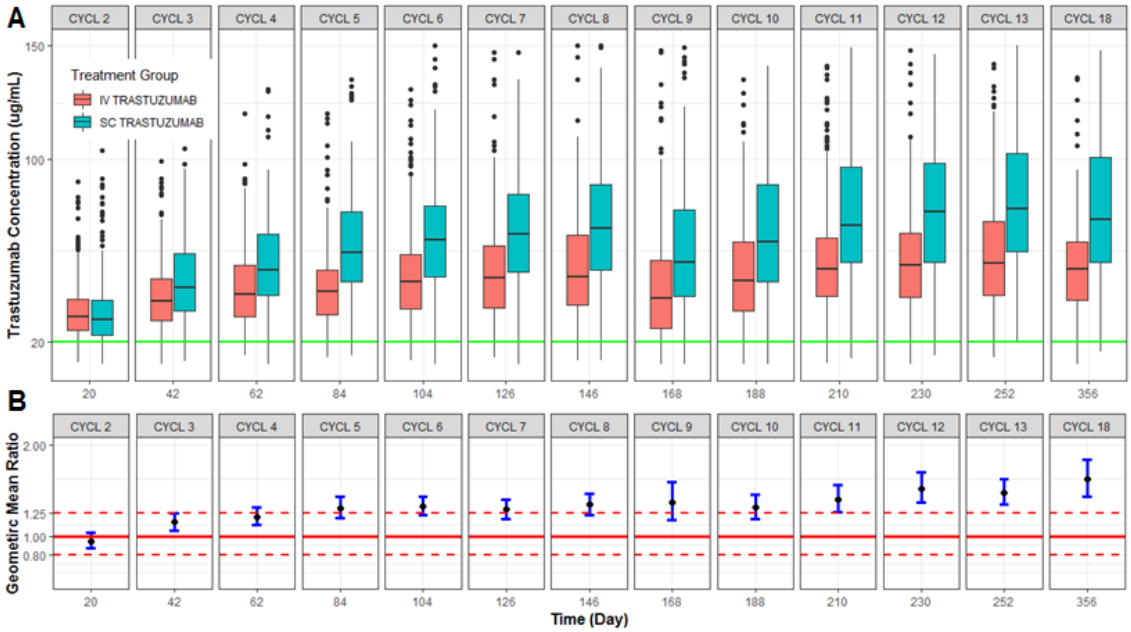
The selected SC trastuzumab fixed dose regimen, 600 mg every 3 weeks (Q3W), was then confirmed as appropriate in the pivotal Phase III study, which demonstrated non-inferiority of SC trastuzumab compared with Herceptin IV for the co-primary endpoints of PK (pre-dose Cycle 8 C_{trough}) and efficacy (pCR). This dose regimen has also shown comparable event-free survival (EFS) and overall survival (OS) after a median follow-up of approximately 72 months. In addition, updated population PK analysis with PK data from HannaH confirmed that the steady-state trastuzumab C_{trough} values with SC trastuzumab were at least as high as those with Herceptin IV in EBC (neoadjuvant and adjuvant) and MBC patients across treatment cycles prior to or after surgery.

PK comparison in general in the pivotal study HannaH

The dose of 600 mg Q3W for SC trastuzumab was confirmed in the pivotal study BO22227 (HannaH), in which Her2+ EBC patients were randomized 1:1 to receive eight cycles of either Herceptin IV with loading dose of 8 mg/kg and maintenance dose of 6 mg/kg, or Herceptin SC 600 mg Q3W, concomitantly with chemotherapy. Randomization was stratified by stage of disease and estrogen receptor status. Chemotherapy consisted of docetaxel 75 mg/m^2 Q3W for four cycles followed by four cycles of 5-fluorouracil 500 mg/m^2, epirubicin 75 mg/m^2 and cyclophosphamide 500 mg/m2 (FEC) given Q3W.

A comparison of the C_{trough} over time for the SC trastuzumab 600 mg Q3W and the IV trastuzumab 6 mg/kg with loading dose of 8 mg/kg show that C_{trough} in SC trastuzumab arm was consistently higher than that in the IV rituximab arm (Figure 1A). The lower limit for confidence interval (CI) of C_{trough} geometric mean ratio (GMR) of the SC to IV dosing regimen is consistently higher than the non-inferiority margin of 0.8 over treatment cycles (Figure 1B). Specifically, the 90% confidence interval of the GMR for C_{trough} at pre-dose cycle 8 was estimated to be (1.2,1.4), suggested the PK non-inferiority criteria was met.

Figure 1: Comparisons of the Trastuzumab C_{trough} Over Time After the Administration of SC Trastuzumab and IV Trastuzumab



A: Comparisons of the Trastuzumab C_{trough} over time, green line indicates therapeutic line of 20 mcg/mL;
B: Geometric Mean Ratio and Confidence interval.
Source: Reviewer's analysis

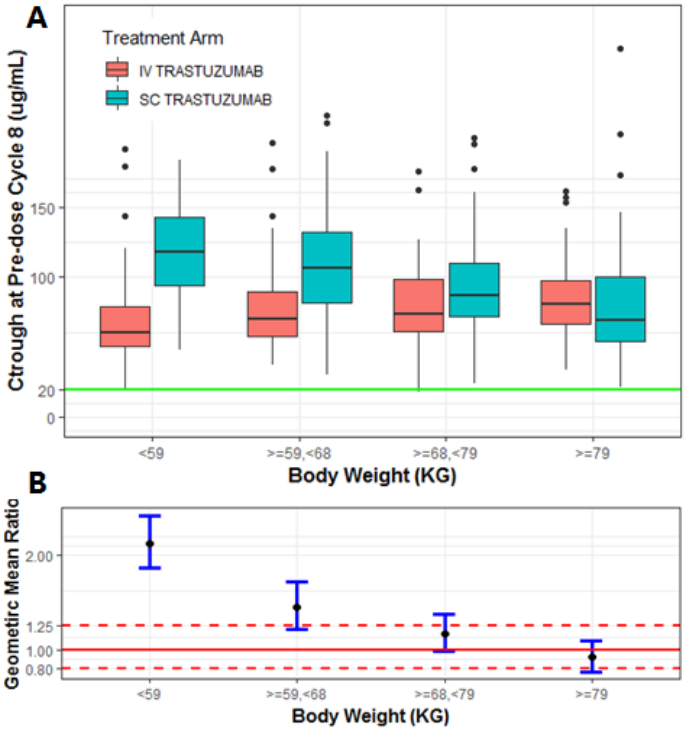
Trastuzumab Exposure across Body Weight Cohorts

Body weight (WT) and serum alanine aminotransferase (SGPT) were identified as significant covariates in the population PK analysis for trastuzumab (See Section 19.4). As a result, the label recommend dose for IV trastuzumab is body weight-based dose regimen of 6 mg/kg with

loading dose of 8 mg/kg. Given that BW-based dosing allows individualization of doses, a transition to fixed dosing could lead to under- or over-dosing of patients in the extremes of the body weight spectrum. This possibility was explored in our review and our findings are summarized below.

As shown in Figure 2, in pivotal HannaH, trastuzumab C_{trough} at pre-dose cycle 8 in the SC trastuzumab arm was generally equal or higher than that after the IV trastuzumab across body weight quartiles (Figure 2A), with the lower limit of GMR 90% confidence interval at the boundary of or higher than the 0.8 margin (Figure 2B). As expected, the trastuzumab exposure in patients with lower body weight is higher than those with higher body weight, as exemplified by the around 2-fold difference between the SC trastuzumab and IV trastuzumab in <59 kg body weight group (Figure 2B).

Figure 2: Comparisons of the Trastuzumab C_{trough} After the Administration of SC Trastuzumab and IV Trastuzumab Within Body Weight Quartiles



Source: Reviewer's analysis

Further exploratory analysis suggest majority of patients has trastuzumab exposure higher than the therapeutic concentration of 20 µg/mL, even in the body weight extremes (Table 6).

Table 6: Summary of Trastuzumab Exposure in Body Weight Extremes

C_{trough} (mcg/mL) at Pre-dose Cycle 8								
Treatment Arm	Weight Category	N	Mean	SD	Median	Min	Max	C_{trough} < 20 µg/mL
IV Trastuzumab	≤51	28	41.1	15.6	43.1	14.2	85.9	2
	>51, <90	187	58.8	31.9	50	17.4	222	1
	≥90	20	67.2	24.9	66.1	25.3	110	0
SC Trastuzumab	≤51	18	107	58	101	49.4	312	0
	>51, <90	190	79.3	42.1	72.1	6.04	400	5
	≥90	26	54.9	33.4	48.3	16.5	176	2
$AUC_{0\text{-}21days}$ (µg/mL*day) following the Dose at Cycle 7 (up to Pre-dose Cycle 8)								
IV Trastuzumab	≤51	28	1658	322	1690	758	2290	
	>51, <90	187	2084	605	2000	1080	5480	
	≥90	20	2350	580	2250	1100	3400	
SC Trastuzumab	≤51	18	3019	1305	2865	1380	7240	
	>51, <90	190	2266	762	2190	593	4430	
	≥90	26	1764	960	1605	628	5310	

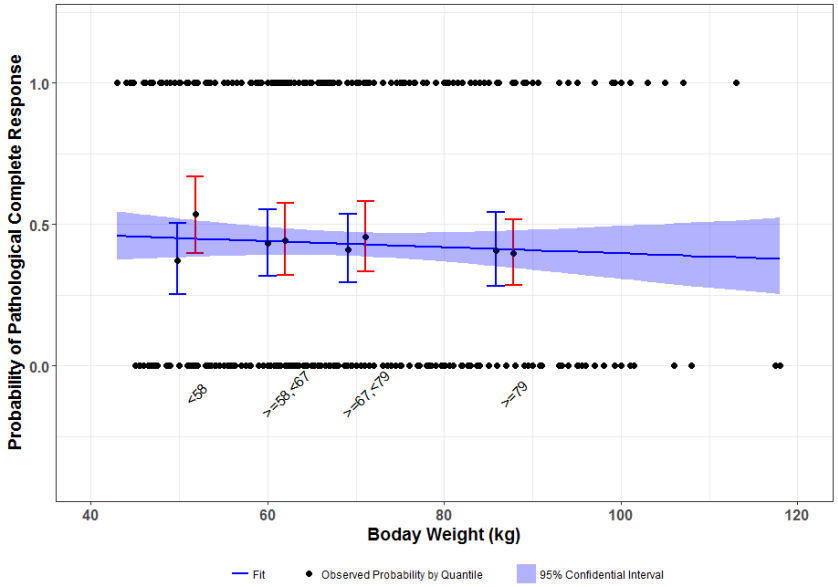
Source: adapted from Table 25 and Table 26 of the BO22227 Update Primary CSR, Report No. 1057070, September 2013.

Overall, SC trastuzumab 600 mg Q3W was shown to achieve trastuzumab exposure equal to or higher than IV trastuzumab under label recommended dose of 6 mg/kg with loading dose of 8 mg/kg. As a result, the proposed fixed dose of 600 mg SC trastuzumab provides adequate trastuzumab exposures among all body weight categories.

Is flat dose of 600 mg acceptable for all BW groups?
Yes, fixed dose of SC trastuzumab achieves no worse efficacy across BW quartiles and with slightly higher rate of serious AEs as compared to IV trastuzumab in general.

Exploratory Efficacy Subgroup Analysis
As trastuzumab exposure were shown to be different among patient with different body weight, exploratory body weight-based exposure-response and subgroup analyses were conducted. No close association was identified between the efficacy primary endpoint pathological complete response (pCR) and body weight in the logistic regression that pooling patient body weight and efficacy data from both SC trastuzumab and IV trastuzumab arms in Study HannaH (Figure 3).

Figure 3: Evaluation of Association between Body Weight and pCR



Error bar in red indicate SC trastuzumab and blue indicate IV trastuzumab.
Source: Reviewer's analysis

Comparison of pCR rate within body weight quartiles suggested the no worse rate of pCR after receiving SC trastuzumab 600 mg Q3W as compared to IV trastuzumab under label recommend dose (Figure 3, Table 7). Despite the numerically higher rate of pCR in the patient with lowest body weight who received SC trastuzumab, as compared to the patients under the same body weight range who receive IV trastuzumab, and to patients with higher body weight who received SC trastuzumab, there is lack of further evidence to draw definite conclusion on the exposure-response relationship between efficacy and body weight, or between efficacy and trastuzumab exposure.

Table 7: Effect of BW on Rate of pCR

Body Weight (kg)	Rate of pCR [n/N (%)]	
	IV Trastuzumab	SC Trastuzumab
<58	23 / 62 (37.1)	30 / 56 (53.6)
>=58, <67	32 / 74 (43.2)	28 / 63 (44.4)
>=67, <79	28 / 68 (41.2)	31 / 68 (45.6)
>=79	24 / 59 (40.7)	29 / 73 (39.7)

Source: Reviewer's analysis

Safety Subgroup Analysis
Due to the same reason of different exposure among patient with different body weight after fixed dose of 600 mg Q3W for SC trastuzumab, body weight-based subgroup comparison of the safety profile between SC trastuzumab and IV trastuzumab was conducted (Table 8). Rate of AE and rate of dose delay modification due to AE were generally numerically higher in SC trastuzumab arm as compared to the IV trastuzumab in general and across body weight quartile

groups. The safety profile was consistent across body weight ranges within each treatment arm indicating lack of definitive Exposure-Response relationship for safety.

Table 8: Effect of BW on Serious Adverse Events /Trastuzumab Dose Modification Rate

Body Weight (kg)	Serious AE [n/N (%)]		Dose Delay or Interrupt [n/N (%)]	
	IV Trastuzumab	SC Trastuzumab	IV Trastuzumab	SC Trastuzumab
< 59	14 / 68 (21)	9 / 62 (15)	35 / 68 (51)	22 / 62 (35)
≥59, < 68	6 / 72 (8)	14 / 65 (22)	20 / 72 (28)	30 / 65 (46)
≥68, < 79	11 / 58 (19)	13 / 58 (22)	17 / 58 (29)	19 / 58 (33)
≥79	8 / 53 (15)	17 / 70 (24)	24 / 53 (45)	29 / 70 (41)
Overall	*39/251 (16)*	*53/255 (20)*	*96/251 (38)*	*100/255 (39)*

Source: Reviewer's analysis

Similarly, in trastuzumab exposure-based subgroup analysis, rate of serious AE and rate of dose modification due to AE were numerically higher in SC trastuzumab arm as compared to the IV trastuzumab arm within trastuzumab exposure quartiles and were consistent across trastuzumab exposure range within each treatment arm (Table 9).

Table 9: Effect of Ctrough on Serious Adverse Events and Trastuzumab Dose Modification Rate

C_{trough} at pre-dose Cycle 8 Quartiles(mcg/mL)	Serious AE [n/N (%)]		Dose Delay or Interrupt [n/N (%)]	
	IV Trastuzumab	SC Trastuzumab	IV Trastuzumab	SC Trastuzumab
<43.3	14 / 83 (17)	8 / 30 (27)	23 / 79 (29)	12 / 26 (46)
>=43.3, <62	10 / 59 (17)	9 / 50 (18)	19 / 55 (35)	16 / 47 (34)
>=62, <81	2 / 48 (4)	17 / 69 (25)	8 / 42 (19)	17 / 66 (26)
>=81	4 / 33 (12)	16 / 80 (20)	12 / 32 (38)	21 / 72 (29)
Missing	15 / 59 (25)	15 / 61 (25)	34 / 43 (79)	34 / 44 (77)

Source: Reviewer's analysis

As trastuzumab can result in cardiomyopathy and pulmonary toxicity, the effect of trastuzumab exposure on the rate of cardiomyopathy and pulmonary toxicity related adverse events was assessed. The result suggested that the rates of AE of special interest were comparable across exposure quartiles and balanced between SC trastuzumab and trastuzumab IV arms (Table 10).

Table 10: Effect of Trastuzumab Exposure on Cardiomyopathy and Pulmonary Toxicity AEs

AE Category	AE PHASE	Average AUC of Cycle 8 and Cycle 13 (µg/mL*day)	IV TRASTUZUMAB (n/N)	SC TRASTUZUMAB (n/N)
Cardiac Disorders	Adjuvant	<1720	2/50	4/40
		>=1720,<2175	5/58	6/45
		>=2175,<2665	3/54	5/50
		>=2665	8/37	7/71
	Neoadjuvant	<1720	3/72	2/59
		>=1720,<2175	6/78	2/52
		>=2175,<2665	8/68	3/67
		>=2665	6/42	10/94
		Missing	2/15	3/15
Respiratory, Thoracic and Mediastinal Disorders	Adjuvant	<1720	8/50	6/40
		>=1720,<2175	7/58	6/45
		>=2175,<2665	9/54	12/50
		>=2665	6/37	13/71
	Neoadjuvant	<1720	16/72	14/59
		>=1720,<2175	19/78	9/52
		>=2175,<2665	19/68	14/67
		>=2665	11/42	31/94
		Missing	5/15	3/15

Source: Reviewer's analysis

Does the Change of Formulation Influence Trastuzumab Immunogenicity?

A numerically higher Incidence of treatment induced anti-drug antibody (ADA) in SC trastuzumab arm, as compared to IV trastuzumab arm was observed (Table 11).

Table 11: Incidence of Anti-Trastuzumab Antibodies

Number of Patients	IV Trastuzumab (N=298)	SC Trastuzumab (N=297)
With ADA Results	298	297
With Baseline (BL) but no post BL	2	2
Evaluable for ADA to Trastuzumab	296	295
Treatment Induced ADA	28	46
NAB Positive	1	3
Treatment Enhance ADA	2	1
NAB Positive	2	0
Treatment Unaffected ADA	16	15
NAB Positive	3	4
ADA Incidence (%)	10.1% (30/296)	15.9% (47/295)

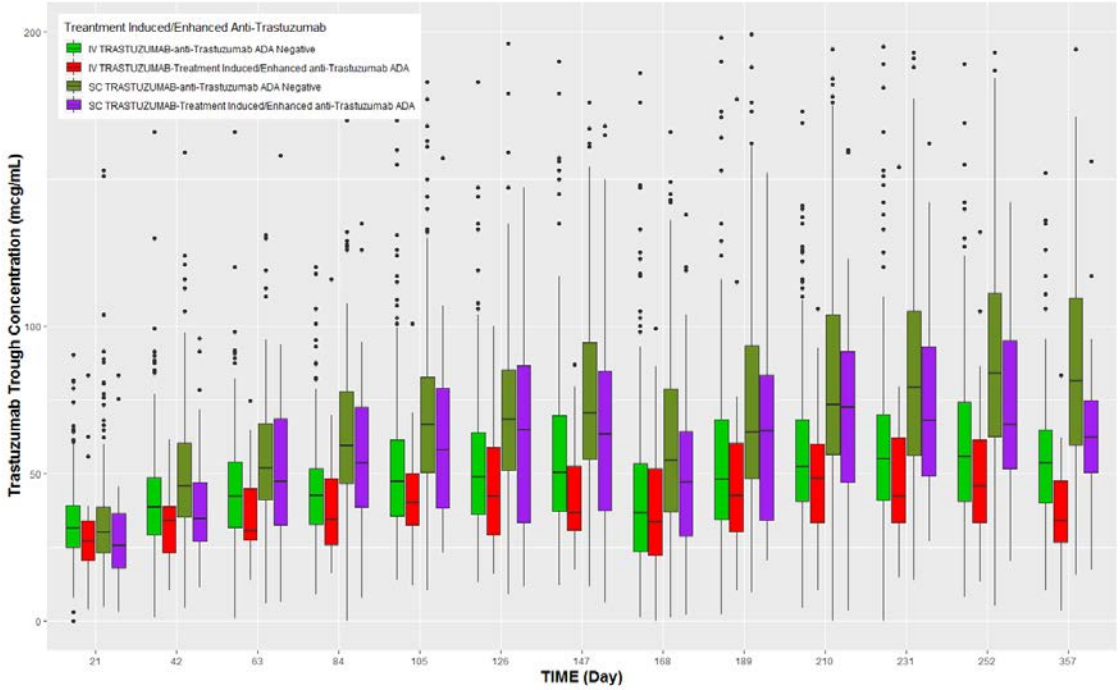
Source: Adapted from applicant's Clinical Study Report of HannaH, section 6.12

The detection and confirmation of the presence of anti-trastuzumab antibodies was through bridging immunogenicity assay. The assay format involved incubating controls and samples with biotin and ruthenium modified Herceptin (RO0452317) for 16-24 hours, transferred to pre-blocked streptavidin-coated plates. Following incubation and washing, the plate was transferred for signal reading and data acquired.

The drug tolerance of the ADA detection methodology was assessed with positive control antibody samples over concentration range of 11 to 4000 ng/mL in the present of trastuzumab concentration of 100 to 50,000 ng/mL. It is indicated that anti-trastuzumab antibody detection signal become dimmer and cannot be detected with ADA concentration of <200 ng/mL in present of 50,000 ng/mL trastuzumab drug. The issue of drug tolerance may affect SC trastuzumab arm to a larger extent as the trastuzumab concentration at the time of ADA detection is slightly higher than that of IV trastuzumab. As a result, the rate of ADA may be under estimated for SC trastuzumab [refer to section OCP Appendices (Technical documents supporting OCP recommendations) for more detailed evaluation].

Clinical consequence of the increased rate of ADA due to the formulation change was examined. The assessment suggests that numerically enhanced ADA rate in SC trastuzumab does not lead to lower C_{trough} relative to IV trastuzumab, as the ADA+ cohorts in SC trastuzumab arm has C_{trough} comparable or higher than IV trastuzumab, regardless of ADA status (Figure 4).

Figure 4: Trastuzumab Exposure in ADA Positive and Negative cohorts in SC Trastuzumab and IV Trastuzumab Arms



Source: Reviewer's analysis

ADA status-based subgroup analyses were conducted for efficacy and safety. The analyses suggested that rate of pCR was not worse among patient with treatment induced/enhanced anti-trastuzumab ADA (Table 12).

Table 12: Effect of ADA on pCR Rate

Anti-Trastuzumab ADA Status	Rate of pCR	
	IV Trastuzumab	SC Trastuzumab
ADA Negative	100 / 267 (37.4)	95 / 249 (38.2)
ADA Positive	11 / 30 (36.7)	29 / 45 (64.4)

Source: Reviewer's analysis

Similar rate of serious AE and rate of dose adjustment were observed comparing ADA positive and ADA negative cohorts within SC trastuzumab and IV trastuzumab treatment arms (Table 13).

Table 13: Effect of ADA on Safety Profile

ADA Status	Serious AE [n/N (%)]		Dose Adjustment [n/N (%)]	
	IV Trastuzumab	SC Trastuzumab	IV Trastuzumab	SC Trastuzumab
ADA Negative	40 / 252 (16)	51 / 244 (21)	97 / 252 (38)	92 / 244 (38)
ADA Positive	5 / 30 (17)	12 / 44 (27)	7 / 30 (23)	20 / 44 (45)

Source: Reviewer's analysis

Based on above evidences, the numerically higher incidence of ADA in SC trastuzumab arm does not appear to result in a lower C_{trough}, or worse efficacy nor safety relative to the IV trastuzumab.

X X

Huiming Xia
Primary Reviewer

Pengfei Song
Team Leader

X X

Fang Li
Pharmacometrics Reviewer

Jingyu (Jerry) Yu
Pharmacometrics Team Leader

7 Sources of Clinical Data and Review Strategy

7.1 Table of Clinical Studies

Table 14 below lists the clinical studies submitted by the applicant in support of the BLA application.

Table 14: Clinical Studies Supporting the BLA Application

Trial No.	Trial Design	Regimen/schedule/route	Study endpoints	Number of patients	Study population
Studies to Support Efficacy					
BO22227 HannaH (Phase III)	Randomized, open label, parallel group, multiple dose, multicenter	**<u>Neoadjuvant Phase</u>** SC trastuzumab arm: fixed dose of 600 mg q3w for 8 cycles (administered before chemotherapy). IV trastuzumab arm: first (loading) dose of 8 mg/kg, thereafter 6 mg/kg q3w (maintenance doses) for 8 cycles (administered before chemotherapy). Both arms: chemotherapy -Docetaxel 75 mg/m2 q21d, Cycles 1-4 -5 Fluorouracil 500 mg/m2 q21d, Cycles 5-8 -Epirubicin 75 mg/m2 q21d, Cycles 5-8 -Cyclophosphamide 500 mg/m2, q21d, Cycles 5-8 **<u>Adjuvant Phase</u>** -Additional 10 cycles of IV or SC trastuzumab as per randomization, to complete 1 year of treatment -Adjuvant tamoxifen or aromatase inhibitors for hormone receptor-positive patients per local practice -Radiotherapy per local practice	PK, efficacy and safety study in the neoadjuvant-adjuvant setting.	**Total 596 (591) patients:** 299 (297) patients in IV trastuzumab arm 297 (294) patients in SC trastuzumab arm	Female patients with HER2−positive EBC with operable, locally advanced or inflammatory breast cancer
Studies to Support Safety					

BO22227 HannaH (Phase III)	Randomized, open-label, parallel group, multiple-dose, multicenter	**Neoadjuvant Phase** SC Trastuzumab arm: fixed dose of 600 mg q3w for 8 cycles (administered before chemotherapy). IV Trastuzumab arm: first (loading) dose of 8 mg/kg, thereafter 6 mg/kg, q3w (maintenance dose) for 8 cycles (administered before chemotherapy). <u>Both arms: chemotherapy</u> -Docetaxel 75 mg/m2 q21 days, cycles 1-4 -5-Fluorouracil 500 mg/m2 on Day 1, cycles 5-8 -Epirubicin 75 mg/m2 q21 days, cycles 5-8 -Cyclophosphamide 500 mg/m2, q21 days, cycles 5-8 **Adjuvant Phase** -Additional 10 cycles of IV trastuzumab or SC trastuzumab as per randomization, to complete one year of treatment -Adjuvant tamoxifen or aromatase inhibitors for hormone receptor-positive patients per local practice -Radiotherapy per local practice	PK, efficacy and safety study in the neoadjuvant-adjuvant setting	**Total 595 pts:** 298 patients IV trastuzumab 297 patients SC trastuzumab	*Female patients with HER2+ EBC with operable, locally advanced or inflammatory breast cancer*
MO28048 SafeHER (Phase III)	Prospective, two-cohort, non-randomized, multicenter, multinational, open-label study.	**Cohort A:** SC trastuzumab at a fixed dose of 600 mg, assisted administration into the thigh over a period of approximately 5 minutes, using conventional handheld syringe with hypodermic needle, for a total of up to 18 cycles q3w. **Cohort B:** SC trastuzumab	Safety and tolerability	**Enrolled: 2577 pts** <u>Cohort A:</u> SC trastuzumab Vial arm, n=1867. Safety Population, n=1864 <u>Cohort B:</u> SC trastuzumab SID arm,	HER2-positive EBC patients

		at a fixed dose of 600 mg presented in a single-use injection device (SID). Administration was performed into the thigh over a period of approximately 5 minutes using the SID for a total of up to 18 cycles q3w.		n=710. Safety Population, n=709	
Other Submitted Studies					
MO22982 PrefHER (Phase II)	Randomized, multicenter, open-label, crossover trial.	SC trastuzumab: fixed dose of 600 mg q3w on Day 1 of each study treatment cycle, administered via SID or from Vial (using hand-held syringe). IV trastuzumab: 8 mg/kg initial loading dose followed by a 6 mg/kg maintenance dose q3w, on Day 1 of each cycle. Total of 18 cycles of trastuzumab as follows: number of cycles before entry into the trial (up to 10) (4 cycles of SC trastuzumab + 4 cycles of IV trastuzumab [crossover period]) + number of cycles after the crossover period to complete 18 cycles (continuation period [if <10 cycles were received before entry into the trial]). Single 5 mL IV infusion containing 10,000 U or 30,000 U of rHuPH20 administered over 5 minutes.	Safety	**Randomized: 488 patients** Cohort 1: 248 patients (SC trastuzumab SID→ IV trastuzumab arm, N: 124; IV trastuzumab → SC trastuzumab SID arm n: 124). Cohort 2: 240 patients (SC trastuzumab Vial→ trastuzumab IV arm, n=121; IV trastuzumab → SC trastuzumab Vial arm, n=119).	HER2-positive EBC patients

7.3 Clinical Study Designs

7.3.1 HannaH (Study B022227)

This was a phase III, randomized, open-label study to compare the pharmacokinetics, efficacy and safety of subcutaneous (SC) trastuzumab with intravenous (IV) trastuzumab administered in women with HER2 positive with operable, locally advanced or inflammatory breast cancer. This study will be referred to as HannaH throughout the review.

Protocol Amendments

The original protocol, dated February 17, 2009, was amended twice. No patients were randomized under the original protocol.

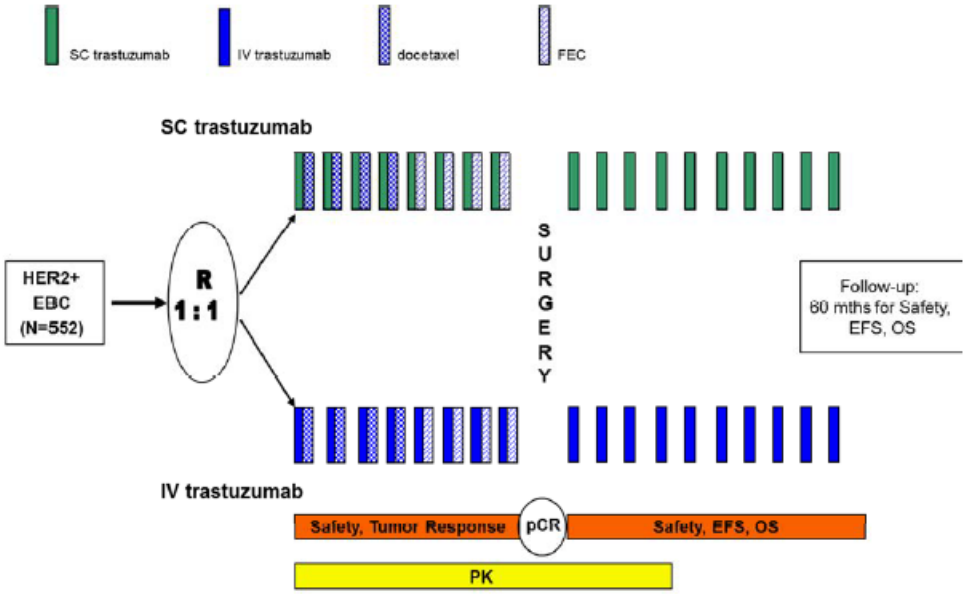
- **Protocol Amendment Version B** (29 June 2009): Initiated to change the body weight-adjusted S dosing to a 600 mg fixed SC dose every 3 weeks. A total of 596 patients were randomized after this amendment.
- **Protocol Amendment C** (4 October 2012): introduced to extend the treatment-free follow-up phase from 2 years to 5 years and the survival follow-up phase from 2 years after the last dose of investigational medicinal product until the end of the study. Of the patients who entered the treatment-free follow-up phase, 420 patients consented to this protocol. There were no changes to the conduct of the study following Protocol Amendment C.

Study Design:

The study design is depicted in Figure 5 below. Enrolled patients had operable, locally advanced or inflammatory breast cancer with tumor size of ≥1 cm. Patients were randomized 1:1 to receive eight cycles of either IV trastuzumab or SC trastuzumab, concomitantly with chemotherapy and randomization was stratified by stage of disease and estrogen receptor status. Chemotherapy consisted of 75 mg/m2 docetaxel given q3W for four cycles followed by four cycles of 5-fluorouracil 500 mg/m2, epirubicin 75 mg/m2 and cyclophosphamide 500 mg/m2 (FEC) given every 3 weeks.

Patients underwent surgery after the eight cycles of trastuzumab treatment. Post-surgery, patients received an additional 10 cycles of IV or SC trastuzumab as per randomization to complete 1 year of treatment with a trastuzumab-containing product. Post-operative radiotherapy was administered as per local practice, also without interruption of trastuzumab treatment. Hormone receptor-positive patients could receive adjuvant treatment with tamoxifen or aromatase inhibitors. After the end of study treatment, patients were followed for safety and efficacy for at least 5 years, or until disease recurrence, whichever occurred earlier.

Figure 5: HannaH Study Design



Source: HannaH Study Protocol

Patients who withdrew due to progression of disease or recurrence at any time during the study were managed as per local practice and followed for survival every six months until the end of study. Patients not consenting to Protocol Amendment C were followed for a maximum of 2 years after the end of study treatment.

Patients who discontinued study treatment prematurely due to lack of tolerability prior to surgery, were managed as per local practice and were followed for survival every six months until the end of the study. Patients who discontinued trastuzumab treatment after surgery prematurely without recurrence were permitted to stay on the trial and were followed for EFS, OS, and safety.

The trial enrolled 596 patients in 81 sites in 24 countries with the first patient randomized to treatment on 10/19/2009 and the last patient enrolled on 12/01/2010.

Primary Endpoints

The HannaH study had two co-primary endpoints: pathological complete response (pCR) of the breast at the time of definitive surgery after Cycle 8 and trastuzumab C trough at Cycle 7 (predose Cycle 8). pCR was assessed by the local pathologist and not independently reviewed.

Secondary endpoints:

tpCR (total pathological complete response)

tpCR is defined as absence of invasive neoplastic cells at microscopic examination of the primary tumor remnants in the breast and the axillary lymph nodes after surgery following primary systemic therapy.

Event-free survival (EFS)
EFS is defined as time to local, regional or distant recurrence, contralateral breast cancer or death due to any cause. Post-surgery, screening for relapse/metastatic disease was performed after completion of trastuzumab treatment and during follow-up phase at months 6, 12, 24, 36, 48, and 60. The assessments included a mandatory mammogram. Chest X-ray, bone scan, and liver imaging were required only if symptoms or clinical suspicion were present.

ORR (Overall Response Rate)
ORR is defined is defined as clinical complete or partial best tumor response. Because patients with inflammatory breast cancer were allowed to enter the study in the absence of measurable lesions, ORR in this group will be reported within a separate subgroup analysis that includes all patients with inflammatory breast cancer.

The protocol and Response Evaluation Criteria in Solid Tumors (RECIST Version 1.0) require confirmation of response, but in this neo-adjuvant setting, response will be considered without confirmation; response will be assessed according to the steps specified below:

- Progressive disease (PD): This will be concluded if PD is evaluated at any tumor assessment prior to or at day of surgery (or end of neo-adjuvant treatment phase for patients without surgery).
- Non-evaluable (NE): If there is no PD as specified above and there is no tumor assessment (or only "unable to assess") after at least 18 weeks from start of study (study Day 126 or later) but before or at day of surgery (or end of neo-adjuvant treatment phase for patients without surgery) OR if there is ≥ 1 tumor assessment in that time frame but the last available tumor assessment in time is "unable to assess."
- Complete response (CR): This will be concluded if there is no PD and no NE as specified above and CR is evaluated at the last tumor assessment before or at day of surgery (or end of neo-adjuvant treatment phase for patients without surgery).
- Partial response (PR): This will be concluded if there is no PD and no NE and no CR as specified above and PR is evaluated at the last tumor assessment before or at day of surgery (or end of neo-adjuvant treatment phase for patients without surgery).
- Stable disease (SD): This will be concluded if none of the cases are as specified above.

Overall Survival (OS)
OS is defined as the time from the date of randomization to the date of death, regardless of the cause of death. Patients alive at the time of the analysis are censored at the date of the last follow up assessment. Patients without follow up assessment are censored at the day of last dose and patients with no post baseline information are censored at the time of randomization.

Inclusion Criteria:
- Patients must have signed and dated an informed consent form
- Female

- Age > 18 years
- Non-metastatic primary invasive adenocarcinoma of the breast which is clinical stage I (T1, N0, M0) to IIIC (any T, N3, M0) including inflammatory and multicentric breast cancer
    - with tumor size ≥ 1 cm
    - histologically confirmed
    - centrally confirmed HER2 positive (IHC3+ or ISH+) in the invasive component of the primary tumor
- At least one measurable lesion in breast or lymph nodes, according to RECIST v1.0 criteria, except for inflammatory carcinoma (T4d)
- Performance status ECOG of 0-1
- Baseline LVEF ≥ 55% measured by echocardiography or MUGA scan prior to first dose of trastuzumab

Exclusion Criteria

- History of any prior (ipsi- and/or contralateral) invasive breast carcinoma
- Past or current history of malignant neoplasms, except for curatively treated:
    - Basal and squamous cell carcinoma of the skin
    - in situ carcinoma of the cervix
- Metastatic disease
- Any prior therapy with anthracyclines
- Prior use of anti-HER2 therapy for any reason or other prior biologic or immunotherapy
- Concurrent anti-cancer treatment in another investigational trial, including immunotherapy
- Serious cardiac illness or medical conditions that would preclude the use of trastuzumab, specifically: history of documented CHF, high-risk uncontrolled arrhythmias, angina pectoris requiring medication, clinically significant valvular disease, evidence of transmural infarction on ECG, poorly controlled hypertension
- Medical conditions that would preclude the use of 5-fluorouracil, epirubicin, cyclophosphamide or docetaxel, including: cystitis, urinary obstruction, active infections or severe mucositis
- History of severe allergic and immunological reactions, e.g. difficult to control asthma
- Known hypersensitivity to any of the study drugs or any of the excipients, known hypersensitivity to murine proteins
- Known dihydropyrimidine dehydrogenase (DPD) deficiency
- Any of the following abnormal laboratory tests at baseline:
    - Biochemistry
        - serum total bilirubin > 1.25 x upper limit of normal (ULN)
        - alanine amino transferase (SGPT, ALT) or aspartate amino transferase (SGOT, AST) > 2.5 x ULN
        - alkaline phosphatase (ALP) > 2.5 x ULN
        - serum creatinine > 1.5 x ULN;
    - Hematology:

        - absolute neutrophil count (ANC) < 1.5 x 109/L
        - platelets < 100 x 109/L
        - hemoglobin < 10 g/dl
    - Pregnant or lactating women
    - Women of childbearing potential or less than one year after menopause (unless surgically sterile) who are unable or unwilling to use adequate contraceptive measures during study treatment
    - Patients unwilling or unable to comply with protocol procedures

Key study assessments and procedures for the HannaH study were:

- A screening/baseline examination should be performed between -28 and -1 days before the first study dose of study drug (Day 1). Patients who fulfill all the inclusion and none of the exclusion criteria can be randomized into the study.
- Diagnosis of Breast Cancer and Surgical Assessment: Diagnosis of primary breast cancer will be performed histologically as per local standard of care. The site surgeon will assess the breast tumor during screening and will identify the planned surgical procedure required after completion of cycle 8 treatment. HER 2 testing at diagnosis will be performed and confirmed in a central laboratory.
- Clinical Tumor Response: evaluated according to modified RECIST criteria. In cases of Inflammatory breast cancer, tumors will be assessed for response with CR, PR, SD, or PD.

The schedule of assessments during the treatment phase prior to surgery are shown below in Table 15, while the assessments during the treatment phase after surgery are shown below in Table 16.

Table 15: Schedule of Assessments (Neoadjuvant Phase)

	Screening	Baseline	Treatment Period														
Study Week			1			4	7	10	13	16	19					22	
Cycle			1			2	3	4	5	6	7					8	S[13]
Day of Cycle	-28 to -1	-7 to -1	1	- 2 -	15	1	1	1	1	1	1	2	- 4 -	8	- 15	1	1
Informed Consent[6]	X																
Demographics	X																
Medical History	X																
Physical Examination[1]	X		X						X								
Vital signs[1]	X		X						X								
ECOG performance status[1]	X		X						X								
Height	X																
Weight[1]	X		X			X	X	X	X	X	X					X	
Chest X-ray[2]	X																
Liver imaging	(X)																
Bone scan[3]	(X)																
Bilateral mammogram[4]	X																
Clinical tumor assessment by caliper and ultrasound (including lymph nodes)[5]		X					X		X		X						X
ECG	X								X								
LVEF (Echo or MUGA)	X								X								
Hematology and Biochemistry[1,6]		X	X[14]			X	X	X	X	X	X					X	
Serum Pregnancy Test		X															
Urinalysis (Dipstick)[1]	X								X								X
HER2 status local lab[7]	X																
Hormone receptor status (ER ,PgR) local lab[7]	X																
Tumor sample for central HER2 testing[7]	X																
Pathologist tumor assessment																	X

	Screening	Baseline	Treatment period													
Study Week			1			4	7	10	13	16	19				22	
Cycle			1			2	3	4	5	6	7				8	S[13]
Day of Cycle	-28 to -1	-7 to -1	1	2	15	1	1	1	1	1	1	2	4	8	15	1	1
PK blood sample (SC arm), (2 ml)[8]			X[15]	X	X	X[15]	X[15]	X[15]	X[15]	X[15]	X[15]	X	X	X	X	X[15]	
PK blood sample (IV arm), (2 ml)[8]			X[16] X[17]	X	X	X[16] X[17]	X[16] X[17]	X[16] X[17]	X[16] X[17]	X[16] X[17]	X[16] X[17]					X[16] X[17]	
Immunogenicity blood sample		X															
Blood sample (optional) for FcγR polymorphism (3 ml)		X															
Biomarker tumor sample (optional) for HER2 conversion and/or exploratory biomarker analysis[7]	X																X
Trastuzumab (SC or IV)			X[18]			X	X	X	X	X	X					X	
5-Fluorouracil[9]									X	X	X					X	
Epirubicin[10]									X	X	X					X	
Cyclophosphamide[11]									X	X	X					X	
Docetaxel[12]			X			X	X	X									
Adverse events			all AEs and SAEs														
Concomitant medication			continuous														

Source: Hannah Clinical Study Protocol (BO22227)

Table 16: Schedule of Assessments (Adjuvant Phase)

Study Week	25			28	31	34					37	40	43	46	49	52
Cycle	9			10	11	12					13	14	15	16	17	18
Day of cycle	1	2	15	1	1	1	2	4	8	15	1	1	1	1	1	1
Physical examination	X										X					X
Vital signs	X										X					X
ECOG performance status	X										X					X
Weight	X										X					X
Chest X-ray																X
Liver imaging																(X)
Bone scan[8]																(X)
Bilateral mammogram[1]																X
Hematology and Biochemistry[2]	X										X					X
PK blood sample (SC), (2 ml)[9]	X[5]	X	X	X[5]	X[5]	X[5]	X	X	X	X	X[5]					
PK blood sample (IV), (2 ml)[3]	X[6] X[7]	X	X	X[6] X[7]	X[6] X[7]	X[6] X[7]	X	X	X	X	X[6]					
ECG	X										X					X
LVEF (Echo or MUGA)	X										X					X
Trastuzumab (SC)[4]	X			X	X	X					X	X	X	X	X	X
Trastuzumab (IV)	X			X	X	X					X	X	X	X	X	X
Adverse events	all AEs and SAEs															
Concomitant Medication	continuous															

Source: Hannah Clinical Study Protocol (BO22227)

Dose Modification, Delay, and Discontinuation

IV and SC trastuzumab may be delayed to assess or treat adverse events (see Table 17 below). If IV trastuzumab administration is delayed more than 7 days from schedule a re-loading dose of 8 mg/kg needs to be administered before continuing again with the maintenance dose of 6 mg/kg. No dose adjustment is needed in case of delayed administration of SC trastuzumab, as a fixed dose of SC trastuzumab is given in this study.

Table 17: Dose Modifications in Case of Trastuzumab-Related Toxicity

Toxicity related to study treatment	Action
1. Non-hematological, grade 1 or 2 (excluding cardiac) toxicity	Continue with study treatment (all medication in the cycle)
2. Non-hematological, grade 3 or 4 (excluding cardiac) toxicity	Hold study treatment (all medication in the cycle) until recovery to grade ≤ 2. Toxicity resolved to grade ≤ 1 within a maximum of 5 weeks calculated from last administration: Resume study treatment. Toxicity did NOT resolve to grade ≤ 2 within a maximum of 5 weeks calculated from last administration: Discontinue trastuzumab permanently. Take patient off study. Continue treatment as deemed suitable by local investigator.
3. Recurrence of non-hematological, grade 3 or 4 (excluding cardiac) toxicity upon re-challenge	Discontinue trastuzumab permanently. Take patient off study. Continue treatment as deemed suitable by local investigator.
4. Cardiac toxicity (significant asymptomatic drop in LVEF (≥ 10 percentage points from baseline to a LVEF < 50%)	Study treatment (all medication in the cycle) to be held, continued or resumed according to the algorithm depicted in Appendix 4.
5. Cardiac toxicity (symptomatic congestive heart failure)	Trastuzumab to be discontinued permanently (patient to be taken off study)
6. Cardiac toxicity (other than significant asymptomatic LVEF drop or CHF)	Actions must follow rules 1. to 3. for non-hematological toxicities
7. Hematological toxicity – Neutropenia < 1.5 x 109/L	Hold study treatment (all medication in the cycle) until neutrophils ≥ 1.5 x 109/L.

Source: Hannah Clinical Study Protocol BO22227

Statistical Analysis Plan

Sample size justification for pCR comparison

Assuming pCR response rates of at least 40% in both arms 552 patients are necessary to conclude non-inferiority in pathological complete response rate with a power of 80% using a one-sided 97.5% confidence limit for the difference of the response rates and a non-inferiority margin of 12.5%. This number of patients accounts for a 10% drop-out rate in the patient population.

The justification of the 40% pCR rate is based on the data from the NOAH trial that achieved a pCR rate of 43% in patients with locally advanced disease including inflammatory breast cancer with a combination regimen including anthracyclines and taxanes.

Sample size justification for C trough comparison

PK sample size calculations are based on the coefficient of variation (CV) for the trough concentrations of trastuzumab from previous studies in MBC and EBC patients after q3w treatment. Since the situation prior to surgery is comparable to the MBC setting, an inter-patient CV of 60% is assumed. Hence, 130 patients per arm (i.e., a total of 260 patients) is needed to demonstrate Ctrough comparability with a power of 80% if the true means of the two formulations do not differ by more than 5%.

A population PK approach has been adopted for the analysis which allows to restrict the number of blood samples to be taken from each patient. However, the draw-back to this approach is that a relatively large number of patients needs to be included from which the data need to be collected. In the PK loading study (MO16982) only 37 of the 72 patients gave a useable amount of PK data for non-compartmental analysis. The number of patients with useable PK-data increased to 70 when the data were evaluated by model dependent (population PK) methods.

Compliance with Good Clinical Practices

The applicant stated and certified that the HannaH study was conducted in accordance with the principles of the "Declaration of Helsinki", and in compliance with Good Clinical Practices. Details of Ethics and Study Conduct were included in sections 9, 12.1, 12.2, 12.3, and 15.4 of the HannaH study protocol.

Study Populations

The intent-to-treat (ITT) population consists of all patients who had at least one tumor assessment after first study-drug administration. Patients are assigned to treatment groups as randomized.

The efficacy per protocol (EPP) population consists of all patients from the ITT population excluding those with eligibility or on-study violations.

The PK per protocol (PKPP) population consists of all the patients who had at least one measurable trastuzumab serum concentration and excludes patients with major protocol violations. Patients who have missing Ctrough measurements before the Cycle 8 dose or before the Cycle 13 dose will be excluded from the PK analysis for observed Ctrough but will be included for the PK analysis for predicted Ctrough.

The safety population (SP) population consists of all the patients who have received at least one dose of study medication (chemotherapy or trastuzumab). Patients will be analyzed as treated.

Statistical Methods for Efficacy Analyses

Primary Efficacy Endpoint - pCR

The primary efficacy endpoint pCR is analyzed in the EPP population. The following hypotheses will be tested: H_0: $\Pi_{SC} \leq \Pi_{IV} - \delta$ vs. H_1: $\Pi_{SC} > \Pi_{IV} - \delta$, where Π_{SC} and Π_{IV} are the pCRs in the

trastuzumab SC arm and the trastuzumab IV treatment arm, respectively, and δ is the non-inferiority margin (12.5%).

Non-inferiority in the pCR rate will be established if the lower limit of the one-sided 97.5% confidence interval for the difference in pCR rate computed using the continuity correction of Hauck and Anderson is above - 12.5% (absolute percentage points). The difference in pCR rate is defined as the pCR rate in the trastuzumab SC arm minus the pCR rate in the trastuzumab IV arm. pCR rates and 95% confidence limits according to Pearson-Clopper will also be calculated for single treatment groups.

Secondary Endpoints
tpCR and ORR rates and 95% confidence limits according to Pearson-Clopper will be calculated for the individual study arms. A 95% confidence interval for the difference in tpCR and ORR rate with use of the continuity correction of Hauck and Anderson will be provided.

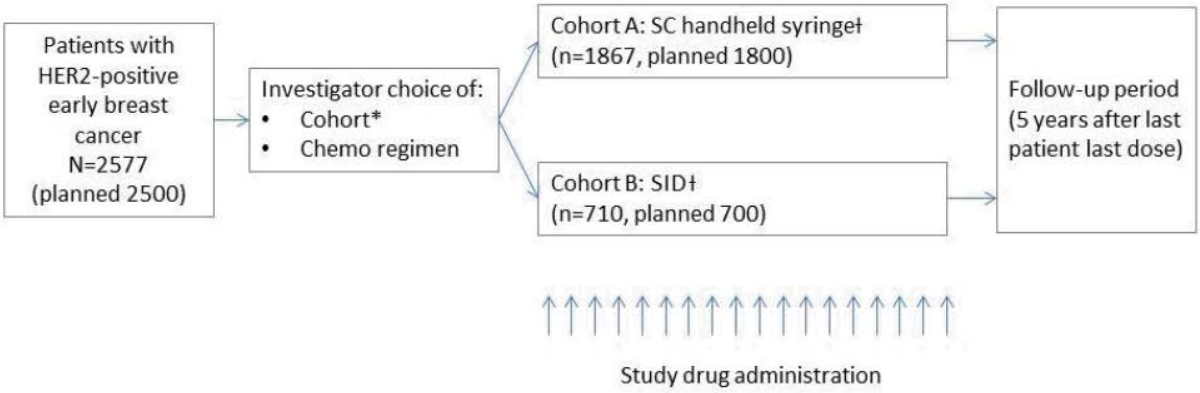
Time-to-event data (EFS and OS) will be summarized descriptively using estimates from the Kaplan-Meier survival curves. The two treatment arms will be compared with an unstratified two-sided log-rank test.

FDA Comments: In general, FDA prefers the ratio of proportions of pCR as the primary analysis instead of the difference of proportions, with symmetric confidence intervals to support an evaluation of no clinically meaningful differences.

7.3.2 SafeHER (MO28048)

SafeHER was a phase III prospective, two-cohort non-randomized, multicenter, multinational, open label study with the primary objective to assess the overall safety and tolerability of two SC trastuzumab administration methods in HER2-positive early (stage I-IIIC) stage breast cancer(Figure 6). Investigators enrolled patients into one of two cohorts (the difference being with the route of administration of study drug: either SC or single injection use). The applicant, for business purposes discontinued development of the single use injection method and only included data for cohort A as per previously agreed upon by the FDA. Patients with stage I-IIIC HER2+ breast cancer were enrolled to receive study drug either concurrently or sequentially with chemotherapy. The choice of which was at the discretion of the investigator. The majority of patients received SC trastuzumab in the adjuvant setting, with only 24 patients receiving SC trastuzumab in the neoadjuvant setting. For patients receiving SC trastuzumab with concurrent chemotherapy, SC trastuzumab was administered first, followed by chemotherapy, with 70% of patients receiving anthracycline containing regimens (60% concurrently, 30% sequentially) and 10% with no chemotherapy. The safety population (n=1864) included all patients who received at least one dose of SC trastuzumab. Patients received 600 mg SC trastuzumab for a total of 18 cycles. The median duration of follow up was 23.7mo (from 1st dose of drug).

Figure 6: Study Design for SafeHER



Source: Page 28, Figure 1 of the CSR for SafeHER

Study Endpoints

Primary:

- Assess overall safety and tolerability of Herceptin SC in HER2-positive EBC patients with assisted administration using a conventional syringe

Secondary

- Efficacy: DFS and OS
- Patient satisfaction with Herceptin SC administration using the SID device

Exploratory

- To assess immunogenicity of Herceptin SC and recombinant hyaluronidase (rHuPH20)
- To examine and characterize tolerability of Herceptin SC over a 6-hour time period after the start of the first administration and over a 2-hour time period after the start of subsequent Herceptin SC administrations
- To monitor SID usability in a subgroup of 48 patients in cohort B

Inclusion Criteria:

1. Signed written informed consent approved by the reviewing IEC
2. Female or male aged 18 years or above
3. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
4. Histologically confirmed early invasive HER2-positive carcinoma of the breast with no evidence of residual, locally recurrent or metastatic disease and defined as clinical stage (T1, N0, M0) to IIIC (any T, N3, M0) that was eligible for treatment with Herceptin. Note: Patients treated without neoadjuvant or adjuvant chemotherapy, such as patients with low risk node negative tumors ≤1.0cm, elderly patients (>65 years of age) or patients with HER2-positive EBC but denying chemotherapy, were also eligible to participate in the study, but their enrolment was limited to approximately 10% of the total study population
5. Her2-positive EBC, defined as IHC 3+ or a positive ISH testing by validated and approved methods within a certified laboratory

6. Screening LVEF ≥55% as measured by echocardiography, multi-gated acquisition (MUGA) scan or magnetic resonance imaging (MRI) per local practice
7. Agreement to use an adequate, non-hormonal means of contraception by women of childbearing potential (defined as pre-menopausal and not surgically sterilized or <1 year after the onset of menopause) and by male participants with partners of childbearing potential only. Examples of adequate contraceptive measures are an intra-uterine device, a barrier method (condoms, diaphragm) in conjunction with spermicidal jelly, or total abstinence. Oral, injectable, or implant hormonal contraceptives were not acceptable for females participating in the study.
8. Intact skin at site of SC injection on the thigh.

Exclusion Criteria:

Cancer Related Criteria:

1. Previous neoadjuvant or adjuvant breast cancer treatment with an approved or investigational anti-HER2 agent
2. History of other malignancy which could have affected compliance with the protocol or interpretation of results (including previous invasive ipsilateral or contralateral breast cancer). Patients with curatively treated carcinoma in site of the cervix or basal cell carcinoma, and patients with other curatively-treated malignancies, other than breast cancer, who have been disease-free for at least 5 years, were eligible.
3. Past history of ductal carcinoma in situ (DCIS) within the last 5 years that had been treated with systemic therapy OR with radiation therapy to the ipsilateral breast where invasive cancer subsequently developed. Patients who had their DCIS treated with surgery only were allowed to enter the study.
4. Metastatic disease

Hematologic, Biochemical, and Organ Function:

5. Inadequate bone marrow function (as indicated by any of the following):
    a. Total white blood cell count (WBC)<2,500/mm^3 (<2.5x10^9/L)
    b. Neutrophil count <1,500/mm^3 (<1.5 x 10^9/L)
    c. Platelets <100,000/mm^3 (<100 x 10^9/L
    d. Hemoglobin <10g/dL
6. Impaired hepatic function (as indicated by any of the following):
    a. Serum total bilirubin >1.5 x upper limit of normal (ULN)
    b. Alanine amino transferase (ALT)>2.5 x ULN
    c. Aspartate amino transferase (AST)>2.5 x ULN
    d. Alkaline phosphatase (ALP) >2.5 x ULN
7. Impaired renal function, as indicated by serum creatinine >1.5x ULN
8. Serious Cardiac illness or medical conditions including but not confined to:
    a. History of documented heart failure or systolic dysfunction (LVEF <50%)
    b. High-risk uncontrolled arrhythmia (ventricular tachycardia) of higher-grade atrioventricular (AV) block (second degree AV-block type 2 [Mobitz 2] or third degree AV-block)
    c. Angina pectoris requiring anti-anginal medication
    d. Clinically significant valvular heart disease

e. Evidence of transmural infarction on electrocardiogram (ECG)
f. Poorly controlled or uncontrolled hypertension (blood pressure consistently over 140/90 mmHg, despite treatment), or history of hypertensive crisis or hypertensive encephalopathy

9. Other concurrent serious diseases that could have interfered with planned treatment including severe pulmonary conditions/illness
10. Prior maximum cumulative dose of doxorubicin >360mg/m^2 or maximum cumulative dose of epirubicin >720mg/m^2 or equivalent
11. Known hypersensitivity to trastuzumab, murine proteins, or excipients, or a general hypersensitivity to adhesives (Cohort B only)
12. History of severe allergic or immunological reactions, e.g. difficult to control asthma.

General Exclusion Criteria:

13. Pregnancy or lactation
14. Unable or unwilling to comply with the requirements of the Protocol, as assessed by the investigator
15. Concurrent enrolment in another clinal trial using an investigational anti-cancer treatment, including hormonal therapy, bisphosphonates therapy and immunotherapy, within 28 days prior to the first dose of study treatment
16. Major surgical procedure or significant traumatic injury within 14 days prior to the first dose of study treatment or anticipated need for major surgery during the course of the study treatment except for breast cancer surgery for patients receiving study drug in the neoadjuvant setting. Patients had to be free of any clinically significant sequalae of prior surgery before receiving their first dose of study treatment
17. More than 12 weeks between the end of the last chemotherapy cycle and the first dose of study treatment, in case these treatments were imitated sequentially. This criterion did not apply to patients were starting Herceptin SC without previous or concurrent chemotherapy or concurrently with chemotherapy
18. Current peripheral neuropathy of Grade 3 or greater per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0.

Dose Modification, Delay, and Discontinuation

The following dose modifications were allowed for SC trastuzumab on the SafeHER study (Figure 7).

Figure 7: SC Trastuzumab Related Toxicity (SafeHER)

Toxicity related to study treatment	Action
1. Non-hematological, grade 1 or 2 (excluding cardiac) toxicity	Continue with study treatment (all medication in the cycle)
2. Non-hematological, grade 3 or 4 (excluding cardiac) toxicity	Hold study treatment (all medication in the cycle) until recovery to grade ≤ 2. Toxicity resolved to grade ≤ 2 within a maximum of 5 weeks calculated from last administration: Resume study treatment. Toxicity did NOT resolve to grade ≤ 2 within a maximum of 5 weeks calculated from last administration: Discontinue Herceptin SC permanently. Take patient off study. Continue treatment as deemed suitable by local investigator.
3. Recurrence of non-hematological, grade 3 or 4 (excluding cardiac) toxicity upon re-challenge	Discontinue Herceptin SC permanently. Take patient off study drug. Continue treatment as deemed suitable by local investigator.
4. Cardiac toxicity (significant asymptomatic drop in LVEF (≥ 10 percentage points from baseline to a LVEF < 50%)	Study treatment (all medication in the cycle) to be held, continued or resumed according to the algorithm depicted in Appendix 5.
5. Cardiac toxicity (symptomatic congestive heart failure)	Herceptin SC to be discontinued permanently (patient to be taken off study)
6. Cardiac toxicity (other than significant asymptomatic LVEF drop or CHF)	Actions must follow rules 1 to 3 for non-hematological toxicities
7. Hematological toxicity – Neutropenia < 1.5 x 10^9/L	Hold study treatment (all medication in the cycle) until neutrophils ≥ 1.5 x 10^9/L.

Source: Page 37, Table 2 of the CSR for SafeHER

The schedule of assessments is displayed in Figure 8 **and the Clinical Assessments included:**

1. Medical history and demographic data
2. Vital signs
3. Physical examination
4. Electrocardiograms
5. Performance status
6. Blood sampling for PK and immunogenicity assessments

Figure 8: Schedule of Assessments for SafeHER

Schedule of Assessments

Study week (Treatment Cycle #)	Screening	Study treatment 3-weekly (18 cycles)				Safety Follow-up visit [q] [r]	Follow-up visits [k] [r]
	day -28 to 1	Week 1 to 22 Cycles 1 to 8 [r][u]	Week 25 Cycle 9 [r]	Week 28 to 49 Cycles 10 to 17 [r]	Week 52 Cycle 18 [r]	4 weeks after last study treatment	(minimum 5 years after last study treatment)
Explain study and obtain signed Informed Consent [a]	x						
Demographic profile [b] and medical history	x						
HER2 Determination	x						
Review inclusion/exclusion criteria	x						
Physical Exam [c]	x	Approximately 3-monthly (every 4 cycles) [p]				x	x [k]
Weight, height [d]	x		x [d]				x [d]
Vital Signs [e]	x	Approximately 3-monthly (every 4 cycles) [e]				x	
ECOG performance status	x	Approximately 3-monthly (every 4 cycles) [p]				x	
Cardiac monitoring -12-lead ECG -LVEF [f] -Signs/symptoms	 x x [f] x	Approximately 3-monthly (every 4 cycles) [p]				X [s]	Cardiac assessments at 6, 12 and 24 months, and at 3, 4 and 5 years following treatment cessation
Pregnancy test [g]	x	as clinically indicated					

Study week (Treatment Cycle #)	Screening	Study treatment 3-weekly (18 cycles)				Safety Follow-up visit [q] [r]	Follow-up visits [k] [r]
	day -28 to 1	Week 1 to 22 Cycles 1 to 8 [r][u]	Week 25 Cycle 9 [r]	Week 28 to 49 Cycles 10 to 17 [r]	Week 52 Cycle 18 [r]	4 weeks after last study treatment	(minimum 5 years after last study treatment)
Blood samples for immunogenicity and PK testing [h]	x [h]		x [h]				x (6-month after last study treatment)
Haematology and biochemistry [i]	X [t]		x		x	x	
Imaging scan to exclude residual/recurrent disease [j]	x						
Routine Breast-cancer follow-up [k]		Assessments as per institutional practice or ASCO adjuvant follow-up guidelines 2006 to be reported 6-monthly [k]					
AEs and SAEs [l]	x	x	x	x	x	x	x
Concomitant medication [m]	x	x	x	x	x	x	x [m]
Trastuzumab SC [n]		x	x	x	x		
Exploratory Observation Time [v]		x	x	x	x		
SID monitoring questionnaire [w]		x	x	x	x		
Treatment compliance		x	x	x	x		
SID satisfaction questionnaire [o]		After Cycle 4 [o]				x	
Survival		x	x	x	x	x	X (at 24 months and at 3, 4 and 5 years after last treatment)

First dose of study drug = study Cycle 1, Day 1

Source: Page 9662 and 9663, Appendix 1 of the CSR for SafeHER

Statistical Analysis Plan

A total sample size of 2500: 1800 in cohort A and 700 in cohort B. There were no formal statistical hypotheses and all safety endpoints were presented by 95% confidence intervals and descriptively explained. The study population included all enrolled patients who received at least one dose of the study medication.

The primary objective

- Safety, to include: All adverse events (AE), injection site reactions (ISR), administration related reactions (ARRs), Grade ≥ 3 AEs, Serious adverse events (SAE), AEs leading to premature discontinuation of study treatment, AEs causing interruption of trastuzumab

SC, Cardiac AEs, Congestive Heart Failure (CHF) related AEs, premature withdrawals from study and study medication, exposure to treatment, laboratory parameters, left ventricular ejection fraction (LVEF), vital signs, electrocardiogram (ECG), weight, Eastern Co-operative Oncology Group (ECOG) performance status

The secondary objective

- Disease Free survival (DFS)
- Overall Survival (OS)
- Patient satisfaction with trastuzumab SC administration using the SID (patient in Cohort B who went on to self-administration of the study drug)

The exploratory objective

- To assess the immunogenicity of trastuzumab and recombinant hyaluronidase (rHuPH20) in subset of patients receiving trastuzumab SC using the SID (Cohort B) at selected sites
- To examine and characterize tolerability of the trastuzumab SC over a 6-hour time period after the start of the first administration and over a 2-hour time period after the start of subsequent trastuzumab administrations [only in patients using the SID (Cohort B)]
- Monitoring of SID usability in a subgroup of 48 patients in Cohort B

Protocol Amendments

Amendment 1:

- Allowed patients to be treated with Herceptin SC according to the EBC indication
- Allowed a sub-population of patients to be enrolled under similar circumstances to HANNAH
- Protocol allowed the patient treatment to be closely aligned to that of standard clinical care in patients with EBC
- Enrollment of patients eligible for neoadjuvant Herceptin SC
- Clarification of recommended chemotherapy regimens in the neo-adjuvant setting
- Extension of treatment-free follow up period from 2 to 5 years
- Changes in SAE reporting: all SAEs regardless of relationship to study drug were reported

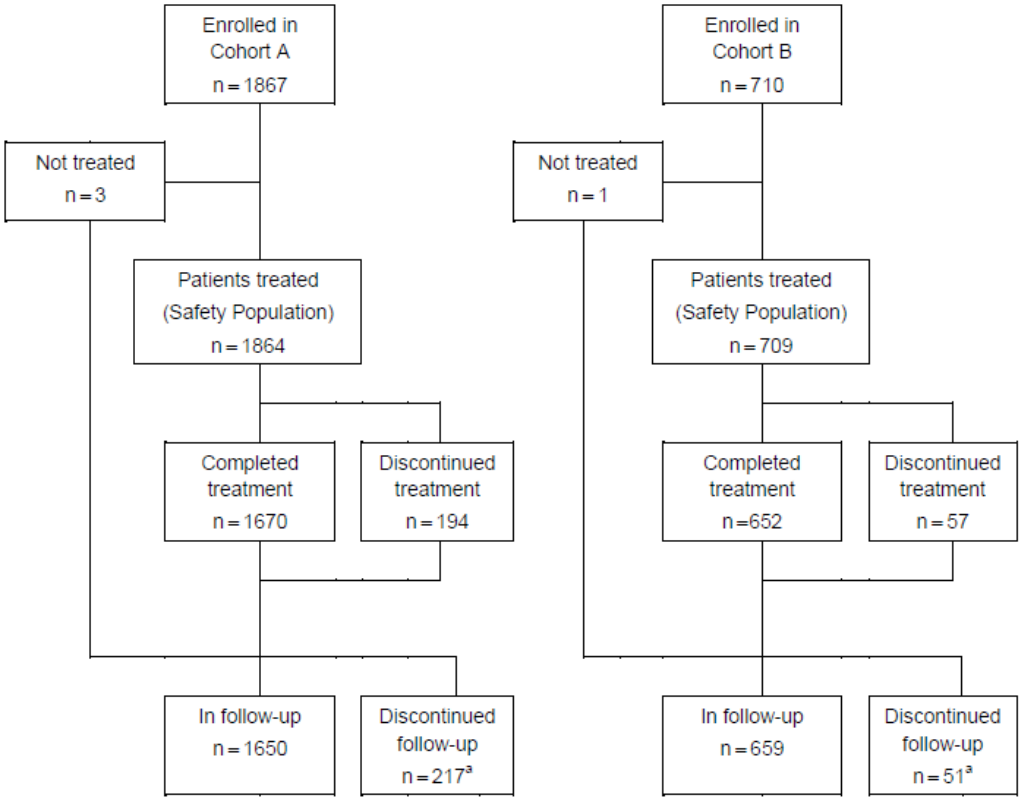
Amendment 2:

- The definition of the treatment period was extended from 28 days post last dose to 33 days

Patients disposition

The patient disposition at the cutoff for the primary analysis is listed in Figure 9.

Figure 9: Patient Disposition at the Primary Analysis (SafeHER)



Source: Page 46, Figure 2 of the CSR for SafeHER

FDA Comments: The purpose of SAFEHER was to assess safety and tolerability of SC trastuzumab. The study design is overall acceptable.

7.3.3 PrefHER (MO22982)

This amendment history covers all changes from protocol version 1.0, May 2011 to protocol version 3.0, dated February 2012:

- Addition of information to support rationale for study design (use of SC trastuzumab)
- Addition of a second cohort to the PrefHER study (cohort 2, SC vial)
- Reduction of total number of treatment cycles from 22 to 18.
- Removal of requirement for additional cardiac assessment if patient has been assessed previously.
- Option to receive SC trastuzumab after the crossover period (cohort 1, SID)
- Clarification to inclusion criteria 3 has been made to specify the time between a patient finishing chemotherapy and enrollment into the study. This time period has been clarified as a maximum of approximately 3 months.
- Assessment for Immunogenicity
- Safety Guidance for adverse event grading
- Change in vial size
- Correction of minor typographical errors

PrefHER was a preference study in the adjuvant treatment setting in patients with HER2−positive EBC that had completed surgery and chemotherapy (chemotherapy could have been in the neoadjuvant or adjuvant treatment setting). The primary objective of the trial was to evaluate the proportion of patients indicating an overall preference for either SC trastuzumab injection or IV trastuzumab infusion. Secondary objectives included evaluation of health care provider (HCP) satisfaction with SC trastuzumab, HCP perceived time savings with preparation and administration of SC trastuzumab, safety and tolerability, and efficacy (event free survival [EFS]). Exploratory objectives included evaluation of factors that influence patient preference for SC trastuzumab injection.

The study recruited women (≥18 years old) with histologically confirmed HER2-positive EBC who had completed surgery and chemotherapy (neoadjuvant or adjuvant) and who had no evidence of residual, locally recurrent, or metastatic disease after completion of surgery and chemotherapy (neoadjuvant or adjuvant). Patients must have completed all neoadjuvant chemotherapy but could enter the trial while adjuvant radiotherapy was ongoing. Patients may have already received IV trastuzumab as part of a concurrent regimen with neoadjuvant chemotherapy or in a sequential regimen following neoadjuvant chemotherapy. However, patients must have had at least eight out of the total 18 planned q3w intravenous trastuzumab cycles remaining.

Patients were randomized following the completion of neoadjuvant chemotherapy and surgery in a 1:1 randomization to one of two sequences of trastuzumab treatment in Cohort 1:

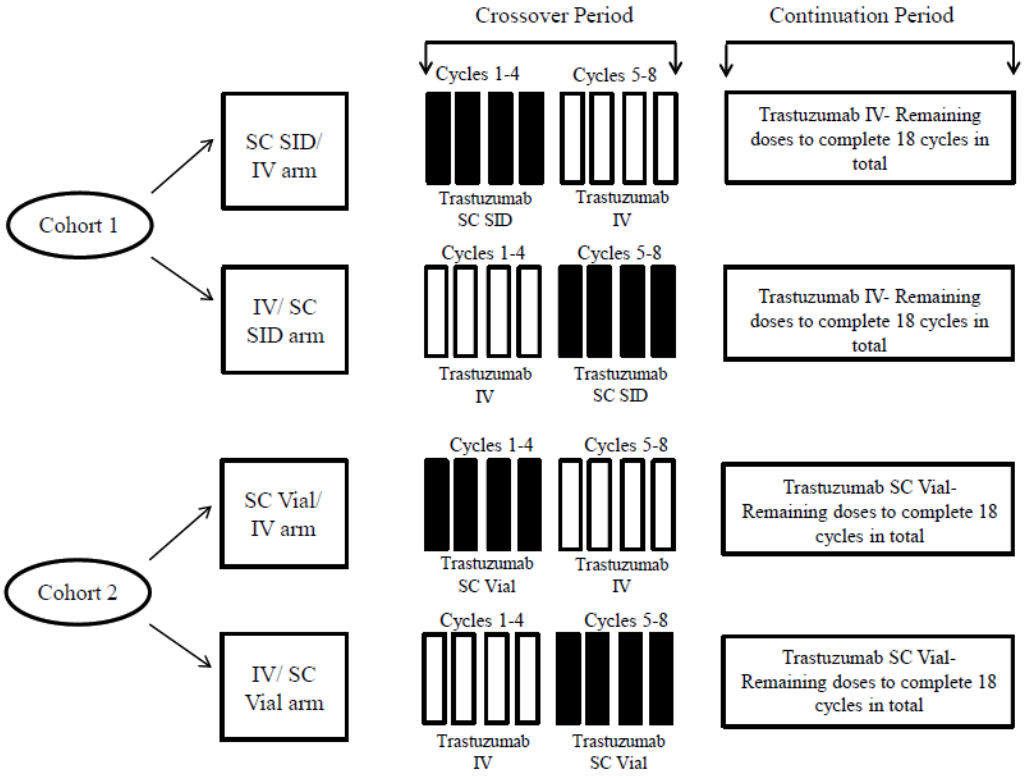
- Arm A: 4 cycles of SC trastuzumab single-use injection device (SID) followed by 4 cycles of IV trastuzumab
- Arm B: 4 cycles of IV trastuzumab followed by 4 cycles of SC trastuzumab SID

A second cohort (Cohort 2) was added to the trial (via protocol amendment) to provide additional information regarding patient and HCP preference for either Herceptin SC Vial or IV trastuzumab administration. This second cohort also evaluated two sequences of trastuzumab:

- Arm A: 4 cycles of SC trastuzumab Vial followed by 4 cycles of IV trastuzumab
- Arm B: 4 cycles of IV trastuzumab followed by 4 cycles of SC trastuzumab Vial

As the presentation of data for PrefHER in this regulatory submission focuses on the SC trastuzumab Vial (Cohort 2: IV trastuzumab and SC trastuzumab Vial sequences). Results for patients enrolled in Cohort 1 (IV trastuzumab and SC trastuzumab SID sequences) were not submitted by the applicant as agreed upon at the preBLA on October 7, 2017, as the applicant stated the SID is no longer in development for business reasons. However, a complete overview of the PrefHER study design is provided below in Figure 10.

Figure 10: PrefHER Study Design



IV = intravenous; SC = subcutaneous; SID = single-use injection device.

Source: Section 2.7.3, page 26 of the Summary of Clinical Review

As prior neoadjuvant and/or adjuvant treatment may have also included trastuzumab, randomization of patients in each cohort was stratified by de novo (first time exposure to trastuzumab) versus non de novo (previous exposure to trastuzumab) status.

In cohort 2, 121 patients in arm A received 4 cycles of SC trastuzumab followed by 4 cycles of intravenous trastuzumab and 119 patients in arm B received 4 cycles of intravenous trastuzumab followed by 4 cycles of SC trastuzumab. Both arms received a total of 18 cycles of a trastuzumab-containing product. For patients who had already started adjuvant trastuzumab (as monotherapy following completion of chemotherapy or in combination with adjuvant chemotherapy followed by trastuzumab monotherapy), the first dose of trastuzumab on the PrefHER study was given 3 weeks after the last dose of trastuzumab that was received prior to randomization in the PrefHER study.

The PrefHER study treatment period included the first eight treatment cycles following randomization, during which the crossover design was implemented. Subsequently, all patients continued to receive additional cycles of adjuvant treatment with trastuzumab (continuation period) to complete a total of 18 cycles of trastuzumab (unless disease recurrence, unacceptable toxicity, or patient withdrawal necessitated early cessation of treatment). The dose and schedule of IV trastuzumab throughout the study were those of the standard

approved regimen, i.e., an 8 mg/kg loading dose followed by 6 mg/kg maintenance doses q3w. SC trastuzumab was given q3w at the fixed dose of 600 mg regardless of patient weight, and not requiring a loading dose. Dose reductions of SC trastuzumab or IV trastuzumab were not permitted for any reason; however, dosing delays to manage toxicities were recommended as per the standard of care and for not longer than 7 days. Patients who experienced infusion-related symptoms could be pre-medicated with paracetamol and antihistamines for subsequent injections.

The primary analysis of PrefHER with a clinical cutoff date of 23 May 2013 was planned per protocol to occur after all patients in both cohorts had completed the study treatment period of eight cycles of therapy following randomization (i.e., the crossover period). The study ended (last patient last visit) on December 3, 2015, 3 years after the randomization of the last patient in the study. The final efficacy analysis for this study included 3-year EFS rates based on the clinical cutoff date of December 7, 2015.

The sample size considerations for the PrefHER study design assumed a rate of 65% of patients preferring SC trastuzumab aiming at a distance from the estimated proportion to the CI limits of ±7.5%. A total of 160 patients were needed to evaluate preference. An observed rate of 65% of patients preferring SC trastuzumab could be estimated to be within 57.5% and 72.5% with a probability of 95%. To allow for 20% of the patients not providing an evaluable preference assessment, approximately 200 patients were planned to be randomized into each cohort in the trial.

FDA Comments: The randomization scheme was stratified by whether or not the patient had received trastuzumab prior to trial entry, therefore the issue of recall error was acknowledged; however, the recall with this cross-over study design was consistent to previous preference studies. The susceptibility to bias of preference for SC was expected; however, there were also patients with this preference distributed across both treatment arms making this acceptable. The methods used to conduct the telephone interviews appear to be consistent with best practices of survey research (e.g., the applicant sought expert opinion and patient input for item generation of the interview guide, translated the interview guide using forward and backward translation, and pilot-tested the interview guide). While interviewer bias is a common limitation of telephone interviews/surveys, the extent of such a bias is unknown and cannot be fully eliminated. In an effort to mitigate this limitation, the applicant recorded the telephone interviews for quality control purposes. The patient preference telephone interviews appear to be conducted in a standard manner.

7.4 Review Strategy

The HannaH, SafeHER, and PrefHER studies served as the primary basis for the review. The clinical efficacy review was conducted by Dr. Danielle Krol and the safety review was done by Dr. Candace Mainor 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:

- Review of FDA regulatory history and meeting minutes pertaining to the development of the subcutaneous product.
- Review of applicant submitted CSR, protocol, protocol amendments, and pertinent datasets for Study BO22227 (HannaH) and MO28048 (SafeHER)
- Review of CSR, protocol, protocol amendments and patient reported questionnaire and answers for study MO22982 (PrefHER).
- Review of selected case report forms (CRFs) for HannaH and SafeHER
- Review of selected patient narratives for adverse events of special interest and deaths in HannaH and SafeHER
- 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 subcutaneous products

Safety and efficacy data including data analysis datasets, and clinical study reports were reviewed. In order to reproduce key efficacy and safety analysis, including additional exploratory analysis, JMP, JReview, FDA's AutoSafety Tool and MAED tools were used. Analysis were performed by the clinical review team unless otherwise specified.

8 Statistical and Clinical and Evaluation

8.1 Review of Relevant Individual Trials Used to Support Efficacy

8.1.1 HannaH (Study B022227)

The study design of HannaH is discussed in Section 7.2.1 above. HannaH was the only clinical study submitted by the applicant to support the efficacy of SC trastuzumab.

Study Populations

The SC trastuzumab study arm is referred to as "SC" and the intravenous trastuzumab study arm is referred to as "IV" in the tables that follow. Table 18 shows the number of patients enrolled in the various study populations in HannaH study. A total of 596 patients were randomized, 297 to the subcutaneous arm and 299 to the IV arm.

Table 18: Analysis Populations in HannaH Study

Population	SC N	IV N	Total N
All randomized	297	299	596
Safety	297	298	595
ITT	294	297	591
EPP	260	263	523

SC: subcutaneous trastuzumab
IV: intravenous trastuzumab
Source: demoext.xpt

A total of 591 patients (294 patients the SC arm and 297 patients in the IV arm) were included in the ITT population. Five patients (two patients in the IV arm, three patients in the SC arm) were excluded from the ITT population because they did not have at least one efficacy assessment after baseline.

The EPP population included 523 patients (263 patients in the IV trastuzumab arm and 260 patients in the SC trastuzumab arm). A total of 73 patients were excluded from the EPP population due to at least one major protocol violation, 36 patients from the IV trastuzumab arm and 37 patients from the SC trastuzumab arm. The most common reason for exclusion from the EPP was that patients received less than eight cycles of chemotherapy (21 patients in each treatment arm). The reasons are summarized in Table 22 below.

The safety population included all patients who received at least one dose of study medication and comprised 595 patients (298 patients in IV trastuzumab and 297 patients in SC trastuzumab).

FDA Comments: Patients excluded for missing efficacy assessments and protocol violations are similar across both arms in the ITT and the EPP sets. There are no significant findings or differences between the analysis populations.

Demographics

This was an international study with a total of 523 patients in the EPP population (591 in the ITT set) enrolled in 24 countries, which are listed in Table 19.

Table 19: Enrollment by Country in the HannaH Study

	ITT Population		EPP Set	
Country	**SC N=294 n (%)**	**IV N=297 n (%)**	**SC N=260 n (%)**	**IV N=263 n (%)**
Brazil	28 (10)	23 (8)	27 (10)	23 (9)
Canada	2 (1)	1 (0)	2 (1)	0 (0)
China	4 (1)	2 (1)	4 (2)	2 (1)
Columbia	3 (1)	2 (1)	3 (1)	2 (1)
Czech Republic	8 (3)	9 (3)	7 (3)	8 (3)
Estonia	1 (0)	0 (0)	1 (0)	0 (0)
France	13 (4)	13 (4)	11 (4)	13 (5)
Germany	20 (7)	24 (8)	20 (8)	23 (9)
Guatemala	2 (1)	1 (0)	2 (1)	1 (0)
Hungary	11 (4)	7 (2)	5 (2)	4 (2)
Italy	6 (2)	5 (2)	6 (2)	4 (2)
Mexico	0 (0)	1 (0)	0 (0)	1 (0)
Panama	3 (1)	5 (2)	1 (0)	3 (1)
Peru	14 (5)	13 (4)	13 (5)	12 (5)
Poland	22 (7)	25 (8)	19 (7)	20 (8)
Republic of Korea	28 (10)	23 (8)	27 (10)	22 (8)
Russia	60 (20)	73 (25)	51 (20)	65 (25)
Slovakia	7 (2)	5 (2)	6 (2)	5 (2)
South Africa	16 (5)	15 (5)	13 (5)	11 (4)
Spain	8 (3)	11 (4)	8 (3)	9 (3)
Sweden	2 (1)	2 (1)	1 (0)	2 (1)
Taiwan	17 (6)	20 (7)	16 (6)	17 (6)
Thailand	14 (5)	14 (5)	12 (5)	13 (5)
Turkey	5 (2)	3 (1)	5 (2)	3 (1)

SC: subcutaneous trastuzumab
IV: intravenous trastuzumab
Source: demoext.xpt

FDA Comments: Patients were well-balanced between the SC and IV arms. While there were no sites in the United States, this is unlikely to impact the generalizability of SC trastuzumab to the U.S. population as the efficacy and safety of trastuzumab-containing products are not expected to differ based on race or ethnicity.

The demographic and baseline characteristics of the patients enrolled in the HannaH study are shown in Table 20 below for the ITT and EPP patient populations. All patients enrolled were female.

Table 20: Demographic and Baseline Disease Characteristics in the ITT and EPP Patient Populations in the HannaH Study

	ITT Population		EPP Set	
Country	**SC N=294 n (%)**	**IV N=297 n (%)**	**SC N=260 n (%)**	**IV N=263 n (%)**
Age (years)				
Mean (SD)	50.33 (11.08)	49.47 (10.83)	50.17 (10.95)	49.59 (10.86)
Median (range)	50 (25,81)	50 (24,77)	50 (25,81)	50 (24,77)
Age Categories				
<65	261 (89)	274 (92)	233 (90)	243 (92)
>=65	33 (11)	23 (8)	27 (10)	20 (8)
Race Categories				
White	197 (67)	207 (70)	171 (66)	181 (69)
Asian	64 (22)	61 (21)	60 (23)	56 (21)
Black	10 (3)	6 (2)	9 (3)	6 (2)
American Indian/Alaska Native	3 (1)	3 (1)	1 (0)	1 (0)
Other	20 (8)	20 (7)	19 (7)	19 (8)
Region Categories				
Asia Pacific	63 (21)	59 (20)	59 (23)	54 (21)
Eastern European Area	114 (39)	122 (41)	94 (36)	105 (40)
South Africa	16 (5)	15 (5)	13 (5)	11 (4)
South America	50 (17)	45 (15)	46 (18)	42 (16)
Western EU (incl. Canada)	51 (17)	56 (19)	48 (18)	51 (19)
Breast Cancer Type				
Inflammatory	20 (7)	19 (6)	19 (7)	15 (6)
Locally Advanced	123 (42)	115 (39)	105 (40)	99 (38)
Operable	151 (51)	163 (55)	136 (52)	149 (57)
Breast Cancer Subtype				
Unknown	1 (0)	0 (0)	0 (0)	0 (0)
Ductal	272 (93)	273 (92)	240 (92)	240 (91)
Lobular	12 (4)	17 (6)	12 (5)	17 (6)
Other	9 (3)	7 (2)	8 (3)	6 (2)
Reproductive Status				
Childbearing potential with contraceptive protection	142 (48)	152 (51)	125 (48)	136 (52)
Post-menopausal	122 (41)	103 (35)	107 (41)	90 (34)

Surgically sterilized	30 (10)	42 (14)	28 (11)	37 (14)
Estrogen Receptor Status				
Negative	140 (48)	148 (50)	125 (48)	132 (50)
Positive	154 (52)	148 (50)	135 (52)	130 (49)
Unknown	0 (0)	1 (0)	0 (0)	1 (0)
Progesterone Receptor Status				
Negative	175 (60)	178 (60)	154 (59)	156 (59)
Positive	119 (40)	116 (39)	106 (41)	104 (40)
Unknown	0 (0)	3 (1)	0 (0)	3 (1)
ECOG at Baseline				
Unknown	1 (0)	1 (0)	1 (0)	1 (0)
0	250 (85)	254 (86)	221 (85)	223 (85)
1	43 (15)	42 (14)	38 (15)	39 (15)
HER2 Status				
Negative	26 (9)	28 (9)	22 (8)	25 (10)
Positive	268 (91)	269 (91)	238 (92)	238 (90)
T stage				
Unknown	1 (0)	0 (0)	0 (0)	0 (0)
T1	19 (6)	23 (8)	18 (7)	19 (7)
T2	129 (44)	130 (44)	113 (43)	119 (45)
T3	52 (18)	49 (16)	47 (18)	45 (17)
T4	93 (32)	95 (32)	82 (32)	80 (30)
Measurable Disease at Baseline				
No	2 (1)	4 (1)	2 (1)	3 (1)
Yes	292 (99)	293 (99)	258 (99)	260 (99)

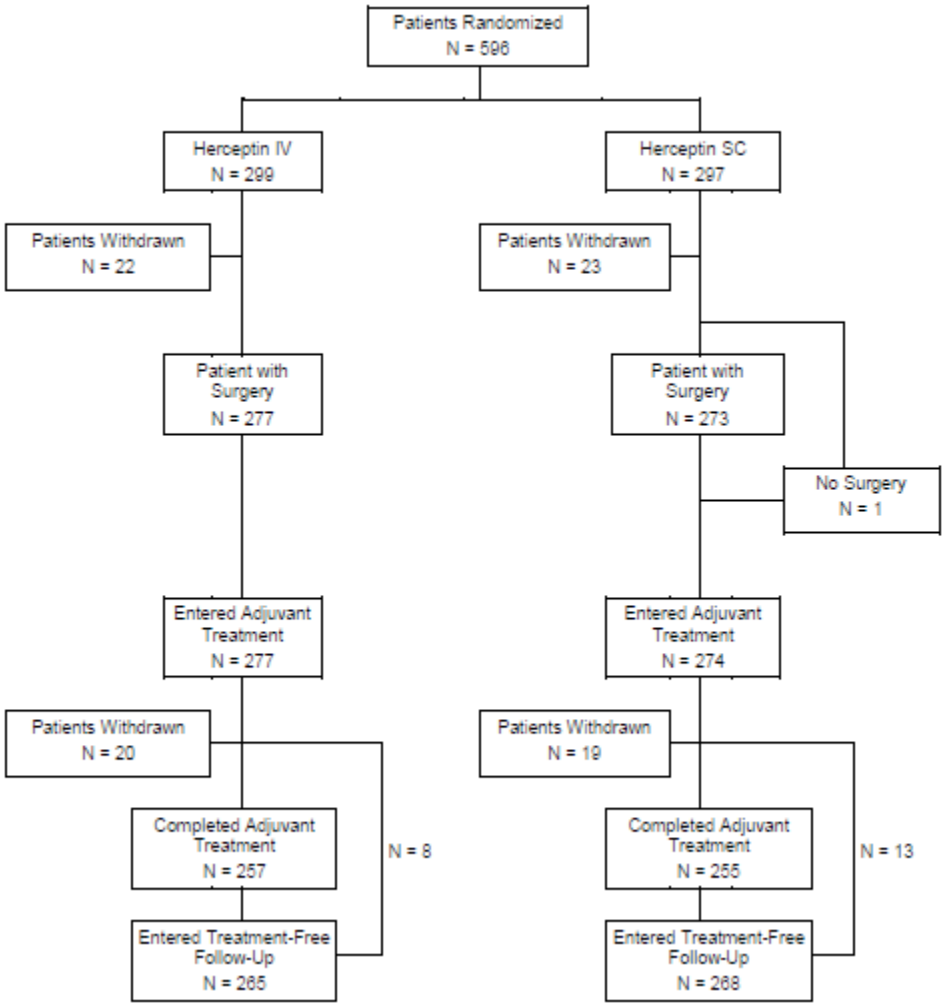
Source: demoext.xpt

FDA Comments: Baseline patient demographics and disease characteristics were well balanced between the two arms.

Patient Disposition

Patient disposition for the HannaH study is described in the tables below. Table 21 summarizes the patient disposition for all randomized patients during the neoadjuvant and adjuvant phases of the study until they entered treatment-free follow-up.

Table 21: Patient Disposition for All Randomized Patients During the Neoadjuvant and Adjuvant Phases of HannaH



Source: Figure 3 of the BO22227 (HannaH) Summary of Clinical efficacy

FDA Comments: 596 patients were recruited to the HannaH study. A total of 550 patients (277 patients in IV trastuzumab, 273 patients in SC trastuzumab) underwent surgery, and 551 patients entered the adjuvant treatment phase (277 patients in the IV trastuzumab arm and 274 patients in the SC trastuzumab arm). The primary analysis of the co-primary endpoints was performed with a clinical cutoff of 12 July 2011 after all 596 randomized patients had undergone surgery (unless they were prematurely withdrawn) and at least 100 patients in each arm had completed the full treatment phase of 1 year.

At the time of the final analysis with a data lock on January 24, 2017, patients had been followed up (treatment and treatment-free follow-up phases) for a median duration of approximately 72 months in both the IV trastuzumab and SC trastuzumab arms.

Patients who completed the adjuvant treatment phase and patients prematurely withdrawn from adjuvant treatment for reasons other than disease recurrence entered treatment-free follow-up; 533 patients (265 patients [88.6%] in IV trastuzumab, 268 patients [90.2%] in SC trastuzumab). Overall these were well balanced between the two arms with no concerning findings.

Protocol Violations/Deviations
Relevant protocol deviations are summarized in the table below.

Table 22: Relevant Protocol Deviations (HannaH)

Protocol Deviation	N
IV trastuzumab loading dose infusion duration <60min	7
Abnormal laboratory tests at baseline	7
No follow-up LVEF exam performed within 4 weeks of a significant LVEF drop in an asymptomatic patient	3
Administration of chemotherapy dose greater than docetaxel 100mg/m2, 5-FU 600mg/m2, epirubicin 90 mg/m2, cyclophosphamide 60mg/m2	4
Baseline EVEF is < 55% measured by echocardiography or MUGA scan prior to first dose of trastuzumab	1

Source: Section 4.4 from CSR research report NO. 1079038

FDA Comments: Overall, 22 patients had a major protocol violation that did not lead to exclusion from analysis population, 15 in the IV trastuzumab arm and 7 patients in the SC arm. It is not likely that these reported protocol deviations would significantly impact the interpretation of the study results as these were infrequent.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use
The following medications were allowed to be used by the discretion of the investigator:

- Paracetamol (acetaminophen), antihistamines and other supportive medications for the treatment of infusion related reaction related to SC and IV trastuzumab.
- Hematopoietic growth factors may be used to treat symptomatic neutropenia.
- Patients with anemia should be treated according to routine clinical practice; with hemoglobin being maintained above 10 g/dL.
- Anti-emetics per protocol of each clinical site.
- Mesna should be given with cyclophosphamide.
- Post-surgery radiotherapy
- Adjuvant tamoxifen, LHRH agonists or aromatase inhibitors with hormone receptor positive (estrogen and/or progesterone receptor) positive disease after surgery.
- Bisphosphonate therapy.

The following treatments were not permitted:

- Treatment with other systemic anti-cancer agents (e.g. chemotherapy, hormonal therapy different from the above mentioned, immunotherapy) or other treatments not part of protocol-specified anti-cancer therapy.
- Concurrent investigational agents of any type.

8.1.2 HannaH Study Results

Efficacy Results – Primary Endpoint

In the primary analysis EPP population the pCR rates were 40.7% (95% CI: 34.7%, 46.9%) in the IV arm and 45.4% (95% CI: 39.2%, 51.7%) in the SC arm, resulting in an absolute difference of 4.7% in favor of the SC arm. The results of the primary endpoint in the EPP and ITT population are shown in Table 23 and Table 24.

Table 23: pCR in the EPP Set of Patients in the HannaH Study

pCR in EPP	**SC N=260 (%)**	**IV N=263 (%)**
pCR = Absence of invasive neoplastic cells in breast	118 (45.4)	107 (40.7)
Exact 95% CI for pCR Rate	(39.2,51.7)	(34.7, 47)
Difference in pCR (SQ minus IV arm)	4.70	
95% CI for the difference in pCR	(-4.0, 13.4)	

SC: subcutaneous trastuzumab
IV: intravenous trastuzumab
Source: events.xpt

Table 24: pCR in the ITT Patient Set in the HannaH Study

pCR in ITT	**SC N=294 (%)**	**IV N=297 (%)**
pCR = Absence of invasive neoplastic cells in breast	124 (42.2)	111 (37.4)
Exact 95% CI for pCR Rate	(36.5, 48.0)	(31.9, 43.1)
Difference in pCR (SQ minus IV arm)	4.80	
95% CI for the difference in pCR	(-3.3, 12.9)	

SC: subcutaneous trastuzumab
IV: intravenous trastuzumab
Source: events.xpt

The trial also met the C-trough co-primary endpoint objective. Details of this PK endpoint are in Section 6.1 above.

FDA Comments: The trial met its co-primary objective and demonstrated comparability in the pCR rates since the lower bound of the one-sided 97.5% CI for the difference in pCR in -4.0 which is greater than -12.5 and hence comparability is demonstrated. Additional sensitivity analyses further support comparability of the pCR rates in the ITT population.

Efficacy Results – Secondary and other relevant endpoints

Additional secondary efficacy endpoints are summarized in this section. The tpCR rates in the EPP patient population are summarized in Table 25 and are 39% (95%CI: 33.3, 46) on the SC arm as compared to 34% (95%CI: 28.5, 40) on the IV arm. The difference of 5% (95%CI: -3.5,13.5) is in favor of the SC arm.

Table 25: Summary of Total Pathological Complete Response in EPP Patient Population (HannaH)

tpCR	**SC N=260 (%)**	**IV N=263 (%)**
Absence of invasive neoplastic cells	102 (39)	90 (34)
Exact 95% CI	(33.3, 46)	(28.5, 40)
Difference in tpCR (SC minus IV arm)	5.01 (-3.5,13.5)	

SC: subcutaneous trastuzumab
IV: intravenous trastuzumab
Source: events.xpt

The ORR results are summarized in Table 26 and are 87% (95%CI: 82.5, 91.0) and 89% (95%CI: 84.4, 92.4) for the SC and IV arms, respectively, with the difference in favor of the IV arm.

Table 26: **Summary of ORR in EPP Patient Population (HannaH)**

ORR	**SC N=258 (%)**	**IV N=260 (%)**
Responders	225 (87)	231 (89)
Non-responders	33 (13)	29 (11)
95% CI for Response Rates	(82.5, 91.0)	(84.4, 92.4)
Difference in Response Rates	-1.64 (-7.4, 4.2)	
Odds Ratio	0.86 (0.50, 1.46)	
Complete Response	56 (22)	55 (21)
Partial Response	169 (66)	176 (68)
Stable Disease	16 (6)	10 (4)
Progressive Disease	6 (2)	5 (2)
Missing	11 (4)	14 (5)

SC: subcutaneous trastuzumab
IV: intravenous trastuzumab
Source: events.xpt

FDA Comments: The results in the ITT population for tpCR and ORR are similar to those observed in the EPP patient population.

Table 27 summarizes the EFS and OS results in the ITT population. At the time of the final analysis, the median duration of follow-up for EFS was of 71.9 months (range 1 – 76 months) in the SC arm and 72.0 months (range 1 – 82 months) in the IV arm. The HR for EFS is 0.98 (95% CI: 0.74; 1.29). A Kaplan-Meier plot of EFS is provided in Figure 11. 99 patients (33.3 %) in the IV arm and 96 patients (32.7%) in the SC arm had experienced an event (disease recurrence or progression [local, regional, distant, or contra-lateral] or death due to any cause).

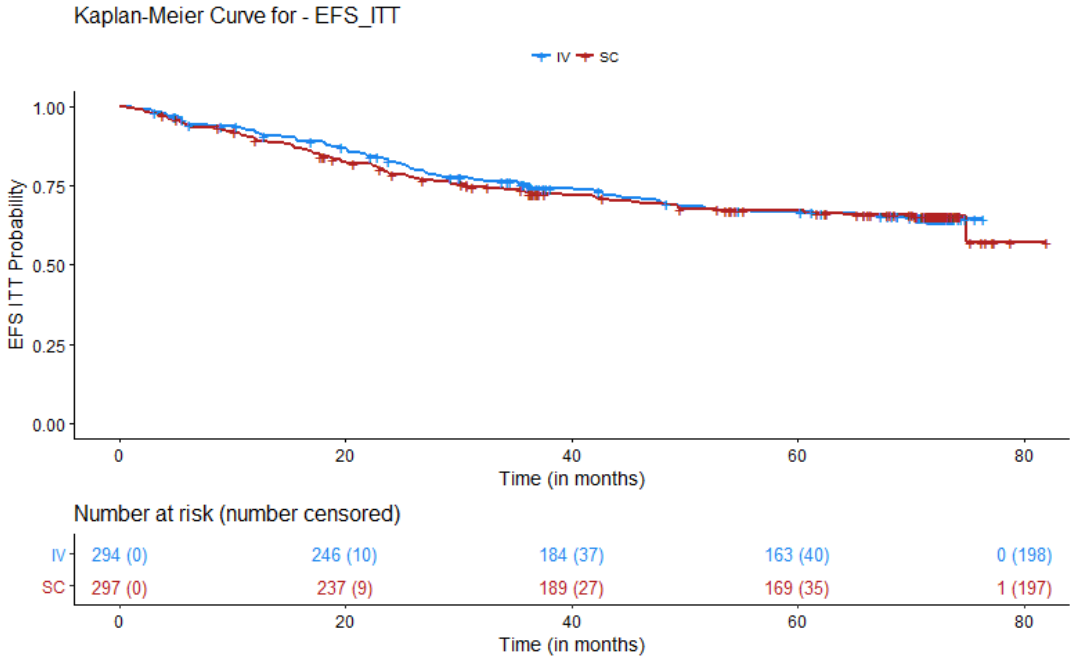
The HR for OS is 0.94 (95% CI:0.61; 1.45). The Kaplan-Meier plot for OS is shown in Figure 12. A total of 43 (15%) patients in the IV arm and 40 (14%) patients in the SC arm had died in the ITT population.

Table 27: **Summary of EFS and OS in the ITT Patient Population (HannaH)**

	SC N=294	**IV N=297**
EFS		
Patients with event (%)	96 (33)	99 (33)
Patients without event (%)	198 (67)	198 (67)
Median (95% CI)	NR (NE, NE)	NR (75, NE)
HR (95% CI)	0.98 (0.74, 1.29)	
OS		
Patients with event (%)	40 (14)	43 (15)
Patients without event (%)	254 (86)	254 (86)
Median (95% CI)	NR	NR
HR (95% CI)	0.94 (0.61, 1.45)	

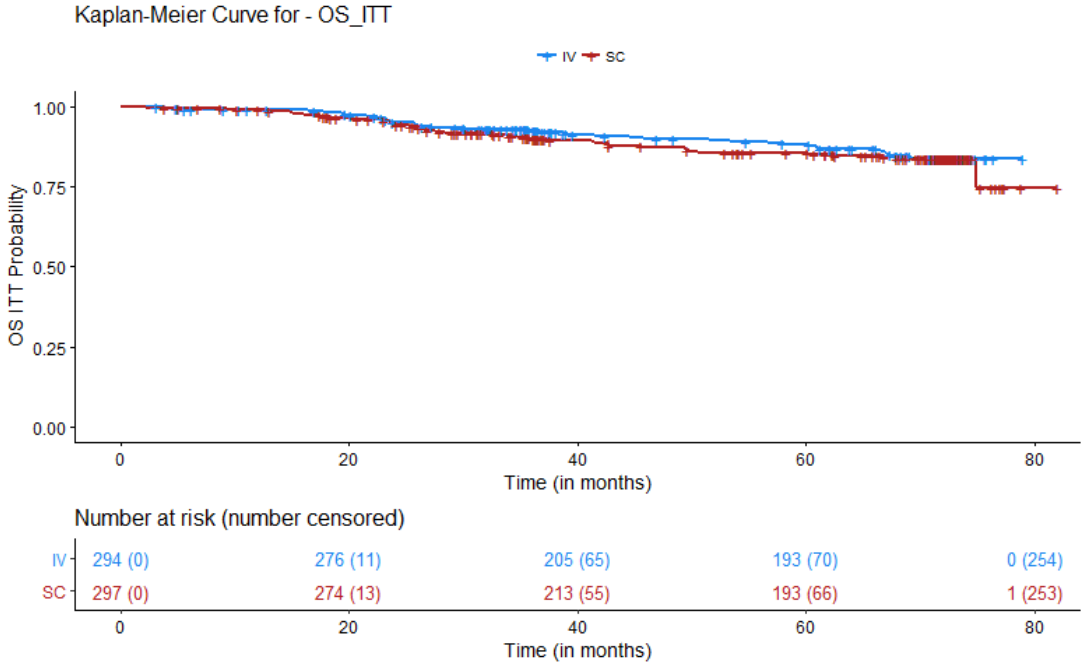
SC: subcutaneous trastuzumab
IV: intravenous trastuzumab
Source: events.xpt

Figure 11: KM Curves for EFS in the ITT Population (HannaH)



SC: subcutaneous trastuzumab
IV: intravenous trastuzumab
Source: events.xpt

Figure 12: KM Curves for OS in the ITT Population (HannaH)



SC: subcutaneous trastuzumab
IV: intravenous trastuzumab
Source: events.xpt

FDA Comments: The analysis of EFS and OS is analyzed in the ITT population so that all patients on the trial could be included in the analysis. This was the defined population for these endpoints. In the EPP set of patients the EFS and OS analysis yielded similar results.

Durability of Response
The durability of response is addressed throughout the efficacy review given that EFS and OS were time to event secondary endpoints.

Persistence of Effect
With the limited number of EFS and OS events observed thus far, there does not appear to be any meaningful difference in subcutaneous and intravenous trastuzumab.

Efficacy Results – Exploratory COA (PRO) endpoints
Patient Reported Outcomes (PRO) was not studied in the HannaH study. See Section 8.3 below for discussion of the results of the PrefHER study.

Additional Analyses Conducted on the Individual Trial
The pCR rates were analyzed by the body weight quartiles to investigate any treatment effect differences by body weight in an exploratory analysis. The subgroup analysis results are summarized in Table 28. The pCR rates were higher in the SC arm as compared to the IV in all the weight categories except of the highest body weight quartile (≥79 kgs).

Table 28: Analysis of pCR by the Weight Quartiles in the EPP Patient Population (HannaH)

Weight category (kg)	SC N=260 (%)	IV N=263 (%)
<58	30 / 56 (54)	23 / 62 (37)
58 to <67	28 / 63 (44)	32 / 74 (43)
67 to <79	31 / 68 (46)	28 / 68 (41)
≥79	29 / 73 (40)	24 / 59 (41)

SC: subcutaneous trastuzumab
IV: intravenous trastuzumab
Source: events.xpt

FDA Comments: These results of pCR by the weight quartiles are similar to those observed in the overall EPP patient population and comparable between the two arms. Overall, the SC arm had slightly higher pCR rates compared to the IV arm but given the small sample sizes per arm, this is unlikely to be a meaningful efficacy difference.

8.1.3 Assessment of Efficacy Across Trials
Not applicable as HannaH was the only study submitted by the applicant in support of efficacy for the BLA.

8.1.4 Integrated Assessment of Effectiveness

HannaH was phase III, randomized, open-label study to compare the pharmacokinetics, efficacy and safety of subcutaneous (SC) trastuzumab with intravenous (IV) trastuzumab administered in women with HER2 positive early breast cancer (EBC). The study met its co-primary endpoints of pCR (absence of invasive neoplastic cells in the breast) and C_{trough} at the end of cycle 7. These results support the comparability of SC trastuzumab to IV trastuzumab. No other clinical studies were submitted by the applicant to support efficacy.

8.2 Review of Safety

8.2.1 Safety Review Approach

The safety evaluation for this application is based on the HannaH and SafeHER studies. The HannaH and SafeHER study designs were described in sections 7.2.1 and 7.2.2 above.

There was particular attention to the assessment of cardiac adverse events (AEs) due to the known cardiac effects of trastuzumab-containing products. Left ventricular ejection fraction (LVEF) was assessed by echocardiography (Echo) or MUGA. For study HannaH, electrocardiograms (ECGs) and LVEF were performed at screening, week 13, weeks 25, 37, and 52 and every 6 months thereafter (months 6-60 after the last dose of the drug). For study SafeHER, ECGs and LVEF were collected at screening, cycle 5, 9, 13, and 18, and then at 6, 12, 24 months, 3 yrs, 4 yrs, and 5 yrs after treatment cessation.

There was also attention to the development of anti-trastuzumab and anti-rHuPH20 antibodies. In HannaH, validated antibody assays were used to detect and confirm. The results for immunogenicity were not submitted for SafeHER by the applicant with this BLA as it was an exploratory objective for Cohort B (SID cohort) and results were only presented for Cohort A (SC cohort), as previously agreed upon by the FDA.

There was also particular attention to the assessment of body weight and its correlation to PK values and AEs due to the flat dosing of the SC trastuzumab.

8.2.2 Review of the Safety Database

Overall Exposure

The safety population was defined as all subjects who received at least one dose of the study medication. One patient was excluded from the safety population in HannaH due to not receiving any study medication.

The safety population consisted of 595 patients in HannaH (SC trastuzumab n=297, IV trastuzumab n=298) and 1864 patients in SafeHER (all received SC trastuzumab). The exposure to SC and IV trastuzumab in the HannaH and SafeHER studies is listed below in Table 29.

Table 29: Safety Population Study Drug Exposure for HannaH and SafeHER

	HannaH		SafeHER
Neoadjuvant Period	**SC (mg) N=297**	**IV (mg) N=298**	**SC (mg) N=1864**
Mean	4723	3405	N/A
Standard Deviation (SD)	644	845	
Median	4800	3344	
Range	600-6600	520-6840	
Adjuvant Period	**SC (mg) N=274**	**IV (mg) N=275**	**SC (mg) N=1864**
Mean	5737	4014	N/A
SD	816	986	
Median	6000	3977	
Range	600-7200	432-7800	
Overall	**SC (mg) N=297**	**IV (mg) N=298**	**SC (mg) N=1864**
Mean	10016	7109	10195
SD	2165	2139	2031
Median	10800	7150	10800
Range	600-11230	520-14640	600-11400

SC: subcutaneous trastuzumab
IV: intravenous trastuzumab
Source: exposure.xpt (HannaH) and dddose.xpt (SafeHER)

FDA Comments: The exposure was higher in the SC trastuzumab arm than the IV arm in the HannaH study. However, safety analyses in the sections below showed the adverse events was similar between the SC and IV arms, aside from an increase in administration-related reactions in the SC arm due to the route of administration. The exposure to SC trastuzumab was similar between the HannaH and SafeHER studies.

Relevant characteristics of the safety population of HannaH is in Table 30. In HannaH, the overall demographics were well balanced between the two arms. The median age of the patients was similar between the SC and IV trastuzumab arms, most of the patients (86%) in both arms had an ECOG of 0, and the majority of the study participants were white (67%).

Table 30: Safety Population Demographic Overview for HannaH

	SC N= 297 (%)	IV N= 298 (%)
Age		
Mean (SD)	50.25 (11)	49.5 (11)
Median (range)	50 (25-81)	50 (24-77)
≤65	268 (90)	276 (93)
>65	29 (10)	22 (7)
ECOG		
0	253 (86)	255 (86)
1	43 (14)	42 (14)
Race		
White	200 (67)	208 (70)
Asian	64 (22)	61 (20)
Other	33 (11)	29 (10)
Region		
Western Europe	52 (18)	56 (19)
Eastern Europe	114 (38)	123 (41)
South Africa	17 (6)	15 (5)
Asia Pacific	63 (21)	59 (20)
South America	51 (17)	45 (15)
ER		
Positive	141 (49)	148 (49)
Negative	151 (51)	149 (51)
Disease Stage		
T1	20 (7)	23 (8)
T2	130 (44)	130 (44)
T3	52 (18)	49 (16)
T4	94 (32)	96 (32)
Weight Category		
<59 kg	71 (24)	77 (26)
≥59 <68	70 (24)	84 (28)
≥68 <79	71 (24)	70 (23)
≥79	85 (29)	67 (23)

SC: subcutaneous trastuzumab
IV: intravenous trastuzumab
Source: demoext.xpt

Relevant characteristics of the safety population of SafeHER is listed in Table 31. In SafeHER, the median age of the patients was 54 (range: 20-88), most of the patients (84%) had an ECOG of 0, and the majority of the study participants were white (76%).

Table 31: Safety Population Demographic Overview for SafeHER

	N = 1864 (%)
Age	
Mean (SD)	54 (12)
Median (range)	54 (20-88)
≤75	1768 (95)
>75	96 (5)
ECOG	
0	1556 (84)
1	305 (16)
Race	
White	1421 (76)
Black	25 (1)
Asian	295 (16)
Other	65 (4)
Region	
Western Europe	992 (53)
Eastern Europe	293 (16)
Africa	62 (3)
Asia Pacific	324 (17)
Americas	193 (10)
ER	
Positive	696 (37)
Negative	1128 (60.5)
Disease Stage	
T1	911 (49)
T2	744 (40)
T3	138 (7)
T4	62 (3)
Weight Category	

<45 kg	31 (2)
P10 (≤53 kg)	226 (12)
Q1(≤59 kg)	501 (27)
Q2 (>59 kg ; ≤67 kg)	454 (24)
Q3 (>67kg ; ≤77kg)	442 (24)
Q4 (>77 kg)	464 (25)

Q= quartile
SC: subcutaneous trastuzumab
IV: intravenous trastuzumab
Source: dddemo.xtp and ddecog.xpt

FDA Comments: In HannaH, the demographics for the safety population are well balanced in both studies. In SafeHER, there were 4 male patients and otherwise, the patient demographic in SafeHER was similar to the patient demographic in HannaH. Both studies were conducted outside of the United States, but, this is unlikely to impact the safety profile of SC trastuzumab as the safety profile of SC trastuzumab is not expected to differ based on race or ethnicity.

8.2.3 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality
The overall safety data quality submitted by the applicant with the BLA was sufficient for analyses and regulatory decision making.

Categorization of Adverse Events
The applicant defined an adverse events (AE) as: any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

A serious adverse event (SAE) was defined as: any experience that suggested a significant hazard, contraindication, side effect or precaution, and met at least one of the following criteria: fatal, life threatening, required in-patient hospitalization or prolongation of existing hospitalization; resulted in persistent or significant disability/incapacity; congenital anomaly/birth defect, or medically significant or required intervention to prevent one or other of the outcomes listed.

For HannaH, the AEs and SAEs were reported irrespective of type of disorder and drug event relationship until 28 days after last study drug dose. All SAEs, cardiac AEs and drug-related AEs were reported between 28 days and 6 months of last dose of study drug. Cardiac AEs and related AEs/SAEs were reported from 6 months following the last drug dose to the end of the follow up period.

For SAFEHER, all AEs/SAEs were reported until study completion. In addition, for SAFEHER, treatment emergent AE (TEAEs) were defined as AEs occurring on the day or after first administration of study drug until 33 days after last study drug administration

AE were documented in the Medical Dictionary for Regulatory Activities (MedDRA). Version 19.1 was used for HANNAH and version 18.1 for SAFEHER. AEs were graded for severity using the National Cancer Institute Common Terminology criteria for Adverse Events (NCI CTCAE version 3.0).]

Routine Clinical Tests
The schedule of safety evaluations for HannaH included hematology and biochemistry testing at baseline, week 1, 4, 7,10, 13, 16, 19, 22, 25, 37, 52, final visit, and months: 3, 6, 12, 18, 24. The schedule of safety evaluations for SafeHER included blood samples for hematology and biochemistry collected at screening, and day 1 of cycle 9 and cycle 18.

FDA Comments: The frequency of monitoring was considered adequate. Cardiac assessments were adequate. Overall the applicant's clinical safety assessments are adequate.

8.2.4 Safety Results

Major Safety Results
Table 32 is a summary of the treatment-emergent adverse events (TEAEs). TEAEs occurred in both the IV and SC arms of HannaH and in SafeHER. In HannaH, 98% of patients in the SC arm experienced TEAEs and 95% of patients in the IV arm experienced TEAEs. Twenty two percent of patients in the SC arm experienced serious TEAEs and 15% of patients in the IV arm experienced serious TEAEs. In HannaH, there were more serious TEAEs in the SC arm compared to the IV arm which will be discussed further in the sections below.

In SafeHER, most of the patients (90%), experienced a TEAE with 16% experiencing a serious TEAE.

Table 32: Summary of TEAEs for HannaH and SafeHER

	HannaH						SafeHER
	Neoadjuvant		Adjuvant		Overall		Overall
	SC n=297 (%)	IV n=298 (%)	SC n=274 (%)	IV n=275 (%)	SC n=297 (%)	IV n=298 (%)	SC n=1864 (%)
All grade TEAEs	287 (97)	275 (100)	206 (75)	201 (73)	290 (98)	282 (95)	1669 (90)
TEAEs related to study drug	268 (90)	258 (94)	74 (27)	70 (24)	271 (91)	260 (87)	N/A
Grade 3-5 TEAEs	139 (47)	147 (53)	39 (14)	30 (11)	158 (53)	160 (54)	495 (27)
Serious TEAEs	41 (14)	30 (11)	25 (9)	10 (4)	65 (22)	45 (15)	295 (16)
Permanent drug discontinuation	4 (1)	1 (<1)	11 (4)	4 (1)	15 (5)	6 (2)	100 (5)
Deaths	3 (1)	1 (<1)	0	0	4 (1)	5 (2)	8 (<1)

SC: subcutaneous trastuzumab
IV: intravenous trastuzumab
Source: demoext.xpt and aeext.xpt (HannaH); dddemo.xpt and ddae.xpt (SafeHER)

FDA Comments: In HannaH, the incidence of grade 3-5 TEAES were comparable between the SC and IV trastuzumab arms. There were more serious TEAEs in the SC arm compared to the IV arm which will is discussed in Table 35 and Table 36 below. In SafeHER, 16% of patients experienced a serious TEAE which was similar to the incidence of serious TEAEs in the IV arm of HannaH.

Deaths
The number of deaths in each treatment arm for HannaH are shown in Table 33 with the narratives reviewed and summarized below. In the neoadjuvant period, there were 3 deaths in the SC trastuzumab arm (causes of death sudden death, septic shock, and myocardial infarction) and one death in the IV trastuzumab arm (cause of death pneumonia). There were no deaths in the adjuvant period. In the treatment free follow up period, there was one death in the SC trastuzumab arm (cause of death endometrial cancer), and 4 deaths in the IV trastuzumab arm (causes of death myeloid leukemia, death, emphysema, myocardial infarction).

Table 33: Deaths on HannaH

HannaH: Neoadjuvant Period			
Subject	**Arm**	**Event of Death**	**Study Drug Relation (per applicant)**
(b) (6)	SC	Sudden Death	No
	SC	Septic Shock	Yes
	SC	Myocardial Infarction	Yes
	IV	Pneumonia	No
HannaH: Treatment Free Follow up			
(b) (6)	IV	Myeloid Leukemia	No
	SC	Endometrial Cancer	No
	IV	Death	No
	IV	Emphysema	No
	IV	Myocardial Infarction	No

SC: subcutaneous trastuzumab
IV: intravenous trastuzumab
Source: Patient narratives and aeext.xpt

FDA Comments: In the HannaH trial, there were 9 deaths related to AEs, 5 (1.7%) in IV trastuzumab arm and 4 (1.3%) in SC trastuzumab arm. Narratives for each death were reviewed and found to be concordant with the applicant's reported cause of death. The deaths are consistent with what is expected from this patient population. For the patients who died from a cardiac issue, most of them had an underlying cardiac risk factor of hypertension or diabetes. The causes of death are unlikely to have a meaningful safety impact.

- ***Patient (b) (6): 71 yo white woman with operable, poorly differentiated, unifocal T2N1M0, BC. She had a past medical history which includes diabetes mellitus (DM) and hypertension (HTN). The patient had received the most recent chemotherapy and trastuzumab on SD 148. On SD 168, she died suddenly at home. There was no autopsy.***
- ***Patient (b) (6): 77 yo white woman diagnosed with locally advanced, inoperable, moderately differentiated, multifocal (T4aN0M0), hormone receptor negative right breast cancer (BC). She tolerated 4 cycles of docetaxel concurrent with trastuzumab. She received FEC on study day (SD) 85. On SD 117 (last day of chemotherapy was SD 107), she experienced febrile neutropenia and grade 4 thrombocytopenia and fever with constipation. She was treated with antibiotics and filgrastim but worsened to septic shock and died on SD 118.***
- ***Patient (b) (6): 60 yo white woman with a history of HTN, and operable, poorly differentiated, unifocal BC. On SD 6, she presented with grade 2 lethargy, grade 1 hyperhidrosis, grade 2 pain, and grade 1 headache. On SD 9, she felt "feverish" with a temperature of 37.4 and she was treated with codeine/paracetamol. Later that evening, she experienced left sided chest pain with dyspnea. She went to bed and died in her sleep on SD 10.***

- ***Patient (b) (6): 66 yo Latin American and European woman with operable, moderately differentiated, unifocal, BC with baseline pulmonary fibrosis (treated with prednisone, azathioprine and colchicine). On SD 53, she developed pneumonia (fever, body ache, cough, dyspnea) with an absolute neutrophil count of 6.5. On SD 58, she developed acute respiratory failure and was sent to the ICU and she was intubated and subsequently died on SD 70.***
- ***Patient (b) (6): 62 yo white woman with poorly differentiated, unifocal, operable, BC. On SD 606, she presented to the hospital with fever and weakness and diagnosed with grade 4 myeloid leukemia, diagnosed as a second primary malignancy. She died on SD 611.***
- ***Patient (b) (6): 77 yo black woman diagnosed with locally advanced inoperable, moderately differentiated, multifocal BC. On SD 515, she developed advanced endometrial cancer. On SD 626, she presented to the hospital with anemia. On SD 627, she received palliative radiation therapy. On SD 632, her condition worsened. On SD 638 the radiation therapy was stopped and on SD 640, she died.***
- ***Patient (b) (6): 59 yo white woman with a history of HTN, DM, asthma, obesity, and an operable, moderately differentiated, unifocal, BC. The patient died on SD 1506 with no further details provided.***
- ***Patient (b) (6): 72 yo white woman with a history of HTN, DM, hypothyroidism, depression, and operable, poorly differentiated, multi-centric BC. She developed an adverse event due to emphysema and died on SD 1091.***
- ***Patient (b) (6): 48 yo AA with a history of HTN, and operable, moderately differentiated, unifocal BC. On SD 1506, she developed grade 4 myocardial infarction (no details provided). She died the same day. There was no autopsy.***

The number of deaths in each treatment arm for SafeHER are shown Table 34. There were 8 deaths in the treatment period in SafeHER with causes of death including cerebrovascular accident, rectal adenocarcinoma, hydrocephalus, nephrotic syndrome, ovarian epithelial cancer metastatic, neutropenic sepsis, sudden death, and cardio-pulmonary arrest**.**

Table 34: Deaths on Study SafeHER

Patient Identification	Event of Death	Study Drug Relation (per applicant)
(b) (6)	Cerebrovascular Accident	No
	Rectal Adenocarcinoma	No
	Hydrocephalus	No
	Nephrotic Syndrome	No
	Ovarian Epithelial Cancer Metastatic	No
	Neutropenic Sepsis	Yes
	Sudden Death	No
	Cardio-Respiratory Arrest	No

Source: Patient narratives and ddae.xpt

FDA Comments: In the SafeHER study, there were 8 (0.42%) deaths. Narratives for each death were reviewed and found to be concordant with the applicant's reported cause of death. The deaths were consistent with what is expected for this patient population. The causes of death are unlikely to have a meaningful safety impact.

- (b) (6)***: 71 yo woman with a history of hypercholesterolemia, HTN, and stage II, ductal BC. The patient was admitted to the hospital on SD 17 due to thoracic pain and gradual decrease in consciousness level (GCS 4/15) with a blood pressure of 180/80 and positive Babinski. She was intubated. The brain CT did not reveal hemorrhage or stroke. She died the same day.***
- (b) (6)***: 68 yo woman with stage I, T1n0M0, BC. On SD 85, the patient presented with rectal bleeding and was admitted to the hospital. She received 2u pRBC. On SD 87, a colonoscopy was performed, and she was diagnosed with rectal carcinoma. On SD 92, a CT scan showed liver metastases and a biopsy confirmed that diagnosis. She received palliative radiation. She died on SD 471.***
- (b) (6)***: 59 yo woman with a history of HTN and ductal stage III, T2N3M0, BC. On SD 639, she was hospitalized after a 3-week history of unsteady gait. On SD 640, the patient was diagnosed with right frontal/corpus callosum tumor (brain metastases). On SD 656, she underwent a palliative craniotomy and resection of frontal corpus callosum metastasis. Post-surgery, the patient's condition deteriorated. On SD 657 and SD 668, the patient had progressive hydrocephalus with extensive extra axial CSF collection causing midline shift and sulcal effacement. On SD 696, SD 701, SD 704, and SD 708, she underwent lumbar puncture to provide temporary relief. On SD 710, a ventriculoperitoneal shunt was inserted but the patient had no improvement. Her clinical condition deteriorated and she died on SD 729.***
- (b) (6)***: 82 yo woman with a history of HTN, ischemic heart disease, aortic insufficiency, mitral insufficiency, left bundle branch block, first degree AV block, chronic renal insufficiency, and stage II, T2N1Mo BC. On SD 484, a diagnosis of nephrotic syndrome was confirmed with presence of proteinuria of 7.29g/24h. She***

died on SD 561.

- (b) (6)***: 47 yo black woman with stage II, T3N0M0 BC. On SD 437, a CT scan of abdomen confirmed metastatic ascites and peritoneal deposits which were considered life threatening. On SD 471, she was treated with carboplatin and paclitaxel. Then, on SD 745, she died.***
- (b) (6)***: 76 yo woman with a history of HTN, hypercholesteremia, and stage III, T4N3M0 BC. On SD 51, she developed neutropenia, and on SD 53 she received pegfilgrastim. On SD 73, she was admitted with a temperature to 39C. On SD 78, she was admitted to ICU with pneumonia, hypoxia, and neutropenic sepsis. On SD 101, the patient died.***
- (b) (6)***: 50 yo Asian female, with stage III, T3N2M0 BC. She also had a past medical history of HTN. On SD 286, her ejection fraction (EF) decreased and continued to be depressed through SD 327. Overall, during study, her EF decreased from 55 to 45. Then after treatment, on SD 466, she died while sitting in the audience of her husband's lecture.***
- (b) (6)***: 39 yo woman with stage III, T3N1M0 BC and no previous medical history. On SD 751, she presented with dizziness, nausea and vomiting. She was hospitalized but died on SD 753 (with no other details available).***

Serious Adverse Events

Serious TEAEs from HannaH and SafeHER are listed in Table 35 and Table 36 respectively [the preferred terms (PT) included in Table 35, reflect terms that were reported in greater than one patient in the SC trastuzumab arm in HannaH. The PTs included in Table 36, reflect terms that were reported in greater than two patients in SafeHER]

In HannaH, the majority of serious TEAEs were infections and infestations with a reported incidence in 8.1% of the SC trastuzumab arm and 4.4% in the IV trastuzumab arm. The next most common serious TEAE was blood and lymphatic disorders with a reported incidence of 7.1% in the SC trastuzumab arm and 6.7% in the IV trastuzumab arm. Serious TEAEs in cardiac disorders were reported in 2% of patients in the SC trastuzumab arm and 1% in the IV trastuzumab arm.

In SafeHER, the majority of serious TEAEs were infections and infestations with a reported incidence of 4.1%. The next most common serious TEAE was blood and lymphatic disorders with a reported incidence of 2.8%. Serious TEAEs in cardiac disorders were reported in 1.7% of patients.

Table 35: Serious TEAEs from HannaH

MedDRA Terms	SC N= 297 (%)	IV N= 298 (%)
Infections and Infestations		
Cellulitis	2 (<1)	0 (0)
Pneumonia	2 (<1)	4 (1)
Lower Respiratory Tract Infection	2 (<1)	0 (0)
Postoperative wound infection	2 (<1)	0 (0)
Tonsillitis	2 (<1)	0 (0)
Sepsis	1 (<1)	0 (0)
Respiratory Tract infection	1 (<1)	0 (0)
Respiratory Tract Infection Viral	1 (<1)	0 (0)
Septic Shock	1 (<1)	0 (0)
Atypical Pneumonia	1 (<1)	0 (0)
Cystitis	1 (<1)	0 (0)
Encephalitis Viral	1 (<1)	0 (0)
Herpes Zoster	1 (<1)	0 (0)
Breast Abscess	1 (<1)	1 (<1)
Mastitis	1 (<1)	1 (<1)
Post Procedural Infection	1 (<1)	0 (0)
Wound Infection	1 (<1)	0 (0)
Pyelonephritis Acute	1 (<1)	0 (0)
Periorbital Cellulitis	1 (<1)	0 (0)
Abscess	1 (<1)	0 (0)
Tonsillitis Bacterial	1 (<1)	0 (0)
Blood and Lymphatic System Disorders		
Febrile Neutropenia	13 (4)	10 (3)
Neutropenia	7 (2)	9 (3)
Leukopenia	1 (<1)	0 (0)
Thrombocytopenia	1 (<1)	0 (0)
Cardiac Disorders		
Cardiac Failure Congestive	2 (<1)	0 (0)
Myocardial Infarction	1 (<1)	0 (0)
Atrial Fibrillation	1 (<1)	0 (0)
Myocardial Ischemia	1 (<1)	1 (<1)
Arrhythmia	1 (<1)	0 (0)
Respiratory, Thoracic and Mediastinal Disorders		
Pleural effusion	2 (<1)	0 (0)

Pulmonary Embolism	2 (<1)	0 (0)
Injury, Poisoning and Procedural Complications		
Lumbar Vertebral Fracture	1 (<1)	0 (0)
Radius Fracture	1 (<1)	1 (<1)
Pulmonary Radiation Injury	1 (<1)	0 (0)
Vascular Disorders		
Hematoma	1 (<1)	1 (<1)
Thrombophlebitis	1 (<1)	0 (<1)
Lymphorrhoea	1 (<1)	0 (<1)
General Disorders and Administration Site Conditions		
Pyrexia	2 (<1)	0 (0)
General Physical Health Deterioration	1 (<1)	0 (0)
Neoplasms Benign, Malignant and Unspecified		
Endometrial Cancer	2 (<1)	0 (0)
Thyroid Cancer	1 (<1)	0 (0)
Reproductive System and Breast Disorders		
Menorrhagia	1 (<1)	0 (0)
Vaginal Prolapse	1 (<1)	0 (0)
Ovarian Haemorrhage	1 (<1)	0 (0)
Gastrointestinal Disorders		
Nausea	1 (<1)	1 (<1)
Haemorrhoids	1 (<1)	1 (<1)
Psychiatric Disorders		
Depression	1 (<1)	0 (0)
Schizophrenia	1 (<1)	0 (0)
Investigations		
Tumor Marker Increased	1 (<1)	0 (0)
Ejection Fraction	1 (<1)	0 (0)
Musculoskeletal and Connective Tissue Disorders		
Back pain	1 (<1)	0 (0)
Spinal Pain	1 (<1)	0 (0)
Nervous System Disorders		
Dizziness	1 (<1)	0 (0)
Pregnancy, Puerperium and Perinatal Conditions		
Pregnancy	1 (<1)	0 (0)
Abortion Spontaneous	1 (<1)	0 (0)
Renal and Urinary Disorders		
Renal Colic	1 (<1)	0 (0)
Skin and Subcutaneous Tissue Disorders		

	Erythema Multiforme	1 (<1)	0 (0)

SC: subcutaneous trastuzumab
IV: intravenous trastuzumab
Source: demoext.xpt and aeext.xpt

FDA Comment*s: *Overall serious TEAEs were well balanced between the SC and IV trastuzumab arms, and within the expected safety findings for trastuzumab-containing products, and there were no new concerning safety findings.

Table 36: Serious TEAEs from SafeHER

MedDRA Terms		N= 1864 (%)
Infections and Infestations		
	Neutropenic Sepsis	9 (<1)
	Device Related Infection	6 (<1)
	Pneumonia	6 (<1)
	Cellulitis	6 (<1)
	Mastitis	5 (<1)
	Urinary Tract Infection	4 (<1)
	Lower Respiratory Tract Infection	4 (<1)
	Gastroenteritis	3 (<1)
	Pyelonephritis Acute	3 (<1)
	Upper Respiratory Tract Infection	2 (<1)
	Infectious Colitis	2 (<1)
	Escherichia Sepsis	2 (<1)
	Diverticulitis	2 (<1)
	Herpes Zoster	2 (<1)
	Erysipelas	2 (<1)
	Appendicitis	2 (<1)
	Breast Abscess	2 (<1)
Blood and Lymphatic System Disorders		
	Febrile Neutropenia	40 (2)
	Neutropenia	9 (<1)
	Febrile Bone Marrow Aplasia	2 (<1)
	Leukocytosis	2 (<1)
Cardiac Disorders		
	Cardiac Failure Congestive	11 (<1)
	Atrial Fibrillation	3 (<1)
	Angina Unstable	2 (<1)
	Myocardial Infarction	2 (<1)
	Supraventricular Tachycardia	2 (<1)
	Myocardial Ischaemia	2 (<1)
	Coronary Artery Disease	2 (<1)
Gastrointestinal Disorders		
	Diarrhea	8 (<1)
	Nausea	5 (<1)
	Pancreatitis	3 (<1)
	Vomiting	2 (<1)

	Pancreatitis Acute	2 (<1)
General Disorders and Administration Site Conditions		
	Pyrexia	11 (<1)
	Asthenia	2 (<1)
	Device Breakage	2 (<1)
Injury, Poisoning and Procedural Complications		
	Radiation Pneumonitis	2 (<1)
	Radius Fracture	2 (<1)
Nervous System Disorders		
	Headache	4 (<1)
	Transient Ischaemic Attack	2 (<1)
	Syncope	2 (<1)
Musculoskeletal and Connective Tissue Disorders		
	Osteoarthritis	3 (<1)
	Intervertebral Disc protrusion	2 (<1)
Respiratory, Thoracic and Mediastinal Disorders		
	Asthma	3 (<1)
	Dyspnea	2 (<1)
	Pneumonitis	2 (<1)
Reproductive System and Breast Disorders		
	Uterine Polyps	3 (<1)
	Ovarian Cyst	2 (<1)
Vascular Disorders		
	Hypertension	2 (<1)
	Hypertensive Crisis	2 (<1)
Investigations		
	Ejection Fraction Decreased	4 (<1)
Renal and Urinary Disorders		
	Renal Failure	2 (<1)
Metabolism and Nutrition Disorders		
	Hyperglycemia	2 (<1)
Psychiatric Disorders		
	Depression	3 (<1)
	Anxiety	2 (<1)
Hepatobiliary Disorders		
	Cholelithiasis	3 (<1)
Ear and Labyrinth Disorders		
	Vertigo	2 (<1)
Immune System Disorders		

	Drug Hypersensitivity	2 (<1)
Skin and Subcutaneous Tissue Disorders		
	Rash	2 (<1)

Source: dddemo.xpt and ddae.xpt

FDA Comment*s: *Overall, serious TEAEs for SafeHER were within the expected safety findings for trastuzumab-containing products, and there were no new concerning safety findings.

Dropouts and/or Discontinuations Due to Adverse Effects
The pre-specified safety withdrawal criteria for HannaH and SafeHER included symptomatic congestive heart failure and recurrent grade 3 or 4 non-hematologic AE upon re-challenge.

In HannaH, there were 21 subjects who permanently discontinued study drug (Table 37). In the neoadjuvant treatment period:

- SC trastuzumab arm: 4 patients discontinued due to pulmonary embolism (PE), pregnancy, CHF, and arrhythmia
- IV trastuzumab arm: 1 patient discontinued due to pneumonia.

In the adjuvant treatment period:

- SC trastuzumab arm: 11 patients discontinued due to LV dysfunction (5 patients), cardiotoxicity, dyspnea, hypothyroid, pneumonitis, pleural effusion, and thyroid cancer.
- IV trastuzumab arm: 4 patients discontinued due to LV dysfunction (2 patients), cardiomyopathy and atrial flutter

Table 37: Summary of Events Leading to Drug Discontinuation in HannaH

HannaH	SC Arm N= 297 (%)	IV Arm N= 298 (%)
Cardiac Disorders		
Left Ventricular Dysfunction	5 (2)	3 (1)
Cardiac Congestive Failure	1 (<1)	0 (0)
Cardiomyopathy	0 (0)	1 (<1)
Cardiotoxicity	1 (0)	0 (0)
Arrhythmia	1 (0)	0 (0)
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnoea	1 (<1)	0 (0)
Pneumonitis	1 (<1)	0 (0)
Pleural Effusion	1 (<1)	0 (0)
Pulmonary Embolism	1 (<1)	0 (0)
Pneumonia	0 (0)	1 (0)
Endocrine Disorders		
Hyperthyroid	1 (<1)	0 (0)
Investigations		
Ejection fraction	1 (<1)	0 (0)
Neoplasms Benign, Malignant and Unspecified		
Thyroid Cancer	1 (<1)	0 (0)
Pregnancy, Puerperium, and Perinatal Conditions		
Pregnancy	1 (<1)	0 (0)
Infections and Infestations		
Pneumonia	0 (0)	1 (<1)

Source: demoext.xpt and aeext.xpt

FDA Comments: In HannaH, the majority of patients who had to discontinue study drug in the adjuvant portion were due to cardiac dysfunction in both the SC and IV trastuzumab arms. However, these numbers were still below what was reported in the original Herceptin trials reported in the Herceptin USPI (2.5-15%). There were no new concerning safety findings.

In SafeHER, 77 patients discontinued study drug due to cardiac disorders (Table 38). The table list reported events leading to drug discontinuation in at least one patient.

Table 38: Summary of Events leading to Drug Discontinuation in SafeHER

SafeHER	N= 1864 (%)
Cardiac Disorders	
Left Ventricular Dysfunction	18 (1)
Cardiac Failure Congestive	9 (<1)
Congestive Cardiomyopathy	3 (<1)
Coronary Artery Disease	2 (<1)
Acute Myocardial Infarction	1 (<1)
Atrial Fibrillation	1 (<1)
Atrioventricular block first degree	1 (<1)
Cardiac Failure	1 (<1)
Cardiac Failure Chronic	1 (<1)
Myocardial Ischaemia	1 (<1)
Palpitations	1 (<1)
Right Ventricular Failure	1 (<1)
Stress Cardiomyopathy	1 (<1)
Ventricular Hypokinesia	1 (<1)
Infections and Infestations	
Neutropenic Sepsis	2 (<1)
Bronchopneumonia	1 (<1)
Investigations	
Ejection Fraction Decrease	35 (2)
General Disorders and Administration Site Conditions	
Fatigue	2 (<1)
Asthenia	1 (<1)
Decreased Activity	1 (<1)
Drug Intolerance	1 (<1)
Infections and Infestations	
Neutropenic Sepsis	2 (<1)
Tracheobronchitis	1 (<1)
Respiratory, Thoracic and Mediastinal Disorders	
Dyspnoea	3 (<2)
Respiratory Distress	1 (<1)
Pulmonary Fibrosis	1 (<1)
Pulmonary Oedema	1 (<1)
Musculoskeletal and Connective Tissue Disorders	
Myalgia	2 (<1)
Arthralgia	2 (<1)

Nervous System Disorders	
Cerebrovascular Accident	1 (<1)
Demyelinating Polyneuropathy	1 (<1)
Myasthenia Gravis	1 (<1)
Presyncope	1 (<1)
Gastrointestinal Disorders	
Nausea	1 (<1)
Immune System Disorders	
Anaphylactic Reaction	1 (<1)
Drug Hypersensitivity	1 (<1)
Skin and Subcutaneous Tissue Disorders	
Dermatitis exfoliative	1 (<1)
Rash Pruritic	1 (<1)
Vascular Disorders	
Hypertension	2 (<1)
Injury, Poisoning and Procedural Complications	
Pelvic Fracture	1 (<1)
Tooth Loss	1 (<1)
Neoplasms Benign, Malignant and Unspecified	
Rectal Adenocarcinoma	1 (<1)
Psychiatric Disorders	
Anxiety	1 (<1)
Eye Disorders	
Conjunctivitis	1 (<1)

Source: demoext.xpt and aeext.xpt

FDA Comments: In SafeHER, the majority of patients who had to discontinue study drug were because of cardiac disorders. However, these numbers are expected and consistent with what was reported in the original Herceptin trials in the Herceptin USPI (2.5-15%). There were no new concerning safety findings.

Treatment Emergent Adverse Events and Adverse Reactions
The treatment emergent adverse events (TEAEs) that occurred in ≥5% of patients in HannaH (Table 39) and SafeHER (Table 40) are listed below.

Table 39: Treatment Emergent Adverse Events That Occurred In ≥5% Of Patients in HannaH

HannaH (Grade 1-5)	SC N= 297 (%)	IV N= 298 (%)
Alopecia	187 (63)	188 (63)
Nausea	146 (49)	147 (49)
Neutropenia	132 (44)	141 (47)
Diarrhea	101 (34)	110 (37)
Asthenia	75 (25)	75 (25)
Fatigue	70 (24)	80 (27)
Vomiting	69 (23)	70 (23)
Myalgia	61 (21)	54 (18)
Decreased appetite	58 (20)	59 (20)
Stomatitis	57 (19)	51 (17)
Arthralgia	53 (18)	60 (20)
Headache	50 (17)	44 (15)
Rash	48 (16)	44 (15)
Constipation	43 (15)	45 (15)
Radiation skin injury	41 (14)	34 (11)
Pyrexia	37 (13)	35 (12)
Cough	35 (12)	24 (8)
Anemia	34 (11)	41 (14)
Dyspepsia	33 (11)	30 (10)
Peripheral sensory neuropathy	33 (11)	27 (9)
Incision site pain	33 (11)	24 (8)
Leukopenia	31 (10)	46 (15)
Mucosal inflammation	31 (10)	39 (13)
Hot flush	30 (10)	31 (10)
Upper respiratory tract infection	30 (10)	30 (10)
Nail disorder	29 (10)	31 (10)
Dizziness	29 (10)	28 (9)
Pain in extremity	29 (10)	26 (9)
Back pain	27 (9)	25 (8)
Insomnia	26 (9)	31 (10)
Pruritus	26 (9)	27 (9)
Nasopharyngitis	24 (8)	40 (13)
Dysgeusia	24 (8)	22 (7)

Neuropathy peripheral	24 (8)	18 (6)
Hypertension	24 (8)	14 (5)
Oedema peripheral	23 (8)	30 (10)
Abdominal pain	22 (7)	16 (5)
Abdominal pain upper	21 (7)	27 (9)
Dyspnea	21 (7)	22 (7)
Erythema	21 (7)	8 (3)
Skin hyperpigmentation	20 (7)	24 (8)
Palmar-plantar erythrodysaesthesia syndrome	20 (7)	18 (6)
Oropharyngeal pain	19 (6)	19 (6.4)
Epistaxis	19 (6)	18 (6)
Bone pain	19 (6)	10 (3)
Musculoskeletal pain	18 (6)	22 (7)
Procedural pain	18 (6)	16 (5)
Injection site pain	18 (6)	0 (0)
Febrile neutropenia	14 (6)	12 (4)
Alanine aminotransferase increased	16 (5)	16 (6)
Pharyngitis	15 (5)	11 (4)
Amenorrhoea	15 (5)	10 (3)

SC: subcutaneous trastuzumab
IV: intravenous trastuzumab
Source: demoext.xpt and aeext.xpt

FDA Comments: The TEAE were similar between the SC and IV trastuzumab arms with no new concerning safety findings.

Table 40: Treatment Emergent Adverse Events That Occurred In ≥5% Of Patients in SafeHER

SafeHER (Grade 1-5)	n=1864 (%)
Diarrhea	389 (21)
Fatigue	388 (21)
Arthralgia	384 (21)
Nausea	279 (15)
Myalgia	270 (15)
Headache	238 (13)
Asthenia	225 (12)
Pain in extremity	204 (11)
Cough	197 (11)
Pyrexia	196 (11)
Rash	183 (10)
Hot flush	179 (10)
Oedema peripheral	165 (9)
Alopecia	164 (9)
Radiation skin injury	161 (9)
Constipation	159 (9)
Erythema	159 (9)
Hypertension	155 (8)
Nasopharyngitis	152 (8)
Neuropathy peripheral	141 (8)
Anemia	136 (7)
Vomiting	135 (7)
Back pain	129 (7)
Injection site erythema	128 (7)
Dyspnea	122 (7)
Upper respiratory tract infection	119 (6)
Injection site pain	118 (6)
Dizziness	116 (6)
Pruritus	116 (6)
Stomatitis	116 (6)
Paraesthesia	114 (6)
Insomnia	113 (6)
neutropenia	110 (6)
Epistaxis	109 (6)
Mucosal inflammation	106 (6)
Urinary tract infection	102 (6)

Injection site reaction	101 (5)
Peripheral sensory neuropathy	97 (5)
Musculoskeletal pain	94 (5)

Source: dddemo.xpt and ddae.xpt

FDA Comments: Overall TEAEs for SafeHER were within the expected safety findings for trastuzumab-containing products, and there were no new concerning safety findings.

Laboratory Findings
Trastuzumab is not known to cause significant laboratory abnormalities. In Hannah, there were no significant laboratory abnormality differences (hematologic or chemistry) between the trastuzumab SC and trastuzumab IV over time. In SafeHER, there were no clinically meaningful changes in the hematologic or chemistry panels.

Vital Signs
There were no clinically meaningful changes in vital signs reported in either HannaH or SafeHER.

Electrocardiograms (ECGs)
Trastuzumab is not known to cause clinically significant ECG changes. Scheduled ECGs were performed about every three months. In Hannah the reported ECG findings were reviewed there were few patients with clinically significant ECG changes. The reported ECG findings for SAFEHER were reviewed and as reported, up to the safety follow up visit, less than 10 patients had clinically significant abnormal findings.

QT
Trastuzumab-containing products are not known to cause QT prolongation.

Immunogenicity
Refer to the immunogenicity findings discussed above in section 6.

FDA Comments: No safety concerns for laboratory results, ECGs, or QT. Drs. Shadia Zaman and Brian Janelsins reviewed the immunogenicity assay and found there was sufficient information and data provided to support the suitability of the anti-trastuzumab immunogenicity assays to generate meaningful clinical immunogenicity data.

8.2.5 Analysis of Submission-Specific Safety Issues

The major black box warnings in the prescribing information for US-Herceptin include cardiomyopathy, pulmonary toxicity, infusion reactions, and embryo-fetal toxicity. Cardiac toxicities, pulmonary toxicities, and infusion reactions are discussed below. The pregnancies are discussed in section 8.2.9.

Cardiac Toxicity

Table 41 list the cardiac TEAEs in the SC and IV arms of HannaH and Table 42 list the cardiac TEAEs in SafeHER. The cardiac TEAEs were grouped by this reviewer to reflect the ones that are most consistent with cardiomyopathy. In HannaH, the majority of cardiac TEAES were left ventricular dysfunction at 3% and 4% in the subcutaneous and trastuzumab IV arm respectively. The majority of cardiac TEAEs in HannaH were less than grade 3 and resolved. In SAFEHER, the majority of TEAEs were left ventricular dysfunction reported at 2% and ejection fraction decreased reported at 5%. Most of these were less than grade 3 and resolved.

Table 41: Cardiac Toxicities for HannaH

Neoadjuvant and Adjuvant (# pts)	SC N=297			IV N=298		
	G 1-5 (%)	G>3 (%)	Resolved (%)	G 1-5 (%)	G>3 (%)	Resolved (%)
Cardiac failure	1 (<1)	1 (<1)	1 (<1)	1(<1)	0 (0)	0 (0)
Cardiac failure congestive	2 (<1)	2 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
Cardiomyopathy	1 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)
Cardiovascular disorder	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	2 (<1)
Diastolic dysfunction	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
Dilatation atrial	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	(0)
Left atrial enlargement	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	(0)
Left ventricular dilatation	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0(0)
Left ventricular dysfunction	10 (3)	1 (<1)	10 (3)	12 (4)	0 (0)	10 (3)
Left ventricular hypertrophy	1 (<1)	0 (0)	1 (<1)	0 (0)	0(0)	0 (0)
Right ventricular failure	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
Ventricular hypokinesia	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	2 (<1)
Cardiotoxicity	1 (<1)	0 (0)	0 (00	0 (0)	0 (0)	0 (0)
Ejection fraction	1 (<1)	1 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
Ejection fraction decreased	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)
Total[1]	**14 (5)**	**3 (1)**	**14 (5)**	**16 (6)**	**0 (0)**	**10 (3)**

[1]Reflects total number of patients with the grouped AEs. If a patient experienced more than one AE, the patient was only counted once
G: toxicity grade
SC: subcutaneous trastuzumab
IV: intravenous trastuzumab
Source: demoext.xpt and aeext.xpt

Table 42: Cardiac Toxicities for SafeHER

	N=1864		
	G 1-5 (%)	**G>3 (%)**	**Resolved (%)**
Cardiac failure	4 (<1)	0 (0)	0 (0)
Cardiac failure chronic	1 (<1)	0 (0)	1 (<1)
Cardiac failure congestive	11 (<1)	8 (<1)	8 (<1)
Cardiac hypertrophy	1 (<1)	0 (0)	0 (0)
Cardiac valve disease	2 (<1)	0 (0)	0 (0)
Cardiomyopathy	1 (<1)	1 (<1)	1 (<1)
Cardiovascular disorder	1 (<1)	0 (0)	0 (0)
Congestive cardiomyopathy	4 (<1)	0 (0)	1 (<1)
Diastolic dysfunction	12 (<1)	0 (0)	3 (<1)
Dilatation atrial	1 (<1)	0 (0)	1 (<1)
Dilatation ventricular	2 (<1)	0 (0)	2 (<1)
Left Atrial dilatation	11 (<1)	0 (0)	3 (<1)
Left ventricular dysfunction	39 (2)	5 (<1)	27 (1)
Left ventricular failure	2 (<1)	0 (0)	1 (<1)
Left ventricular hypertrophy	4 (<1)	0 (0)	0 (0)
Right atrial dilatation	1 (<1)	0 (0)	1 (<1)
Right ventricular failure	1 (<1)	0 (0)	0 (0)
Systolic dysfunction	6 (<1)	0 (0)	4 (<1)
Ventricular dysfunction	1 (<1)	0 (0)	1 (<1)
Ventricular hypokinesia	5 (<1)	0 (0)	3 (<1)
Cardiac function test abnormal	1 (<1)	0 (0)	0 (0)
Echocardiogram abnormal	1 (<1)	0 (0)	1 (<1)
Ejection fraction decreased	86 (5)	6 (<1)	61 (3)
Pulmonary oedema	1 (<1)	1 (<1)	1 (<1)
Total[1]	**171 (9)**	**19 (1)**	**111 (6)**

[1]Reflects total number of patients with the grouped AEs. If a patient experienced more than one AE, the patient was only counted once
G: toxicity grade
Source: dddemo.xpt and ddae.xpt

FDA Comments: In HannaH, the overall incidence of cardiac TEAEs were similar between the IV and SC arms, which were also expected based on the incidence of cardiomyopathy on the US-Herceptin label. The majority of cardiac TEAEs were less than grade 3 and the majority

resolved. For SafeHER, the majority of cardiac TEAEs were less than grade 3 and the majority resolved. Overall there were no new concerning safety findings.

Pulmonary Toxicity

Table 43 list the frequency of pulmonary toxicity, specifically pneumonitis, acute respiratory distress syndrome (ARDS), and pleural effusions in HannaH and SafeHER. Overall, there were few pulmonary toxicities in either study.

Table 43: Pulmonary Toxicities in HANNAH and SAFEHER

	HannaH		SafeHER
	Overall		Overall
	SC n=297 (%)	IV n=298 (%)	SC n=1864 (%)
Pneumonitis	2 (<1)	0 (0)	9 (<1)
ARDS	0 (0)	0 (0)	2 (<1)
Pleural Effusion	2 (<1)	1 (<1)	3 (<1)

SC: subcutaneous trastuzumab
IV: intravenous trastuzumab
Source: demoext.xpt and aeext.xpt dataset for HannaH; dddemo.xpt and ddae.xpt for SafeHER

FDA Comments: Overall, pulmonary toxicities were rare. None of the patients with pleural effusion had a concurrent diagnosis of malignancy or metastases to the lungs reported on study imaging. These numbers are expected and consistent with what was reported in the original Herceptin trials in the Herceptin USPI. There were no new concerning safety findings.

Hypersensitivity and Administration-related reactions

Table 44 list the frequency of hypersensitivity and administration-related reactions (defined as rash; pruritus, erythema; urticaria; rash pruritic; rash generalized; pruritus generalized; rash erythematous; swelling face; pruritus allergic; generalized erythema; cough; dyspnoea; asthma; sneezing; wheezing; respiratory failure; bronchospasm; bronchospasm; choking; nasal obstruction; hyperventilation; laryngeal oedema; respiratory distress; throat tightness; flushing; hypotension; circulatory collapse; hypersensitivity; drug hypersensitivity; oedema; chest discomfort; face oedema; swelling; flushing; hypotension; infusion related reaction; eye pruritus; periorbital oedema; sensation of foreign body; injection site hypersensitivity; anaphylactic reaction; drug hypersensitivity; allergic oedema; infusion related reaction; ocular hyperaemia; eye swelling; eye oedema; eyelid oedema; lip swelling; tongue oedema; oedema mouth; swollen tongue; cyanosis; blood pressure decreased) in HannaH. The most common reactions were rash (16.2%), cough (11.8%), and dyspnea (7.1%). There was no anaphylaxis reported in the HannaH study. Most of the reactions were less than grade 3, and nearly all resolved.

Table 45 list the frequency of hypersensitivity and administration-related reactions (defined as stated above) in SafeHER. The most common reactions were cough (10.6%), rash (10%), and dyspnea (6.5%). There were 3 patients who experienced an anaphylactic reaction in this trial; one of which resulted in discontinuation of trastuzumab. Most of the reactions are less than grade 3, and most resolved.

Table 44: Hypersensitivity and Administration-Related Reactions in HannaH

HannaH	SC N=297			IV N=298		
	G 1-5 (%)	G>3 (%)	Resolved (%)	G 1-5(%)	G>3 (%)	Resolved (%)
Rash	48 (16)	0 (0)	47 (16)	44 (15)	0 (0)	44 (15)
Cough	35 (12)	1 (<1)	34 (11)	24 (8)	0 (0)	24 (8)
Dyspnoea	21 (7)	0 (0)	21 (7)	22 (7)	0 (0)	22 (7)
Flushing	13 (4)	0 (0)	13 (4)	13 (4)	0 (0)	12 (4)
Anaphylaxis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Drug hypersensitivity	11 (4)	2 (<1)	11 (4)	9 (3)	1 (<1)	9 (3)
Edema	10 (3)	0 (0)	10 (3)	15 (5)	0 (0)	15 (5)
Hypersensitivity	9 (3)	1 (<1)	9 (3)	14 (5)	3 (1)	14 (5)
Chest Discomfort	8 (3)	0 (0)	8 (3)	6 (2)	0 (0)	6 (2)
Infusion related reaction	7 (2)	0 (0)	7 (2)	5 (2)	0 (0)	5 (2)
Hypotension	5 (2)	0 (0)	5 (2)	5 (2)	2 (<1)	5 (2)
Face edema	4 (1)	0 (0)	4 (1)	1 (<1)	0 (0)	1 (0.3)
Rash Pruritic	3 (1)	0 (0)	3 (1)	0 (0)	0 (0)	0 (0)
Eye Pruritus	3 (1)	0 (0)	3 (1)	2 (<1)	0 (0)	2 (<1)
Urticaria	2 (<1)	0 (0)	2 (<1)	2 (<1)	0 (0)	2 (<1)
Rash Generalized	1 (<1)	0 (0)	1 (<1)	1 (<1)	0 (0)	1 (<1)
Rash Erythematous	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
Swelling Face	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
Asthma	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hyperventilation	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
Laryngeal Oedema	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0	0 (0)
Swelling	1 (<1)	0 (0)	1 (<1)	1 (<1)	0 (0)	1 (<1)

Periorbital Oedema	1 (<1)	0 (0	1 (<1)	0 (0)	0 (0)	0 (0)
Infusion site pain	2 (<1)	0 (0)	2 (<1)	0 (0)	0 (0)	0 (0)
Infusion related reaction	7 (2)	0 (0)	7 (2)	5 (2)	0 (0)	5 (2)

SC: subcutaneous trastuzumab
IV: intravenous trastuzumab
Source: demoext.xpt and aeext.xpt

Table 45: Hypersensitivity and Administration-Related Reactions in SafeHER

SafeHER, N=1864	G 1-5 (%)	G>3 (%)	Resolved (%)
Cough	197 (11)	3 (<1)	169 (9)
Rash	183 (10)	3 (<1)	161 (9)
Dyspnea	122 (7)	6 (<1)	99 (5)
Pruritus	116 (6)	0 (0)	103 (6)
Flushing	46 (3)	0 (0)	26 (1)
Hypersensitivity	34 (2)	1 (<1)	32 (2)
Infusion related reaction	30 (2)	0 (0)	29 (2)
Urticaria	19 (1)	2 (<1)	17 (1)
Chest Discomfort	17 (1)	0 (0)	13 (<1)
Drug hypersensitivity	16 (1)	3 (<1)	16 (1)
Face oedema	13 (<1)	0 (0)	12 (<1)
Asthma	12 (<1)	2 (<1)	8 (<1)
Pruritus generalized	8 (<1)	0 (0)	8 (<1)
Rash Pruritic	6 (<1)	0 (0)	6 (<1)
Swelling	6 (<1)	0 (0)	4 (<1)
Sneezing	5 (<1)	0 (0)	4 (<1)
Swelling Face	4 (<1)	0 (0)	3 (<1)
Wheezing	4 (<1)	0 (0)	2 (<1)
Rash Generalized	3 (<1)	0 (0)	3 (<1)
Rash Erythematous	3 (<1)	0 (0)	3 (<1)
Eye Pruritus	3 (<1)	0 (0)	2 (<1)
Injection site hypersensitivity	3 (<1)	0 (0)	3 (<1)
Eye Swelling	3 (<1)	0 (0)	2 (<1)
Respiratory Failure	2 (<1)	1 (<1)	1 (<1)
Periorbital Edema	2 (<1)	0 (0)	1 (<1)
Ocular Hyperaemia	2 (<1)	0 (0)	2 (<1)
Eyelid Oedema	2 (<1)	0 (0)	2 (<1)
Lip Swelling	2 (<1)	0 (0)	2 (<1)
Anaphylactic reaction	2 (<1)	1 (<1)	1 (<1)
Cyanosis	2 (<1)	0 (0)	2 (<1)
Anaphylactic shock	1 (<1)	1 (<1)	1 (<1)
Pruritus Allergic	1 (<1)	0 (0)	1 (<1)
Generalized Erythema	1 (<1)	0 (0)	1 (<1)
Bronchospasm	1 (<1)	0 (0)	1 (<1)
Choking	1 (<1)	0 (0)	1 (<1)
Nasal Obstruction	1 (<1)	0 (0)	1 (<1)

Hyperventilation	1 (<1)	1 (<1)	1 (<1)
Respiratory Distress	1 (<1)	1 (<1)	1 (<1)
Throat Tightness	1 (<1)	0 (0)	1 (<1)
Circulatory Collapse	1 (<1)	0 (0)	1 (<1)
Sensation of Foreign Body	1 (<1)	0 (0)	0 (0)
Allergic Oedema	1 (<1)	0 (0)	1 (<1)
Eye Oedema	1 (<1)	0 (0)	1 (<1)
Tongue Oedema	1 (<1)	1 (<1)	1 (<1)
Oedema Mouth	1 (<1)	0 (0)	1 (<1)

Source: dddemo.xpt and ddae.xpt

FDA Comments: Overall the hypersensitivity and administration-related reactions were similar in the SC and IV arm of HannaH. Most of the reactions were less than grade 3, and they mostly all resolved. In SafeHER, most of the reactions are less than grade 3, and most resolved. Of the three patients who experienced anaphylaxis reaction or anaphylaxis shock, based on the patient narratives, it is unlikely that trastuzumab was the direct cause of those events (see the narratives below). Overall, hypersensitivity reactions have been reported to trastuzumab-products, but for HannaH and SafeHER, there were no new concerning safety findings

1. ***Patient (b) (6): 72 yo white woman with a history of tuberculosis status post partial lung resection, and stage I, T1N0M0, HER2, ER and PR positive BC. The patient received trastuzumab and tamoxifen for treatment. The patient then experienced anaphylactic reaction (the patient had received 8 cycles of trastuzumab prior to this reaction). The last dose of trastuzumab was administered 1 month prior to reported anaphylactic reaction. The Trastuzumab was discontinued due to this event.***
2. ***Patient (b) (6): 45 yo Asian woman with history of herniated disc and stage III, ductal, T3N2M0, HER2/ER/PR positive BC. The patient received her first dose of trastuzumab on SD1 and had received premedication with dexamethasone, omeprazole, diphenhydramine, ranitidine, ondansetron and metoclopramide with concurrent chemotherapy of docetaxel and carboplatin. On SD 4, the patient experienced anaphylactic reaction which resolved on SD5. Trastuzumab therapy was not altered.***
3. ***Patient (b) (6): 65 yo white woman with no prior medical history and stage II, ductal, HER2/ER/PR positive breast cancer status post breast surgery and 3 cycles of epirubicin, cyclophosphamide. On SD1, the patient received trastuzumab and concurrent chemotherapy with docetaxel. On SD 783, the patient experienced cholelithiasis and underwent cholecystectomy. Post-operatively, she received enoxaparin and then she experienced anaphylactic shock. She was treated appropriately, and the event resolved on SD 810. The patients last dose of study drugs prior to the event was SD 372.***

Injection site reactions

The injection site reactions were reported for Hannah in Table 46 and in Table 47 for SafeHER. In Hannah, all of the injection site reactions were less than grade 3 and resolved. In SafeHER, most of the injection site reactions were less than grade 3 and resolved.

Table 46: Injection Site Reactions for HannaH

HannaH	SC N=297			IV N=298		
	G 1-5 (%)	G>3 (%)	Resolved (%)	G 1-5(%)	G>3 (%)	Resolved (%)
injection site erythema	4 (1)	0 (0)	4 (1)	1 (<1)	0 (0)	0 (0)
injection site reaction	4 (1)	0 (0)	4 (1)	0 (0)	0 (0)	0 (0)
injection site discomfort	2 (<1)	0 (0)	2 (<1)	0 (0)	0 (0)	0 (0)
injection site rash	2 (<1)	0 (0)	2 (<1)	0 (0)	0 (0)	0 (0)
injection site joint pain	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
injection site bruising	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
injection site dermatitis	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
injection site induration	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
injection site inflammation	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
injection site macule	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
injection site pruritus	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)

SC: subcutaneous trastuzumab
IV: intravenous trastuzumab
Source: demoext.xpt and aeext.xpt

Table 47: Injection Site Reactions for SafeHER

SafeHER, N=1864	G 1-5 (%)	G>3 (%)	Resolved (%)
Injection site erythema	128 (7)	0 (0)	124 (7)
Injection site reaction	101 (5)	0 (0)	99 (5)
Injection site bruising	18 (1)	0 (0)	18 (1)
Injection site rash	15 (<1)	0 (0)	15 (<1)
Injection site inflammation	10 (<1)	0 (0)	10 (<1)
Injection site discomfort	4 (<1)	1 (<1)	1 (<1)
Injection site paraesthesia	4 (<1)	0 (0)	4 (<1)
Injection site hypersensitivity	3 (<1)	0 (0)	3 (<1)
Injection site warmth	3 (<1)	0 (0)	3 (<1)
Injection related reaction	2 (<1)	0 (0)	2 (<1)
Injection site induration	2 (<1)	0 (0)	2 (<1)
Injection site macule	2 (<1)	0 (0)	2 (<1)
Injection site pruritus	2 (<1)	0 (0)	2 (<1)
Injection site joint pain	1 (<1)	0 (0)	1 (<1)
Injection site extravasation	1 (<1)	0 (0)	1 (<1)
Injection site fibrosis	1 (<1)	0 (0)	1 (<1)
Injection site irritation	1 (<1)	0 (0)	1 (<1)
Injection site mass	1 (<1)	0 (0)	1 (<1)
Injection site nodule	1 (<1)	0 (0)	1 (<1)
Injection site pallor	1 (<1)	0 (0)	1 (<1)
Injection site ulcer	1 (<1)	0 (0)	1 (<1)

Source: dddemo.xpt and ddae.xpt

FDA Comments: Overall in both HannaH and SafeHER, the injection site reactions were mostly grade 1-2 in severity and the majority resolved. Injection site reactions would be expected based on route of delivery. Overall, there were no new concerning safety findings.

Serious TEAEs by Weight

Table 48 list the frequency of serious TEAEs by weight in HannaH and Table 49 list the frequency of serious TEAEs by weight in SafeHER. In HannaH, serious TEAEs were higher in the highest weight quartile compared to the lowest quartile, particularly in infections and infestations and blood and lymphatics. In SafeHER, serious TEAEs were higher in the highest weight quartile compared to the lowest, particularly in infections and infestations and blood and lymphatics**.**

Table 48: Serious TEAEs by Weight in HannaH

Neoadjuvant and Adjuvant (# pts)	SC (n= 297)		IV (n=298)	
	≤59 kg	≥79	≤59 kg	≥79
Infections and Infestations	7 (10)	5 (6)	5 (6)	2 (3)
Blood and Lymphatics	5 (7)	3 (4)	7 (9)	2 (3)
Cardiac disorders	0 (0)	5 (6)	0 (0)	3 (4)
Respiratory, thoracic and mediastinal	0 (0)	4 (5)	1 (1)	1 (1)
Vascular disorders	0 (0)	2 (2)	0 (0)	0 (0)
Gastrointestinal disorders	0 (0)	1 (1)	2 (3)	1 (1)
Neoplasms benign, malignant, unspecified	0 (0)	1 (1)	0 (0)	0 (0)
Nervous system	0 (0)	1 (1)	0 (0)	0 (0)
Pregnancy, puerperium, and perinatal	0 (0)	1 (1)	0 (0)	0 (0)
Psychiatric disorders	0 (0)	1 (1)	0 (0)	1 (1)
Renal and urinary disorders	0 (0)	1 (1)	0 (0)	0 (0)
Endocrine disorders	0 (0)	0 (0)	1 (1)	0 (0)
General disorders	1 (1)	0 (0)	0 (0)	1 (1)
Immune system	0 (0)	0 (0)	0 (0)	1 (1)
Injury, poisoning, procedural	1 (1)	0 (0)	1 (1)	2 (3)
Investigations	0 (0)	0 (0)	0 (0)	0 (0)
Musculoskeletal and Connective tissue	0 (0)	0 (0)	0 (0)	0 (0)
Reproductive System and Breast disorders	1 (1)	0 (0)	1 (1)	0 (0)
Skin and Subcutaneous tissue disorder	0 (0)	0 (0)	0 (0)	0 (0)

SC: subcutaneous trastuzumab
IV: intravenous trastuzumab
Source: demoext.xpt and aeext.xpt

Table 49: Serious TEAEs by Weight in SafeHER

MedDRA Term	N=1864 (%)	
	Wt. 1 N=64 (12.8%)	Wt. 4 N= 96 (21%)
Infections and Infestations	14 (3)	28 (6)
Blood and Lymphatic	12 (2)	19 (4)
Cardiac Disorders	7 (1)	10 (2)
Reproductive system and Breast disorders	7 (1)	2 (<1)
Injury, poisoning, procedural complications	5 (1)	6 (<1)
Neoplasm, benign, malignant, unspecified	4 (<1)	4 (<1)
Respiratory, thoracic and mediastinal disorders	4 (<1)	3 (<1)
Ear and Labyrinth disorders	3 (<1)	0 (0)
General Disorders and Administration site conditions	3 (<1)	7 (2)
Nervous System disorders	3 (<1)	5 (1)
Gastrointestinal disorders	2 (<1)	14 (3)
Metabolism and Nutrition disorders	2 (<1)	2 (<1)
Endocrine disorders	1 (<1)	0 (0)
Hepatobiliary disorders	1 (<1)	2 (<1)
Investigations	1 (<1)	4 (<1)
Psychiatric disorders	1 (<1)	2 (<1)
Skin and subcutaneous tissue disorders	1 (<1)	0 (0)
Vascular disorders	1 (<1)	4 (1)
Eye disorder	0 (0)	0 (0)
Musculoskeletal and Connective Tissue disorders	0 (0)	5 (1)
Pregnancy, puerperium and perinatal conditions	0 (0)	0 (0)
Renal and Urinary Disorders	0 (0)	4 (1)

Wt. 1: <54kg
Wt. 4: >77kg
Source: dddemo.xpt and ddae.xpt

FDA Comments: In HannaH the serious TEAEs were slightly higher in the highest weight quartile compared to the lowest quartile, particularly in infections and infestations and blood and lymphatics which is likely a results of concurrent chemotherapy administration. In SafeHER, serious TEAEs were higher in the highest weight quartile compared to the lowest, particularly in infections and infestations and blood and lymphatics which is likely a results of

concurrent chemotherapy administration. Importantly, given the flat dose of SC trastuzumab, serious TEAES were not higher in the lower weight quartile in either study. Overall, there were no new concerning safety findings.

Table 50 and Table 51 list the frequency of serious TEAEs by weight and association with chemotherapy in HannaH and SafeHER respectively. Serious TEAEs were higher during neoadjuvant treatment periods (HannaH) or during the concurrent chemotherapy treatment period (SafeHER) within the weight groups.

Table 50: Serious TEAEs by Weight and Association with Chemotherapy in HannaH

HannaH	Neoadjuvant				Adjuvant			
	SC (<59) N= 71 (%)	IV (<59) N= 77 (%)	SC (>79) N= 85 (%)	IV (>79) N=67 (%)	SC (<59) N=71 (%)	IV (<59) N= 77 (%)	SC (>79) N=85 (%)	IV (>79) N= 67 (%)
Infections and Infestations	5 (7)	4 (5)	1 (1)	0 (0)	2 (3)	1 (1)	3 (4)	1 (2)
Blood and Lymphatics	5 (7)	7 (9)	3 (4)	2 (3)	0 (0)	0 (0)	0 (0)	0 (0)
Injury, poisoning, procedural	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	2 (3)
Reproductive system	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)
Cardiac disorders	0 (0)	0 (0)	3 (4)	1 (2)	0 (0)	0 (0)	1 (1)	0 (0)
Neoplasm benign/malignant/unspecified	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
MSK and Connective tissue	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Psychiatric disorders	0 (0)	0 (0)	1 (1)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Investigations	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Skin and Subcutaneous tissue	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Nervous system	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Respiratory/Thoracic	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)
Immune System disorder	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Gastrointestinal disorders	0 (0)	2 (3)	1 (1)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Vascular Disorders	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

General/Administration site	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Pregnancy, puerperium, perinatal	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Renal and Urinary disorders	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Total	8 (11)	12 (16)	15 (18)	3 (5)	3 (4)	2 (3)	7 (8)	3 (5)

SC: subcutaneous trastuzumab
IV: intravenous trastuzumab
Source: Reviewer generated using demoext.xpt and aeext.xpt dataset.

Table 51: Serious TEAEs by Weight and Association with Chemotherapy in SafeHER

MedDRA Terms	Wt1 Concurrent N=295 (%)	Wt1 Sequential N=168 (%)	Wt1 No chemo N=38 (%)	Wt4 Concurrent N=275 (%)	Wt4 Sequential N=146 (%)	Wt4 No chemo N=43 (%)
Infections and Infestations	9 (3)	5 (3)	0 (0)	21 (8)	4 (3)	3 (7)
Blood and Lymphatic	11 (4)	1 (<1)	0 (0)	17 (6)	2 (1)	0 (0)
Injury, poisoning, procedural	3 (1)	1 (<1)	1 (3)	5 (2)	1 (<1)	0 (0)
Reproductive system	1 (<1)	5 (3)	1 (3)	2 (<1)	0 (0)	0 (0)
Cardiac disorders	3 (1)	4 (2)	0 (0)	5 (2)	5 (3)	0 (0)
Neoplasm benign, malignant, unspecified	2 (<1)	2 (1)	0 (0)	2 (<1)	2 (1)	0 (0)
Musculoskeletal and Connective tissue	0 (0)	0 (0)	0 (0)	3 (1)	1 (<1)	1 (2)
Psychiatric disorders	1 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)
Investigations	1 (<1)	0 (0)	0 (0)	4 (2)	0 (0)	0 (0)
Skin and Subcutaneous tissue	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Nervous system	2 (<1)	1 (<1)	0 (0)	5 (2)	0 (0)	0 (0)
Respiratory/Thor	2 (<1)	1 (<1)	1 (3)	2 (<1)	0 (0)	1 (3)

acic						
Immune System disorder	1 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)
Gastrointestinal disorders	2 (<1)	0 (0)	0 (0)	11 (4)	3 (2)	0 (0)
Vascular Disorders	1 (<1)	0 (0)	0 (0)	3 (1)	0 (0)	1 (2)
General/Administration site	3 (1)	0 (0)	0 (0)	7 (3)	0 (0)	0 (0)
Pregnancy, puerperium and perinatal	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ear and labyrinth disorder	0 (0)	1 (<1)	2 (5)	0 (0)	0 (0)	0 (0)
Eye disorder	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hepatobiliary	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	2 (5)
Metabolism	2 (<1)	0 (0)	0 (0)	2 (<1)	0 (0)	0 (0)
Renal and Urinary disorders	0 (0)	0 (0)	0 (0)	4 (2)	0 (0)	0 (0)
Endocrine	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)
Total	43 (14)	16 (10)	5 (13)	72 (26)	16 (11)	8 (19)

Wt1/Concurrent: patients ≤59kg who received concurrent chemotherapy + SC trastuzumab
Wt1/No chemo: patients ≤59kg who did not receive chemotherapy
Wt4 Concurrent: patients >77kg who received concurrent chemotherapy + SC trastuzumab
Wt4/No chemo: patients >77kg who did not receive chemotherapy
Source: dddemo.xpt and ddae.xpt

FDA Comments: Serious TEAEs were higher in the highest weight quartile compared to the lowest quartile. However, dose adjustments including dose delays or interruptions were comparable between the weight groups. Importantly, serious TEAEs were not higher in the lowest weight quartile. Serious TEAEs were higher during neoadjuvant treatment periods (HannaH) or during the concurrent chemotherapy treatment period (SafeHER) which suggest confounding factors such as the higher doses of chemotherapy used in the higher weight quartile group.

Cardiac TEAEs by Weight

Table 52 list the frequency of cardiac TEAES by weight in HannaH (The cardiac TEAEs were grouped by this reviewer to reflect the ones that are most consistent with cardiomyopathy). The frequency of cardiac TEAEs were higher in the highest weight quartile compared to the lowest weight quartile in the trastuzumab SC arm. The frequency of cardiac TEAEs were similar in the highest and lowest weight quartile groups in the trastuzumab IV arm. The frequency of cardiac TEAEs were similar in the highest weight quartile in the SC vs. IV arm.

Table 53 list the frequency of cardiac TEAEs by weight in SafeHER (The cardiac TEAEs were grouped by this reviewer to reflect the ones that are most consistent with cardiomyopathy). In SafeHER, the incidence of cardiac TEAEs was higher in the highest weight quartile compared to the lowest weight quartile.

Table 52: Cardiac TEAEs By Weight in HannaH

Neoadjuvant and Adjuvant (# pts)	SC (n= 297)		IV (n=298)	
	≤59 kg	≥79	≤59 kg	≥79
Cardiac failure	0 (0)	1 (1.2)	0 (0)	0 (0)
Cardiac failure congestive	0 (0)	2 (2.4)	0 (0)	0 (0)
Cardiomyopathy	0 (0)	0 (0)	0 (0)	0 (0)
Cardiovascular disorder	0 (0)	0 (0)	0 (0)	1 (1.5)
Diastolic dysfunction	0 (0)	0 (0)	0 (0)	0 (0)
Dilatation atrial	0 (0)	0 (0)	0 (0)	0 (0)
Left atrial enlargement	0 (0)	0 (0)	0 (0)	0 (0)
Left ventricular dilatation	0 (0)	1(1.2)	0 (0)	0 (0)
Left ventricular dysfunction	1 (1.4)	5 (5.9)	6 (5.6)	5 (7.5)
Left ventricular hypertrophy	0 (0)	0 (0)	0 (0)	0 (0)
Right ventricular failure	0 (0)	0 (0)	0 (0)	0 (0)
Ventricular hypokinesia	0 (0)	0 (0)	0 (0)	0 (0)
Cardiotoxicity	0 (0)	1 (1.2)	0 (0)	0 (0)
Ejection fraction	0 (0)	0 (0)	0 (0)	0 (0)
Ejection fraction decreased	0 (0	0 (0)	0 (0)	0 (0)
Total	**1 (1.4)**	**8 (9.4)**	**5 (6.5)**	**6 (9)**

SC: subcutaneous trastuzumab
IV: intravenous trastuzumab
Source: demoext.xpt and aeext.xpt

Table 53: Cardiac TEAEs by Weight in SafeHER

MedDRA Term	N=1864 (%)	
	Wt. 1	Wt. 4
Cardiac failure	0 (0)	4 (0.9)
Cardiac failure chronic	0 (0)	0 (0)
Cardiac failure congestive	4 (0.8)	3 (0.6)
Cardiac hypertrophy	0 (0)	1 (0.2)
Cardiac valve disease	0 (0)	1 (0.2)
Cardiomyopathy	1 (0.2)	0 (0)
Cardiovascular disorder	1 (0.2)	0 (0)
Congestive cardiomyopathy	0 (0)	1 (0.2)
Diastolic dysfunction	1 (0.2)	6 (1.3)
Dilatation atrial	0 (0)	0 (0)
Dilatation ventricular	0 (0)	0 (0)
Left atrial dilatation	0 (0)	6 (1.3)
Left ventricular dysfunction	10 (2)	9 (1.9)
Left ventricular failure	0 (0)	0 (0)
Left ventricular hypertrophy	0 (0)	1 (0.2)
Right atrial dilatation	0 (0)	1 (0.2)
Right ventricular failure	0 (0)	0 (0)
Systolic dysfunction	0 (0)	2 (0.4)
Ventricular dysfunction	1 (0.2)	0 (0)
Ventricular hypokinesia	1 (0.2)	0 (0)
Cardiac function test abnormal	0 (0)	0 (0)
Echocardiogram abnormal	0 (0)	1 (0.2)
Ejection fraction abnormal	0 (0)	1 (0.2)
Ejection fraction decreased	14 (2.8)	29 (6.2)
Pulmonary oedema	1 (0.2)	0 (0)
Total	**32 (6.4)**	**56 (12.1)**

Wt1: ≤59kg
Wt4: >77kg
Source: dddemo.xpt and ddae.xpt

FDA Comments: In HannaH, the frequency of cardiac TEAES were similar in the highest weight quartile regardless of IV vs. SC route of administration. Within the SC arm, the incidence of cardiac AEs were higher in the highest weight quartile compared to the lowest weight quartile. In SafeHER, the incidence of cardiac TEAEs was higher in the highest weight quartile compared to the lowest. This is likely confounded by the higher doses of chemotherapy as seen above with higher frequency of serious TEAEs by weight during treatment periods with

chemotherapy. This finding may reflect the known comorbidities and risk associated with the highest weight quartile. Overall, patients in the lowest weight quartile did not experience increased frequency of cardiac TEAEs.

8.2.6 Clinical Outcome Assessment (COA) Analyses

No patient-reported outcomes were studied in SafeHER.

8.2.7 Safety Analyses by Demographic Subgroups

Trastuzumab-containing products are not expected to have differences in efficacy or safety based on patient race or ethnicity.

8.2.8 Specific Safety Studies/Clinical Trials

The HannaH trial submitted the full CSR at the time of the initial submission. The 120-safety update for SafeHER was submitted. That report presented cumulative data from start of study up to 2018. It included data during the follow up phase (defined as 34 days from last treatment to 6/25/18). Overall, the safety profile was consistent with what was reported during the treatment phase and no new safety signals were observed. It was reported that 1.1% (20/1864) patients experienced a reportable AE, and 0.4% (8/1864) patients died during the reporting period. 4.9% of patients in cohort A experienced a cardiac disorder, 1.9% of patients experienced a serious AE reported as infections and infestations.

This report included information about 10 new deaths: synovial sarcoma, pneumonia, cerebrovascular accident (2 patients), metastatic colon cancer, pancreatic carcinoma, acute cerebrovascular event, pleural effusion, pulmonary sepsis, and unknown cause of death

FDA Comments: There were no new safety signals identified in the follow-up phase. The narratives were reviewed for all of deaths and were consistent with what was reported.

- ***Pt (b) (6): 29 yo woman with ductal, stage II, T2N2M2, Her2 positive and ER/PR negative BC. She underwent mastectomy and received and completed chemotherapy with fluorouracil, cyclophosphamide, and epirubicin and therapy with trastuzumab. On SD 622, she was diagnosed with metastatic synovial sarcoma of the neck to long bone. She received XRT (total 800cGy) and chemotherapy (ifosphomide, epirubicin, cyclophosphamide, dacarbazine, vincristine). She died on SD 893 due to progression of metastatic synovial carcinoma.***
- ***Pt (b) (6): 73 yo woman with ductal, stage II, T2N0M0, Her2 positive, ER positive, PR negative BC. She went on to receive mastectomy, chemotherapy, hormone therapy, radiation therapy, and trastuzumab. On SD 1113, she was diagnosed with pneumonia and sepsis on SD 1181. She was treated with intravenous antibiotics, but she died on SD 1187.***
- ***Pt (b) (6): 71 yo woman with ductal, stage II, T2N1M0, HER2 positive and ER and PR negative BC. She then underwent surgery, concurrent chemotherapy with trastuzumab and completed trastuzumab therapy. On SD 1694, she developed cerebrovascular event. There were no symptoms provided with the narrative. She died on SD 1694.***
- ***Pt (b) (6): 31 yo female patient with stage III, T3N2, Her2 positive ER/PR negative BC. She received 6 cycles of chemotherapy with doxorubicin and docetaxel. She received the***

last dose of study drug on SD 358. On SD 655, a PET-CT confirmed metastatic disease. On SD 1005, the patient died due to unknown causes.

- ***Pt*** (b) (6)***: 57 yo white female with ductal, stage II, T2N1M0, Her2 positive, ER/PR positive BC. She underwent surgery and completed 6 cycles of chemotherapy with epirubicin, 5-fluorouracil, and cyclophosphamide. She also completed treatment with trastuzumab. On SD 1324, she was diagnosed with metastatic colon cancer. An abdominal ultrasound revealed liver lesions. Biopsy confirmed metastatic GI disease. She started irinotecan, bevacizumab and capecitabine. She was found dead in her home on SD 1413.***
- ***Pt*** (b) (6)***: 84 yo woman with h/o ulcerative colitis. She was diagnosed with stage II, T2N1M0, Her2positive, ER/PR negative BC. She completed treatment with study drug on SD 356. On SD 1433, she was diagnosed with atrial fibrillation. On SD 1548, the patient was diagnosed with pancreatic adenocarcinoma. The patient received palliative care and died on SD 1579.***
- ***Pt*** (b) (6)***: 55 yo woman with lobular, stage III, T3N3M0, Her2 positive, ER/PR positive BC. She underwent surgery, completed 6 cycles of chemotherapy with doxorubicin, 5-fluorouracil, a d cyclophosphamide. She also completed trastuzumab therapy. On SD 1578, the investigator contacted patient's daughter, who said she had died of a CVA. No other information was provided.***
- ***Pt*** (b) (6)***: 39 yo woman with ductal, stage III, T4N3M0, Her2 positive and ER/PR positive BC. She underwent surgery and completed chemotherapy with 4 cycles of cyclophosphamide and epirubicin and 2 cycles of docetaxel. She completed trastuzumab therapy. On SD 1458, she developed pleural effusions (no information included about symptoms), she received a bilateral chest tube thoracotomy and then died.***
- ***Pt.*** (b) (6)***: 37 yo woman with stage III, T3N2M0, HER2 positive ER and PR positive breast cancer. She completed chemotherapy concurrently with trastuzumab. On SD 1429, she was diagnosed with a pleural effusion and multiple nodules in both lungs. She died on SD 1434 due to pleural effusion.***
- ***Pt*** (b) (6)***: 69 yo woman with history of COPD/asthma, who was diagnosed with lobular, stage III, T2N2M0, Her2 positive, ER positive, PR negative BC. She was treated with radiation, hormonal therapy, and trastuzumab therapy. On SD 1661, she experienced shortness of breath and cough. She was treated for pulmonary sepsis with antibiotics. On that same day, the patient found in bed, with reduced respiratory rate. ECG showed ST segment elevation MI and she subsequently died.***

8.2.9 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

In HannaH, one patient developed myeloid leukemia, one patient developed papilloma, one developed cervical cancer, one developed thyroid cancer, two patients developed endometrial cancer, and one developed uterine leiomyoma. In SafeHER, eight patients developed uterine leiomyoma, four developed a thyroid neoplasm, one developed colon cancer, one developed renal cell carcinoma, one developed rectal adenocarcinoma, one developed endometrial cancer, one developed ovarian cancer and one developed gastric cancer.

FDA Comments: Trastuzumab is not known to cause secondary malignancies. The concomitant chemotherapy, including anthracyclines, is a confounding factor. Overall, these reports are unlikely to impact the safety of SC trastuzumab.

Human Reproduction and Pregnancy

There were 2 pregnancies reported in HannaH and 4 in SafeHER.

HannaH:

- (b) (6) (SAE, AE leading to treatment discontinuation): The patient was randomized to the SC trastuzumab arm on SD 1 (b) (6). On SD 21, a trans-vaginal ultrasound (US) to place IUD, showed a pregnancy of 10 weeks, 4 days. On the same day, therapy was discontinued. On SD 80, the patient had a spontaneous intra-uterine fetal death and the pregnancy was terminated. This was determined not to be related to the study drugs
- (b) (6) (SAE): The patient was randomized to the SC arm. On SD129, the patient was diagnosed with pregnancy. On SD 136, the patient had a grade 4 spontaneous abortion which was thought to be related to trastuzumab.

SafeHER:

- (b) (6) (SAE): The patient was diagnosed with pregnancy on SD 463. The patient was already s/p 18 cycles of trastuzumab. On SD 467, and US revealed blighted ovum and the investigator decided to do curettage on SD 471. This event was thought to be unrelated to trastuzumab
- (b) (6): The patient was diagnosed with pregnancy on SD 479. She was s/p 18 cycles trastuzumab. The patient went on to give birth to a live male infant on (b) (6).
- (b) (6): The patient was diagnosed with pregnancy on SD 154. She was s/p 7 cycles trastuzumab and subsequent to the pregnancy, the trastuzumab was permanently discontinued. The patient underwent a medical termination on SD 186
- (b) (6): The patient was diagnosed with pregnancy on SD 505. She was s/p 18 cycles trastuzumab. The patient went on to give birth to twins.

On 11/8/18, the agency sent an information request (IR) to the applicant asking them to provide global post-marketing data for the embryo-fetal toxicities related to SC trastuzumab. The applicant responded on 11/15/18. There was a total of 46 cases reporting 68 events. Of the 46 cases, 25 were not attributed to exposure to SC trastuzumab during pregnancy. In the remaining cases, 5 cases reported that there were no AEs after the patient gave birth; oligohydramnios occurred in 3 cases (2 went on to deliver healthy babies), 2 cases concerned

the same pregnancy, 3 cases underwent therapeutic abortions, 2 cases of spontaneous abortion, 6 cases of pregnancy which were lost to follow up.

FDA Comments: Trastuzumab products are known to cause embryo-fetal toxicity. No cases of embryo-fetal toxicity were reported in HannaH or SafeHER. There were no new concerning safety findings

Pediatrics and Assessment of Effects on Growth
There was no exposure to SC trastuzumab in pediatric patients on HannaH or SafeHER.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound
In HannaH, 2 patients received 960 mg of SC trastuzumab: pt. (b) (6) and pt. (b) (6). There were no AEs reported for either patient related to overdose. On 12/13/18 the FDA sent the following IR to the applicant:

(1) Provide patient outcomes (including but not limited to all AEs, duration of toxicity, resolution of toxicity, etc.) that resulted from a wrong route administration error (where SC is inadvertently given IV)
(2) the contributing factors that led to the wrong route of administration errors

The applicant responded on 12/17/18. Twenty-eight cases have reported SC trastuzumab formulation inadvertently administered via IV route. Of those, 3 cases reported non-serious AEs including chills and fever, nausea, rash/pruritis/and hyperkalemia (on a medication known to cause hyperkalemia). One case reported 2 serious AE (hematuria and diarrhea).

The FDA sent an IR on 12/19/18 in reference to the 4 cases ((b) (6)) with reported AEs where patients received the SC product via IV route. The FDA asked the applicant to provide the time of the onset and time to the resolution of AE. In particular for the case with a reported SAE (b) (6), the FDA asked the applicant to provide the diagnostic work up, time course of the onset of the event, time course to the resolution of event, and any updates on the root cause analysis of the error. The applicant responded on 12/20/18 and provided the narrative for those patients.

The FDA sent an IR on 12/11/18 to provide the risk evaluation for the excipient methionine in the SC formulation when given intravenously by mistake. The applicant responded on 12/14/18 and stated that the maximum dose of methionine after inadvertent IV dosing of Herceptin SC is 7.45mg which is 14x less than the toxicologically based limit as established by the applicant.

FDA Comments: Overall, the safety profile of possible AEs related to the incorrect administration of SC trastuzumab were not serious, with only 1 case of serious hematuria and diarrhea which resolved. The applicant has proposed use-related risk analysis to reduce the risk of administration errors. The DMEPA reviewers agreed the applicant's justification that a human factor validation study does not need to be submitted and recommendations were provided to ensure safe use of the product. Refer to the DMEPA review dated December 17, 2018 for full details.

8.2.10 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Since August 2013, SC trastuzumab has been approved in more than 87 countries globally and approximately 127,810 patients have received SC trastuzumab. Cases of medical errors have been reported including inadvertent administration of SC trastuzumab through the IV route or vice versa (8 cases), administration of SC trastuzumab instead of Kadcyla, administration site error (administered in the abdomen instead of the thigh), intracutaneous administration of SC trastuzumab, paraveneous and intrahepatic administration of Herceptin.

FDA Comments: Below are the narratives of the 4 cases were AEs were reported.

- ***AER*** (b) (6) ***: a 65 yo woman who was diagnosed with BC in*** (b) (6) ***and underwent surgery followed by chemotherapy, radiation therapy and hormone therapy with tamoxifen for 5 years. The breast cancer recurred in*** (b) (6) ***and she underwent left mastectomy and deferred chemotherapy. She was also diagnosed with colon cancer and underwent hemicolectomy and was prescribed capecitabine. In*** (b) (6) ***, she was prescribed SC trastuzumab for the HER2 positive advanced BC but was administered dose intravenously. The nurse mixed the trastuzumab SC 1 vial as IV infusion. The patient experienced chilling and fever and was treated with an anti-inflammatory agent. She recovered from event. Unknown if trastuzumab therapy was continued.***
- ***AER*** (b) (6) ***: 57 yo woman with BC who, at an unknown date, started SC trastuzumab. In*** (b) (6) ***, the SC trastuzumab 600mg was administered via IV. She developed nausea, but that resolved in an unspecified time period (but less than 7 days). She also developed a "bump" (19-21 days after administration) and was injected with dexketoprofen trometamol for the "bump". She then developed hyperkalemia (21 days after administration).***
- ***AER*** (b) (6) ***: 51 yo woman who was prescribed IV trastuzumab 360mg once per every three weeks in*** (b) (6) ***. In*** (b) (6) ***, she was infused with part of trastuzumab 600mg instead of 440mg IV by the nurse. She developed itching but took cetirizine.***
- ***AER*** (b) (6) ***: 61 yo woman with Her2 + stage Ib cancer.*** (b) (6) ***, the patient was administered SC trastuzumab intravenously by a nurse. On the same day, the patient developed hematuria and diarrhea. On an unspecified date the events resolved.***

Expectations on Safety in the Postmarket Setting

In view of extensive exposure since the initial approval of Herceptin in 1998, the safety profile of trastuzumab is well known. It appears unlikely that any new safety concern will occur. Although given the method of administration, it is possible that medication errors with administration will occur.

8.2.11 Integrated Assessment of Safety

HannaH was phase III, randomized, open-label study to compare the pharmacokinetics, efficacy and safety of subcutaneous (SC) trastuzumab with intravenous (IV) trastuzumab administered in women with HER2 positive breast cancer (EBC). In HannaH there were 595 patients in the safety population. SafeHER was a phase III, prospective, two-cohort non-randomized,

multicenter, multinational, open label study with the primary objective to assess the overall safety and tolerability of SC trastuzumab in HER2-positive early (stage I-IIIC) stage BC. In SafeHER there were 1864 patients in the safety population. PrefHER was a phase II, international, randomized, multi-center, open-label, two-cohort & two-arm, crossover trial with the primary objective to assess patient preference for administration of IV versus SC trastuzumab and to compare HCP satisfaction and perceived time savings with SC trastuzumab in the HER2−positive EBC adjuvant treatment setting. This trial was not included in the safety analysis because of the crossover period between subcutaneous and intravenous routes of administration which would make it difficult to evaluate the safety profile of IV or SC trastuzumab. Analyses of deaths, serious TEAEs, TEAEs leading to treatment discontinuation, and cardiac, pulmonary, and embryo-fetal toxicities showed results to be similar with what is expected for IV trastuzumab. Overall, no new safety signals were identified in the HannaH and SafeHER studies for SC trastuzumab.

8.3 Clinical Outcome Assessment of Patient Reported Outcomes

The baseline demographics for patients randomized in PrefHER are listed in Table 54 below.

Table 54: Baseline Characteristics for Randomized Patients in PrefHER (Cohort 2)

	SC then IV N=121 n (%)	**IV then SC N=119 n (%)**
Intent to Treat (Yes)	118 (98)	113 (95)
Age		
Mean (SD)	53 (10.97)	53 (10.80)
Median (Range)	50 (29, 78)	53 (27, 76)
Age Categories		
<65	101 (83)	99 (83)
≥65	20 (17)	20 (17)
Race		
Asian	0 (0)	1 (1)
Unknown	25 (21)	24 (20)
White	96 (79)	93 (78)
Country		
DENMARK	8 (7)	5 (4)
FRANCE	27 (22)	25 (21)
GERMANY	21 (17)	23 (19)
ITALY	9 (7)	10 (8)
RUSSIAN FEDERATION	14 (12)	14 (12)
SPAIN	26 (21)	23 (19)
SWEDEN	0 (0)	2 (2)

SWITZERLAND	2 (2)	2 (2)
TURKEY	6 (5)	4 (3)
UNITED KINGDOM	8 (7)	11 (9)
Progesterone Receptor Status		
Negative	51 (42)	60 (50)
Positive	58 (48)	53 (45)
Unknown	12 (10)	6 (5)
Estrogen Receptor Status		
Negative	40 (33)	44 (37)
Positive	77 (64)	73 (61)
Unknown	4 (3)	2 (2)
Stratification factor: Adjuvant Trastuzumab		
De Novo	25 (21)	24 (20)
Non De Novo	96 (79)	95 (80)
IHC Result		
Unknown	2 (2)	1 (1)
++	24 (20)	16 (13)
+++	95 (79)	101 (85)
0/+	0 (0)	1 (1)
ISH Result		
Missing	68 (56)	67 (56)
Negative	0 (0)	3 (3)
Positive	53 (44)	49 (41)

SC: subcutaneous trastuzumab
IV: intravenous trastuzumab
Source: ddbase.xpt

FDA Comments: Eligible patients were women aged 18 years or older with HER2-positive, histologically confirmed primary invasive breast adenocarcinoma, no evidence of residual, locally recurrent, or metastatic disease after completion of surgery and chemotherapy, ECOG performance status of 0 or 1. The baseline patient demographic, tumor characteristics, and treatment history were generally balanced between study groups. Most patients previously received trastuzumab, which raised concerns for bias in the patient questionnaire on whether patients preferred one administration over another.

Patient reported outcomes (PRO) were assessed in the PrefHER trial using patients' experiences and preferences towards either IV or SC trastuzumab. Prior to randomization, patients were interviewed via telephone to assess the factors influencing preference (1st patient interview, named PINT1). At the end of the eighth cycle a second patient interview (named PINT2) was performed. PINT2 items 53 and 54a/54b addressed the two main reasons for preference. Health Care Professional (HCP) satisfaction and perceived time savings were assessed by a Health Care Professional Questionnaire (HCPQ).

Each interview sought to evaluate patient and or health professional prior experience and preference as listed below.

The PINT1:

- Patient's prior exposure to different types of drug administration (including treatment for non-cancer related disease)
- Distance/ease/cost of traveling to and from the cancer center/doctors' office, needle phobia,
- Recent experiences whilst receiving chemotherapy including acceptability of environment, relationship with staff, and
- Any adverse event during chemotherapy treatment including problems with the IV site

The PINT2

- Site of administration,
- Type of IV administration,
- Experiences during study with both methods of administration (e.g. time taken, perceived confidence/competency of staff, injection site reactions (infections, bruising),
- And treatment symptoms (pain, bruising, irritation, anxiety)

PINT2

- Item 53: All things considered, which method of administration did you prefer?
  - Response options: IV/SC/No preference.
- Item 54a/54b: How strong is this preference?
  - Response options: Very, fairly, non-very.
  - What are the two main reasons for your preference?

HCPC:

- All things considered with which method of administration were you most satisfied?
  - Response options: IV/SC/No preference.
- How many minutes preparation time do you think the SC device required after receiving it from the pharmacy
- How many minutes in total do you think placing the SC device and administering the SC Herceptin usually took?
- How many minutes preparation time do you think the Herceptin required for IV use after receiving it from the pharmacy?
- If a patient needed cannulation how many minutes do you think this usually took?
- How many minutes in total do you think connecting the Herceptin infusion and administering it IV usually took?

Patient preference for SC trastuzumab was high. In Cohort 2, the overall preference rate for SC trastuzumab was 86.1% (199/231 patients) and the preference rate for IV trastuzumab was 12.6% (29/231 patients). Refer to Table 55: Patient Preference - Cohort 2 for overall patient preference. Patient preference for Herceptin SC or Herceptin IV administration was analyzed by whether patients had previously been treated with Herceptin (non de novo) or whether they

were naïve to Herceptin (de novo). Refer to Table 56: Patient Preference by de Novo/Non de Novo Status - Cohort 2 for preference by de Novo Status.

Table 55: Patient Preference - Cohort 2

Cohort 2 – ITT Population	**SC Vial/IV N=118**	**IV/SC Vial N=113**	**Overall N=231**
Preferred Method of Administration (n (%))			
IV	16 (13.6)	13 (11.5)	29 (12.6)
SC	99 (83.9)	100 (88.5)	199 (86.1)
No preference	3 (2.5)	0 (0.0)	3 (1.3)

SC: subcutaneous trastuzumab
IV: intravenous trastuzumab
Source: Summary of Clinical Efficacy for PrefHER

Table 56: Patient Preference by de Novo/Non de Novo Status - Cohort 2

Cohort 2 – ITT Population Subgroup	**SC Vial/IV N=118**	**IV/SC Vial N=113**	**Overall N=231**
De Novo			
Preferred Method of Administration (n (%))	1 (5.0)	2 (10.0)	3 (7.5)
IV	19 (95.0)	18 (90.0)	37 (92.5)
SC	0 (0.0)	0 (0.0)	0 (0.0)
No preference			
Non de Novo			
Preferred Method of Administration (n (%))			
IV	15 (15.3)	11 (11.8)	26 (13.6)
SC	80 (81.6)	82 (88.2)	162 (84.8)
No preference	3 (3.1)	0 (0.0)	3 (1.6)

SC: subcutaneous trastuzumab
IV: intravenous trastuzumab
Source: Summary of Clinical Efficacy for PrefHER

The applicant sought to make the labeling claim:

FDA Comments: Refer to Drs. Yasmin Choudhry and Selena Daniels (Clinical Outcomes Assessment) review dated January 30, 2019. The overall preference rate for IV trastuzumab was 12.6% (12/231 patients) and the preference rate for SC trastuzumab vial was 86.1% (199/231). 57.1% of patients (132/231) reported time as their primary reason for preference for subcutaneous administration. 12.1% (28/231) reported reduced pain as their primary reason for preference for the subcutaneous administration. 81.2% of the completed questionnaires indicated that HCPs were most satisfied with the SC trastuzumab administration rate and HCPS reported times savings with the subcutaneous route of administration. In addition, mean reported reduction in patient chair time was 71% per session. The FDA review focused on the patient preference data, as the HCP satisfaction, perceived time savings, and infusion chair time does not describe clinical benefit to patients.

After Cycle 8, 199 of 231 patients (86%) reported preferring subcutaneous administration of trastuzumab over IV trastuzumab with the most common reason cited administration required less time (179/231) in the clinic. After Cycle 8, 29 out of 231 patients (13%) reported preferring IV trastuzumab over SC trastuzumab with the most common reason was fewer local injection reactions. Three out of 231 patients (1%) had no preference for the route of administration. Nine out of 240 (3.8%) withdrew from treatment prior to completion of Cycle 8 and did not complete the post-study preference questionnaire. The randomization scheme was stratified by whether or not the patient had received Trastuzumab prior to trial entry, therefore the issue of recall error was acknowledged; however, the recall with this cross-over study design was consistent to previous preference studies. The susceptibility to bias of

preference for SC was expected; however, there were also patients with this preference distributed across both treatment arms making this acceptable. The methods used to conduct the telephone interviews appear to be consistent with best practices of survey research (e.g., the Applicant sought expert opinion and patient input for item generation of the interview guide, translated the interview guide using forward and backward translation, and pilot-tested the interview guide). While interviewer bias is a common limitation of telephone interviews/surveys, the extent of such a bias is unknown and cannot be fully eliminated. In an effort to mitigate this limitation, the applicant recorded the telephone interviews for quality control purposes. The patient preference telephone interviews appear to be conducted in a standard manner.

SUMMARY AND CONCLUSIONS

8.4 Statistical Issues

The HannaH study was ongoing at the initial meeting with FDA on June 21, 2010 and FDA had not reviewed the final protocol and statistical analysis plan prior to study initiation. In general, the ratio of proportions is preferred as the primary analysis instead of the difference of proportions, with symmetric confidence intervals to support an evaluation of no clinically meaningful differences.

The HannaH trial met its co-primary endpoints of comparable pathological complete response (pCR) in the breast only at the time of definitive surgery after Cycle 8 between the SC trastuzumab and IV trastuzumab and C_{trough} at the end of Cycle 7 (before the Cycle 8 dose). Extrapolation to the proposed indications are based on the comparable PK profiles of IV trastuzumab across the neoadjuvant-adjuvant/adjuvant treatment settings in patients with early breast cancer (EBC) and metastatic breast cancer (EBC), neoadjuvant-adjuvant treatment as used in HannaH is a sensitive setting for establishing clinical similarity of efficacy and immunogenicity, and mode of action of trastuzumab in the EBC and MBC are the same.

The HannaH and SafeHER trials demonstrated that the safety profile of SC trastuzumab was similar with the safety profile of Herceptin, with no new safety signals identified. In the PrefHER study, 86% of patients reported preferring SC trastuzumab over IV trastuzumab and the most common reason cited was administration required less time in the clinic.

8.5 Conclusions and Recommendations

In conclusion, the totality of data allows for extrapolation to the proposed indication. Appropriate labeling was included in labeling for Dosage and Administration for the route of administration of SC trastuzumab and in Warnings and Precautions for cardiomyopathy, hypersensitivity and administration-related reactions, embryo-fetal toxicity, pulmonary toxicity, and exacerbation of chemotherapy induced neutropenia. SC trastuzumab is not indicated for use used in patients with metastatic gastric or gastroesophageal junction adenocarcinoma.

X	X
Laura Fernandes Primary Statistical Reviewer	Shenghui Tang Statistical Team Leader
X	X
Danielle Krol (efficacy and PRO) Candace Mainor (safety) Primary Clinical Reviewer	Jennifer Gao Acting Clinical Team Leader

9. Advisory Committee Meeting and Other External Consultations

No Advisory Committee Meeting was indicated.

10. Pediatrics

On March 9, 2018, Genentech submitted an initial Pediatric Study Plan (iPSP) with a request for a waiver from all requirements of the Pediatric Research Equity Act (PREA) under IND 109168. On March 28, 2018, the Oncology Subcommittee of PeRC agreed to a full iPSP waiver.

11. Labeling Recommendations

11.1 Prescription Drug Labeling

The FDA labeling for HERCEPTIN HYLECTA was based primarily on the clinical experience from this trastuzumab subcutaneous product studied in the HannaH and SafeHER clinical trials and performed in HER2+ women in the neoadjuvant and adjuvant setting. The HannaH study demonstrated comparable efficacy, safety, and pharmacokinetic results between HERCEPTIN HYLECTA (subcutaneous) AND HERCEPTIN (intravenous). In addition, the totality of data submitted, supported the indication for the use of HERCEPTIN HYLETCA to treat metastatic HER2+ breast cancer (*see Section 1 of this review for more information*). For the HER2+ metastatic breast cancer indications, intravenous trastuzumab efficacy and safety experience in this setting was used to inform and provide safety and efficacy information for the HERCEPTIN HYLECTA prescribing information (*see the approved USPI for more information*). The PrefHER trial data was also used to support the Patient Experience (14.3) subsection in the prescribing information. *See 8.1. in this review for more information*.

Summary of Significant Labeling Changes		
Section	**Proposed Labeling**	**Approved Labeling** *(as of February 15, 2019)*
Highlights		
Product Title	[TRADENAME] (trastuzumab and hyaluronidase human-xxxx) injection, for subcutaneous use	FDA removed "human" from the product title (product name in other sections of the labeling); and revised to the following: HERCEPTIN HYLECTA™ (trastuzumab and hyaluronidase-oysk) *See Section 4.2 of this review for more information.*
Dosage and Administration	… Recommended (b) (4) of TRADENAME is 600 mg (b) (4) . No loading dose is required. (b) (4) administered subcutaneously over approximately 2-5 minutes every three weeks. (2.2)	FDA revised this to the following: • The recommended dose of HERCEPTIN HYLECTA is 600 mg/10,000 units (600 mg trastuzumab and 10,000 units hyaluronidase) administered subcutaneously over approximately 2-5 minutes once every three weeks. (2.2)
Dosage Forms and Strengths	(b) (4)	FDA revised this to the following: • Injection: 600 mg trastuzumab and 10,000 units hyaluronidase per 5 mL (120 mg/2,000 units per mL) (b) (4) in a single-dose vial. (3)

Warnings and Precautions	…	FDA added the following information: • Hypersensitivity and Administration-related Reactions (ARRs): Severe ARRs, including anaphylaxis, have been reported with HERCEPTIN HYLECTA. Monitor patients for systemic hypersensitivity reactions. Permanently discontinue HERCEPTIN HYLECTA in patients who experience anaphylaxis or severe hypersensitivity reactions. (5.5)
Adverse Reactions	Adjuvant Breast Cancer …	FDA revised the common adverse reactions (ARs) statement to add ARs for injection site reactions, upper respiratory tract infection, rash, nausea, and edema.
Full Prescribing Information		
1. Indications and Usage	…	FDA revised to add "adults" to the adjuvant and metastatic breast cancer indications to be consistent with the current FDA Labeling Guidance for this section.
2. Dosage and Administration	**2.2 Recommended Doses and Schedules** **…** The recommended dose of TRADENAME is 600 mg (b) (4) . No loading dose is required. (b) (4) administered subcutaneously over approximately 2-5 minutes every three weeks. …	• FDA added "**Do not administer intravenously."** and bolded the do not substitute HERCEPTIN HYLECTA for or with ado-trastuzumab statements. • Revised the recommended dose statements to the following o "The recommended dose of HERCEPTIN HYLECTA is 600 mg/10,000 units (600 mg trastuzumab and 10,000 units hyaluronidase) administered subcutaneously over approximately 2-5 minutes once every three weeks." o "No loading dose is required. No dose adjustments for patient body weight or for different concomitant chemotherapy regimens are required."
	2.3 Important Dosing	FDA reorganized this section to move

	Considerations *(revised to 2.3 Dosage Modifications for Adverse Reactions)* **…**	administration-related statements to **2.4 Administration and Storage**. FDA removed (b) (4)
	2.4 Administration and Storage *(subsection added by FDA)*	FDA added subsection 2.4 to provide information related to medication error prevention, required administration by a healthcare professional, directions to inspect and prepare the injection, material compatibilities, storage requirements (e.g., temperature, syringe storage expiration times, protect from light), and direction not to shake or freeze.
3. Dosage Forms and Strengths	…	FDA added "is a colorless to yellowish, clear to opalescent solution" to provide the required description of identifying characteristics.
5. Warnings and Precautions	**5.1 Cardiomyopathy** …	FDA revised this section to make it clear that the cardiomyopathy risks associated with trastuzumab IV are similar, applicable, and associated with HERCEPTIN HYLECTA. FDA agreed to the proposed cardiomyopathy information for the HannaH and SafeHER studies with minor revisions and the addition of one case of CHF (increasing incidence from (b) (4) to 1%).
	5.3 Exacerbation of Chemotherapy-Induced Neutropenia … **5.4 Pulmonary Toxicity** …	FDA revised the order of these numbered subsections based on descending clinical relevance to move pulmonary toxicity to 5.3 and Exacerbation of CIN to 5.4.
	5.5 Administration-Related Reactions (b) (4)	FDA revised this section to the following: **5.5 Hypersensitivity and Administration-related Reactions** FDA divided the ARRs up into systemic

	(b) (4)	reactions and local cutaneous reactions. For the systemic reactions subsection FDA added: • "Severe administration-related reactions (ARRs), including hypersensitivity and anaphylaxis, have been reported with HERCEPTIN HYLECTA." • Grade 1-4 and Grade 3-4 hypersensitivity and anaphylaxis incidence rates from the HannaH and SafeHER trials. • Serious and fatal reactions have been reported after treatment with intravenous trastuzumab products. • Monitoring, permanent discontinuation, and the availability of emergency medications and equipment statements were also added. • The premedication advice was revised for Grade 1 and 2 ARs that resolve.
6 Adverse Reactions	**…**	FDA removed (b) (4)
	6.1 Clinical Trials Experience **…**	FDA added the following statement: "The safety of HERCEPTIN HYLECTA administered subcutaneously has been established in the HannaH and SafeHER studies conducted in patients with HER2 overexpressing breast cancer. The safety of intravenous trastuzumab has been established in studies H0648g and H0649g conducted in patients with HER2 overexpressing metastatic breast cancer." FDA removed (b) (4)
	<u>Adjuvant Breast Cancer</u>	

	(heading added by FDA)	(b) (4)
		FDA added patient demographic information to the study description: "The median age of patients was 50 (range: 25-81 years), all patients were female, and a majority of patients were white (67%)."
	Hannah (subheading added by FDA)	FDA revised subsection 6.1 to create subsections for the HannaH and SafeHER trials and moved clinical trial and demographic information proposed under these respective new subsections. FDA revised the HannaH trial description to remove (b) (4) to add demographic information [e.g., median age (range), sex, race] for the patients treated in the HannaH trial. FDA revised the common AR statement to include ARs that occurred at > 10% (b) (4) and added ARs for ARRs, decreased appetite, stomatitis, headache, rash, constipation, radiation skin injury, pyrexia, cough, anemia, dyspnea, incision site pain, peripheral sensory neuropathy leukopenia, mucosal inflammation, hot flush, and upper respiratory tract infection. FDA added the incidence rates for each AR term and a statement to provide the definition for ARRs. FDA revised the common AR table (Table 3) to include ARs for which there a plausible causal relationship for HERCEPTIN HYLECTA. FDA removed (b) (4)

		(b) (4) For those ARs that were observed at a lower incidence rate for HERCEPTIN HYLECTA compared with intravenous trastuzumab, a footnote was added to identify that the trial was not designed to demonstrate a statistically significant difference in AR rates.
	SafeHER (subheading added by FDA)	SafeHER FDA added the common ARs statement to include all ARs observed at > 10% (adding ARRs, pyrexia, hot flush, and rash), a statement for the common > Grade 3 ARs, and incidence rates for each AR.
	(b) (4)	
	Metastatic Breast Cancer (based on Intravenous trastuzumab) *(heading added by FDA)*	For the HER2+ metastatic breast cancer indications, intravenous trastuzumab safety information was added to this subsection from studies H0648g and H0649g conducted in patients with HER2 overexpressing metastatic breast cancer.
	6.2 Immunogenicity …	… FDA added the following statement: "The incidence of treatment-induced/enhanced anti-recombinant hyaluronidase antibodies was 21% (62/295) in the HERCEPTIN HYLECTA arm. None of the patients who tested positive for anti-recombinant hyaluronidase antibodies tested positive for neutralizing antibodies." After the statement that the clinical relevance of these antibodies is not

		known, FDA removed, (b) (4) [redacted]
	6.3 Post-Marketing Experience **…**	FDA added the following to provide current safety information for trastuzumab: "Tumor lysis syndrome (TLS): Cases of possible TLS have been reported in patients treated with trastuzumab. Patients with significant tumor burden (e.g. bulky metastases) may be at a higher risk. Patients could present with hyperuricemia, hyperphosphatemia, and acute renal failure which may represent possible TLS. Providers should consider additional monitoring and/or treatment as clinically indicated."
8. Use in Specific Populations	**8.5 Geriatric Use** …	FDA deleted (b) (4) [redacted] FDA revised this section as required in 201.57(c)(9)(v) as follows: "Of the total number of patients in the HannaH and SafeHER studies treated with HERCEPTIN HYLECTA, 19% were 65 and over, while 4.7% were 75 and over. In patients receiving intravenous trastuzumab, the risk of cardiac dysfunction was increased in geriatric patients as compared to younger patients, in both those receiving treatment for adjuvant therapy or

		metastatic disease. Other differences in safety or effectiveness were not observed between elderly patients and younger patients."
11. Description	…	FDA revised this section to add molecular weight for the hyaluronidase component of HERCEPTIN HYLECTA.
12. Clinical Pharmacology	**12.3 Pharmacokinetics** …	FDA revised this section to add a table (Table 7) pharmacokinetic values and to provide the Ctrough values used to determine non-inferiority for HERCEPTIN HYLECTA and intravenous trastuzumab.
14. Clinical Studies	*(blank in proposed labeling)*	FDA added the following statement: The comparability between HERCEPTIN HYLECTA administered subcutaneously and intravenous trastuzumab was established in the HannaH study. The HannaH study was conducted in patients with HER2 overexpressing breast cancer in the neoadjuvant and adjuvant settings with co-primary endpoints of pathological complete response (pCR) and the pharmacokinetic (PK) endpoint of Ctrough at cycle 7 *[see Clinical Pharmacology (12.3)].*
	14.1 Adjuvant (b) (4) **Breast Cancer** *Hannah* …	FDA revised the 14.1 subsection heading to "Adjuvant Breast Cancer" to be consistent with the indications and other headings and references to this information elsewhere in the USPI. FDA added the "HERCEPTIN HYLECTA" as a heading for clarification. FDA removed (b) (4) added the age range for the patients treated in the HannaH trial; and removed (b) (4)

		FDA removed (b) (4) nd changed (b) (4) to "outcomes" to be consistent with best labeling practices. In Table 7, FDA revised (b) (4) and replaced with the 95% CI for the difference in pCR rates. FDA removed (b) (4)
	SafeHER …	FDA revised this section to add a complete study description and the treatment regimen information. *See the final USPI for more information.*
	<u>Intravenous Trastuzumab</u> *(subsection added by FDA)*	To provide complete clinical trial information for the use of trastuzumab in the adjuvant setting, FDA added this section and the clinical trial experience from intravenous trastuzumab.
	14.3 Patient Experience	(b) (4) was removed.
17. Patient Counseling Information	**…**	FDA added a subsection to advise patients about hypersensitivity and administration-related reactions.

12. Risk Evaluation and Mitigation Strategies (REMS)

No REMS were indicated.

13. Postmarketing Requirements and Commitment

Postmarketing commitments:

- Provide the final report for the ongoing formulation robustness study described in Section 3.2.P.2. Pharmaceutical Development – Drug Product, sub-section 1.4.4 "Formulation Robustness at Varying (b) (4) Concentrations".

14. Division Director (DHOT)

X

John Leighton, PhD, DABT

15. Division Director (OCP)

X

Nam Atiqur Rahman, PhD

16. Division Director (OB) or Designated Signatory Authority

X

Thomas Gwise, PhD

17. Division Director (Clinical) or Designated Signatory Authority

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

Name: Laleh Amiri-Kordestani
Supervisory Associate Director
Division of Oncology Products 1

18. Appendices

18.1 References

[1] National Cancer Institute, Surveillance, Epidemiology, and End Result Program (2018, May). Cancer Stat Facts: Female Breast Cancer. Retrieved from: https://seer.cancer.gov/statfacts/html/breast.html

[2] Mitri Z, Constantine T, O'Regan R. The HER2 Receptor in Breast Cancer: Pathophysiology, Clinical Use, and New Advances in Therapy. *Chemother Res Pract*. 2012;2012:743193.

18.2 Financial Disclosure

The disclosures of principal and sub-investigators with reported conflicts of interest for studies BO22227 (HannaH), MO28048 (SafeHER), and MO22892 (PrefHER) are listed below.

Per the applicant, in order to minimize potential bias, multiple investigators, sites and countries were used in all three clinical studies. Also, all investigator positive disclosures were reviewed by the applicant and assessed whether their financial interest in the applicant was significant per the Agency's Guidance for Industry – Financial Disclosure by Clinical Investigators. To ensure potential bias has not affected study integrity, the number of patients enrolled by these positive disclosed Investigators was also evaluated by the applicant.

Study Protocol/ Number	Clinical Site Number	Investigator Name	No. of Patients Enrolled at Site	Disclosures
HANNAH/BO22227		(b) (6)	13	30,000 Euro – Consulting Honorarium
SafeHER/MO28048			8	Grants: -COMET Clinical Trials Consortium -CIHR/Roche
SafeHER/MO28048			15	Honorarium
SafeHER/MO28048			22	Consulting Fee
SafeHER/MO28048			22	Spouse collects consulting fee from Roche
PrefHER/MO22982			24	30,000 Euro – Consulting Honorarium

Source: Financial disclosures submitted by the applicant

Summary of findings:

- A total of 435 out of 437 (99.5%) principal investigators and subinvestigators in Study BO22227/HANNAH responded to the Applicant's request to sign the Financial Disclosure form
- A total of 1933 out of 1997 (96.8%) principal investigators and subinvestigators in Study MO28048/SafeHER responded to the Applicant's request to sign the Financial Disclosure form
- A total of 293 out of 297 (98.7%) principal investigators and subinvestigators in Study BO22982/PrefHER responded to Applicant's request to sign the Financial Disclosure form

Covered Clinical Study: BO22227 (HannaH)

Was a list of clinical investigators provided:	Yes: X	No (Request list from Applicant)
Total number of investigators identified: 437		
Number of investigators who are Applicant employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: None Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: None Significant equity interest held by investigators: None Applicant of covered study: None		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes X	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes X	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 2		
Is an attachment provided with the reason:	Yes: X	No ☐ (Request explanation from Applicant)

Covered Clinical Study: MO28048 (SafeHER)

Was a list of clinical investigators provided:	Yes: X	No (Request list from Applicant)
Total number of investigators identified: 1997		
Number of investigators who are Applicant employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 4		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be		

influenced by the outcome of the study: None Significant payments of other sorts: 4 Proprietary interest in the product tested held by investigator: None Significant equity interest held by investigators: None Applicant of covered study: None		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes X	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes X	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 65		
Is an attachment provided with the reason:	Yes X	No ☐ (Request explanation from Applicant)

Covered Clinical Study: MO22982 (PrefHER)

Was a list of clinical investigators provided:	Yes: X	No (Request list from Applicant)
Total number of investigators identified: 297		
Number of investigators who are Applicant employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: None Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: None Significant equity interest held by investigators: None Applicant of covered study: None		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes X	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes X	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 4		
Is an attachment provided with the reason:	Yes X	No ☐ (Request explanation from Applicant)

18.3 Nonclinical Pharmacology/Toxicology

Not applicable

18.4 OCP Appendices (Technical documents supporting OCP recommendations)

Drug Tolerance in Anti-Drug Antibody (ADA) Detection

Bridging immunogenicity assay was designed for anti-trastuzumab antibody detection. The assay involves incubating controls and samples with biotin and ruthenium modified trastuzumab. The mixtures were then transferred to streptavidin-coated plates. Following incubation and washing step, the plate was transferred to MSD SECTOR Imager 6000 for data acquisition.

Drug Tolerance of the ADA detection assay was determined by incubating positive control antibody samples over the concentration range of 11 to 4000 ng/mL with different concentrations of trastuzumab over the concentration range of 100 to 50000 ng/mL (Table 57)

Table 57: Drug Tolerance of Anti-Trastuzumab Antibody Detection

Herceptin (ng/mL)	0	100	200	1000	10000	20000	50000
Anti-Herceptin Positive Controls (ng/mL)	Mean Signal						
4000	103211.0	90220.0	91064.5	46640.0	7450.5	4010.5	1537.5
400	7580.0	4274.0	2541.0	1692.5	816.5	619.5	248.5
200	3584.5	1438.5	1170.5	916.5	432.5	276.5	158.0
11	288.0	**140.5**	**134.0**	**122.5**	**95.0**	**94.5**	**90.0**

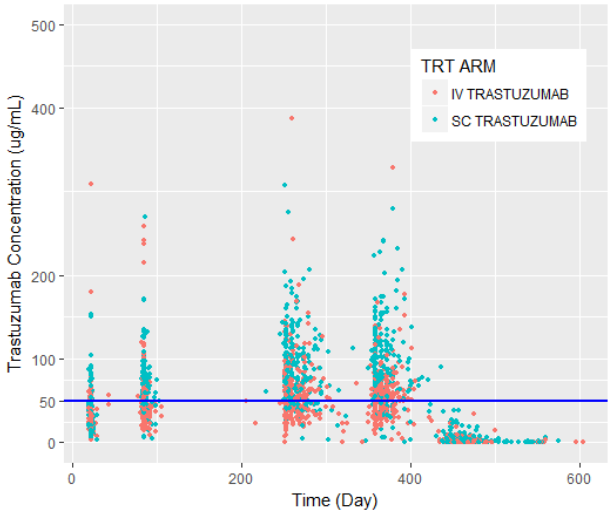
Cut Point =147.3
Bold = signal below cut point

Source: Applicant's bioanalytical report 1038631, Table 8, page 38

The result suggested that anti-trastuzumab antibody under concentration of 200 ng/mL cannot be detected with the presence of trastuzumab ≥ 50000 ng/mL and the signal become dimmer with the present of higher trastuzumab concentration.

To determine if the interference by the present of trastuzumab affect ADA detection in both SC trastuzumab and IV trastuzumab arms equally, trastuzumab concentration at the time ADA detection was compared between the two arms (Figure 13). It shows that, at the time of ADA detection, trastuzumab concentration from SC trastuzumab and IV trastuzumab arms have distributions that overlapping each other, with that in SC trastuzumab in general has higher concentration relative to IV trastuzumab arm, suggesting the interference by trastuzumab may affect SC trastuzumab to a larger extent.

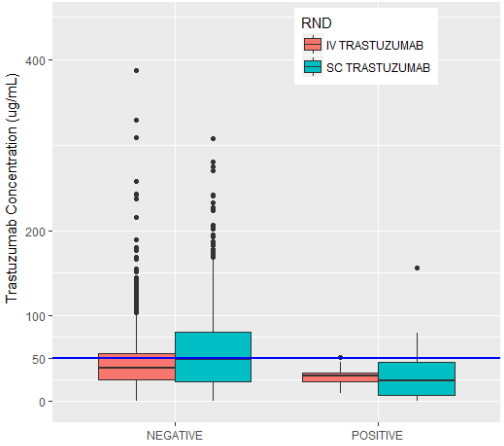
Figure 13: Trastuzumab Concentration at Time of ADA detection in HANNAH Study



Source: Reviewer's analysis

Further subgroup analysis comparing trastuzumab concentration at time of ADA detection in ADA positive/negative groups suggested that majority of ADA positive samples were detected with trastuzumab concentration ≤50000 ng/mL. Among the detected negative patients, SC trastuzumab arm has higher trastuzumab concentration relative to IV trastuzumab, suggested higher probability of false negative due to the presence of trastuzumab drug (Figure 14).

Figure 14: Trastuzumab Concentration at Time of ADA detection based on ADA status in HANNAH Study



Source: Reviewer's analysis

Nevertheless, despite the presence of issue of drug tolerance in ADA/Nab detection (refer to the OBP section for more details regarding Nab detection), the reviewer considered it will not affect the approvability of this BLA application based on the following facts:

- the numerically higher rate of ADA/Nab did not change PK, or efficacy non-inferiority for SC trastuzumab in general (refer to section 6.3.3 for more details)

- the rate of Nab among total patients is expected to be low and prevent further meaningful subgroup analysis
- issues with Nab assays affect both arms approximately equally
- issue with Nab is not new to SC trastuzumab but also affect IV trastuzumab at the time of IV trastuzumab review
- there is no labeling claim with regards to ADA/Nab and in the label

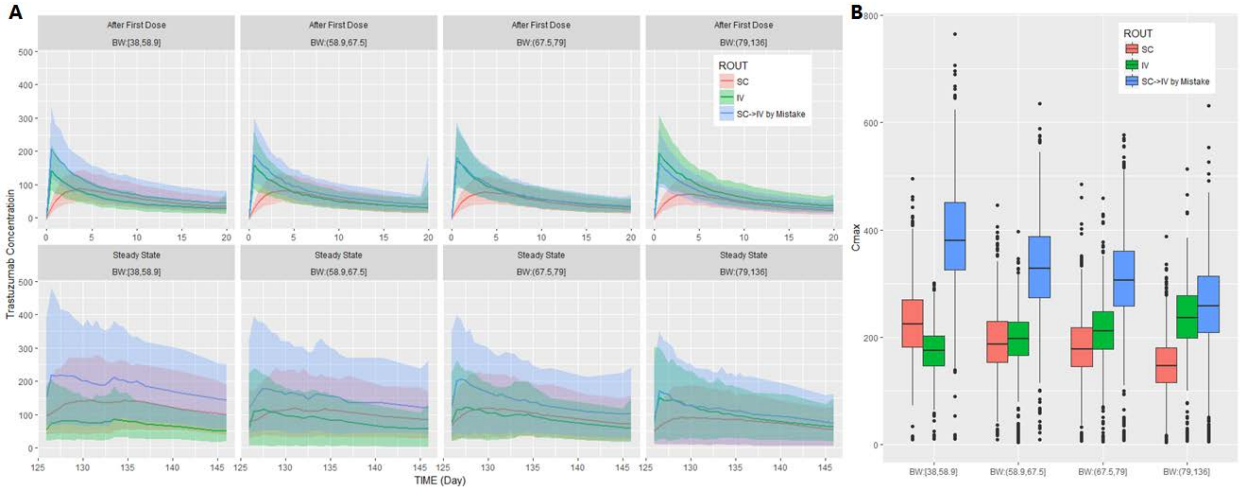
Potential Risk if administrated by IV

The potential risk of SC trastuzumab being administrated through IV infusion due to mistake was evaluated, to determine the labeling language of warning the health care providers to administrate SC trastuzumab correctly via subcutaneous injection. The potential risk is due to the following facts:

- bioavailability of 0.77 for SC trastuzumab
- change of PK profile though IV infusion
- formulation excipients not included in the IV trastuzumab

The potential of enhance trastuzumab for SC trastuzumab administrated by IV infusion was evaluated by modeling and simulation (Figure 15). The simulation results suggested a higher trastuzumab exposure, especially C_{max}, in patients receiving IV infusion of SC trastuzumab, with 10% patients will have C_{max} higher than achieved C_{max} if SC trastuzumab and IV trastuzumab were administrated corrected.

Figure 15: Simulated trastuzumab exposure comparing SC trastuzumab, IV trastuzumab and SC trastuzumab when administrated by IV infusion



A: simulated PK profiles B: Boxplot of C_{max} distribution; Source: Reviewer's analysis

The potential risk due to hyaluronidase is low, given the short half-life of around 5 minutes, and it will be quickly inactivated when administered intravenously per hyaluronidase label.

In the response to FDA's information request (SDN 27, 12/27/2018), the applicant reported inadvertent administration of the SC formulation via IV route rate of 0.02% (28/185740) from global post-marketing data. Of the 28 cased, 3 cases reported 6 non-serious AEs, and 1 case reported 2 serious AEs (hematuria and diarrhea, without lab results, which later resolved).

In addition, according to the applicant's response to FDA's information request (SDN 26, 12/14/2018), the amount of methionine injected would be well below the toxicologically based limit and negligible compared with other marketed IV products containing the excipient. Based on FDA's analyses and Applicant's evidences mentioned above, the reviewer consider the potential risk caused by administration of SC trastuzumab through IV infusion due to mistake is in general low. The following warning language was agreed by FDA and the applicant in the label '*TRASTUZUMAB AND HYALURONIDASE -XXX* is for subcutaneous use only. Do not administer intravenously. Do not substitute TRASTUZUMAB AND HYALURONIDASE -XXX for or with ado-trastuzumab emtansine.'

Hyaluronidase Studies
Recombinant hyaluronidase, rHuPH20, is the excipient in SC trastuzumab formulation. It is approved as a tissue permeability modifier under NDA 021859 and was used as the excipients in the SC rituximab at higher doses of 23400 and 26800 Units (BLA 761064). For current submission, hyaluronidase will be included in the 600 mg trastuzumab /10,000 units hyaluronidase single-dose vial.

The Phase 1 PK study HALO-104-104, in which 12 healthy subjects received an IV infusion of 10,000 U rHuPH20, and 12 subjects received an IV infusion of 30,000 U rHuPH20, suggested dose proportional enzymatic and immunoreactive rHuPH20 exposure and a short half-life of 3.7 to 5.6 minutes for the enzymatic data, and 6.6 to 10 minutes for immunoreactive rHuPH20 data.

In the PD studies, hyaluronidase was demonstrated to be a safe agent. There were no deaths, SAEs, or discontinuations due to AEs in study HALO-104-104 and no signal of allergenicity in healthy subjects receiving hyaluronidase solution in study R04-0851 suggest. Anti-hyaluronidase antibody positive population was in general older than the negative population with overlapping distribution and male subjects had approximately 3-fold higher rates of rHuPH20 antibody positivity than female.

The use of 10,000 units hyaluronidase in the SC trastuzumab single injection vial is considered acceptable safety wise, as higher dose has been applied in BLA 761064 and given the short half-life of hyaluronidase. From effectiveness perspective, PK non-inferiority was achieved by SC trastuzumab as compared to IV trastuzumab, suggested the dose of 10,000 is acceptable to facilitate the perfusion of trastuzumab.

Population PK Analyses
The Applicant submitted a population PK/PD report entitled "Population pharmacokinetic analysis of trastuzumab SC vial and intravenous formulations in women with HER2 positive early breast cancer in the Phase III study HANNAH version 2". Details of the analysis are summarized as following.

Objectives: The objectives of the report were to characterize the population pharmacokinetics of trastuzumab SC and IV formulation and assess possible effect of covariates on the

trastuzumab PK in EBC patients receiving neoadjuvant and adjuvant treatment. The appropriateness of the flat dosing for the SC vial formulation was also further evaluated.

Data: The population pharmacokinetic analysis included PK data from one Phase 1 study BO2227 (data cut-off October 2011). PK samples were collected at peak and trough time points in cycles 1 to 13. In addition, dense samples were collected during cycle 7 (during the neoadjuvant treatment phase) and cycle 12 (during the adjuvant treatment phase) to allow determination of the concentration-time profile and comparison of PK during the neoadjuvant and adjuvant treatment phases. Dosing regimens and PK data collections are summarized in Table 58.

Table 58: Summary of Study BO2227 Dose Regimens and PK Sample Times

Route	Dose	Regime	PK sample times	N
SC	600 mg	q3w	Cycles 1 and 9: pre-dose, days 1 and 15 post- dose; Cycles 2-6, 8, 10, 11 and 13: pre-dose; Cycles 7 and 12: pre-dose, days 1, 2, 4, 8 and 15 post-dose.	297
IV	8 mg/kg loading + 6 mg/kg	q3w	Cycles 1 and 9: pre-dose, end of IV infusion, days 2 and 15 post-dose; Cycles 2-6, 8, 10, 11 and 13: pre-dose and end of IV infusion; Cycles 7 and 12: pre-dose, end of IV infusion and days 2, 4, 8 and 15 post-	298

Source: Table 1 on page 24 of Applicant's population PK report 12-0215v2

In study HANNAH, PK data were collected in a total of 595 patients receiving trastuzumab either as a flat 600 mg SC dose (n=297) or an 8 mg/kg IV loading dose followed by 6 mg/kg IV maintenance doses (n=298), each administered on a q3w schedule, for a total of 18 cycles over one year of therapy. The final population PK dataset after removing outliers contains 15,761 trastuzumab serum PK samples from 592 patients. The demographics and clinical characteristics of the patients are summarized in Table 59**.**

Table 59: Summary of Demographics, Laboratory and Disease Covariates

Formulation	SC	IV	Total
# Patients	297	298	595
# PK planned samples per (pre-/post-surgery)	24 (13/11)	36 (21/15)	
# PK samples (pre-/post-surgery)	6403 (3656/2747)	979 (5953/3837)	16193 (9609/6584)
Sex (F)	29	298	595
Race (W/B/A/I/O)	200/10/64/3/20	208/6/61/3/20	408/16/125/6/40
Age (yr)	51 (26 to 82)	50 (24 to 78)	51 (24 to 82)
Baseline Weight	69 (38 to 136)	66 (41 to 135.5)	67.5 (38 to 136)
CrCL (ml/min)	95.7 (45.7 to	91 (33 to 221.6)	92.8 (33 to 261.4)
Albumin (g/L)	43 (34 to 54)	43 (33 to 60)	43 (33 to 60)
ALK (IU/L)	75 (22 to 340)	72.5 (14 to 464)	74 (14 to 464)
TBIL (mg/dL)	0.54 (0.14 to 1.9)	0.53 (0.16 to	0.53 (0.14 to 1.9)
SGOT (IU/L)	21 (4.6 to 110.8)	20 (6.4 to 58.6)	20.2 (4.6 to
SGPT (IU/L)	20 (2 to 215)	19 (3.5 to 133)	19 (2 to 215)
HER2 (2+/3+/NA)	44/250/3	52/245/1	96/495/4
ECOG (0/1/NA)	253/40/4	260/35/3	513/75/7
ATA (N/Y/NA)	275/20/2	285/10/3	560/30/5
AHA (N/Y/NA)	261/34/2	0/0/298	261/34/300

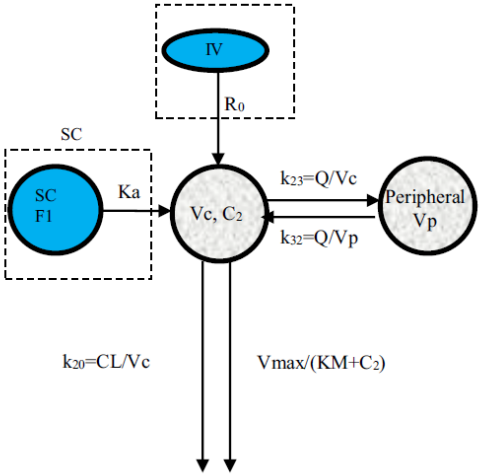
Notes: Continuous variables are summarized as median (range); NA-Not Available due to missing data; Racecategories: W=White; B=Black; A=Asian; I= American Indian or Alaska Native; O=Other. Number of patients with missing continuous covariates: n=1 for CrCL, n=15 for ALBU, n=3 for TBIL, n=4 for SGOT, and n=1 for SGPT. Number of PK samples does not include BQL samples

Source: Table 3 on page 33 of Applicant's population PK report 12-0215v2

Population PK Model Development

Base Model: The selected base model that best described the data was a two-compartment model with parallel linear and non-linear (Michaelis-Menten) elimination from the central compartment. SC absorption was modelled as a first order process. The PK model was parameterized in terms of linear clearance (CL), maximum rate for non-linear clearance (Vmax), concentration at which the non-linear clearance rate is half of Vmax (KM), central volume (Vc), distribution clearance (Q), peripheral volume (Vp), first-order absorption rate (ka) and bioavailability (F1), as illustrated in Figure 16.

Figure 16: Trastuzumab PK Model with Parallel Linear and Non-linear Elimination in Early Breast Cancer Patients



F1 =Bioavailability of SC formulation
ka=1st-order absorption rate of SC
R0 = drug infusion rate
K20 =rate constant for the linear elimination
K23 = rate constant from central to peripheral compartment
K32= rate constant from peripheral to central compartment
CL = linear elimination clearance
Q = distribution clearance
Vc = central volume
Vp = peripheral volume
Vmax = maximum rate of non-linear clearace
Km = concentration at which the non-linear clearance rate is half of Vmax
C2 = concentration of central compartment

Source: Table 3 on page 33 of Applicant's population PK report 12-0215v2

Final Model: Covariate analysis were conducted with forward addition and backward elimination. The effects of Age, Body Weight, Race, CrCL, ALBU, ALK, TBIL, SGOT, SGPT, ECOG status, ATA, HER2 expression level and surgery status on the PK parameters of CL and Vc were evaluated. In the forward addition analysis, covariates with significant impact (p-value < 0.01) on CL included: WT, SGPT, ALBU, CrCL, TBIL, ALK. WT and Race on Vc and WT on Vp. After backward elimination, the effect of ALBU, CrCL TBIL, and ALK on CL and race on Vc were not significant. The final model includes the following parameter-covariate relationships

$$CL_i = \theta_1 \cdot \left(\frac{WT}{68}\right)^{\theta_7} \cdot \left(\frac{SGPT}{19}\right)^{\theta_9} \cdot exp(\eta_{CL})$$

$$Vc_i = \theta_2 \cdot \left(\frac{WT}{68}\right)^{\theta_8} \cdot \exp(\eta_{Vc})$$

$$Vp_i = \theta_4 \cdot \left(\frac{WT}{68}\right)^{\theta_{10}} \cdot \exp(\eta_{Vp})$$

The parameter estimates from the final model including covariate effects are summarized in Table 60.

Table 60: Parameter Estimates and Covariate Effects for Trastuzumab Population Pharmacokinetic Final Model

Parameter	Parameter Description	Value (% RSE)	IIV	Shrinkage (%)
Θ5	Bioavailability of SC formulation (-)	0.771 (1.45)	13.0%	52.2
Θ6	First-order absorption rate, ka	0.404 (2.92)		
Θ1	Linear elimination clearance, CL	0.111 (10.3)	30.0%	11.5
Θ9	Vmax (mg/day)	11.9 (19.9)		
Θ10	Km (mg/L)	33.9 (38.6)		
Θ2	Volume of distribution, central compartment, Vc (L)	2.91 (1.24)	19.1%	22.3
Θ3	Distribution clearance, Q (L/day)	0.445 (10.5)		
Θ4	Volume of distribution, peripheral compartment, Vp (L)	3.06 (3.23)	50.4%	19.1
Θ7	Influence of WT on linear CL	1.04 (11.3)		
Θ8	Influence of WT on Vc	0.443 (11.3)		
Θ12	Influence of WT on Vp	0.5 (22.2)		
Θ11	Influence of SGPT on linear CL	0.144 (20.8)		
$\sigma 1$	Proportional variability (%)	23.9% (3.62)		3.9
$\sigma 2$	Additive variability (µg/mL)	4.5 (21.7)		
Note: Off-diagonal covariance term is $\Omega_{CL, Vc}$ =-0.0109, $\Omega_{CL, Vp}$ =-0.0455, $\Omega_{Vc, Vp}$ =-0.0249; RSE for residual variability terms (σ1, σ2) is relative to the estimated variance (σ_1^2, σ_2^2).				

Source: Table 3 on page 38 of Applicant's population PK report 12-0215v2

Model Evaluation

Bootstrap: A total of 1000 replicates, the number of runs recommended to assess 95% confidence intervals were executed. Typical values for PK parameter and covariate effects obtained in the final model were compared with the median and 95% confidence interval (taken as the 2.5-97.5% quantiles of the bootstrap replicates) of bootstrapped parameter estimates. Of the 1000 datasets generated for bootstrapping, 941 (94.1%) runs minimized successfully. **Table 61** shows the PK parameter estimates and median and 95% Cis derived from the successful runs. The median values from bootstrapping are similar to the original PK estimates, and the 95% CIs overlap.

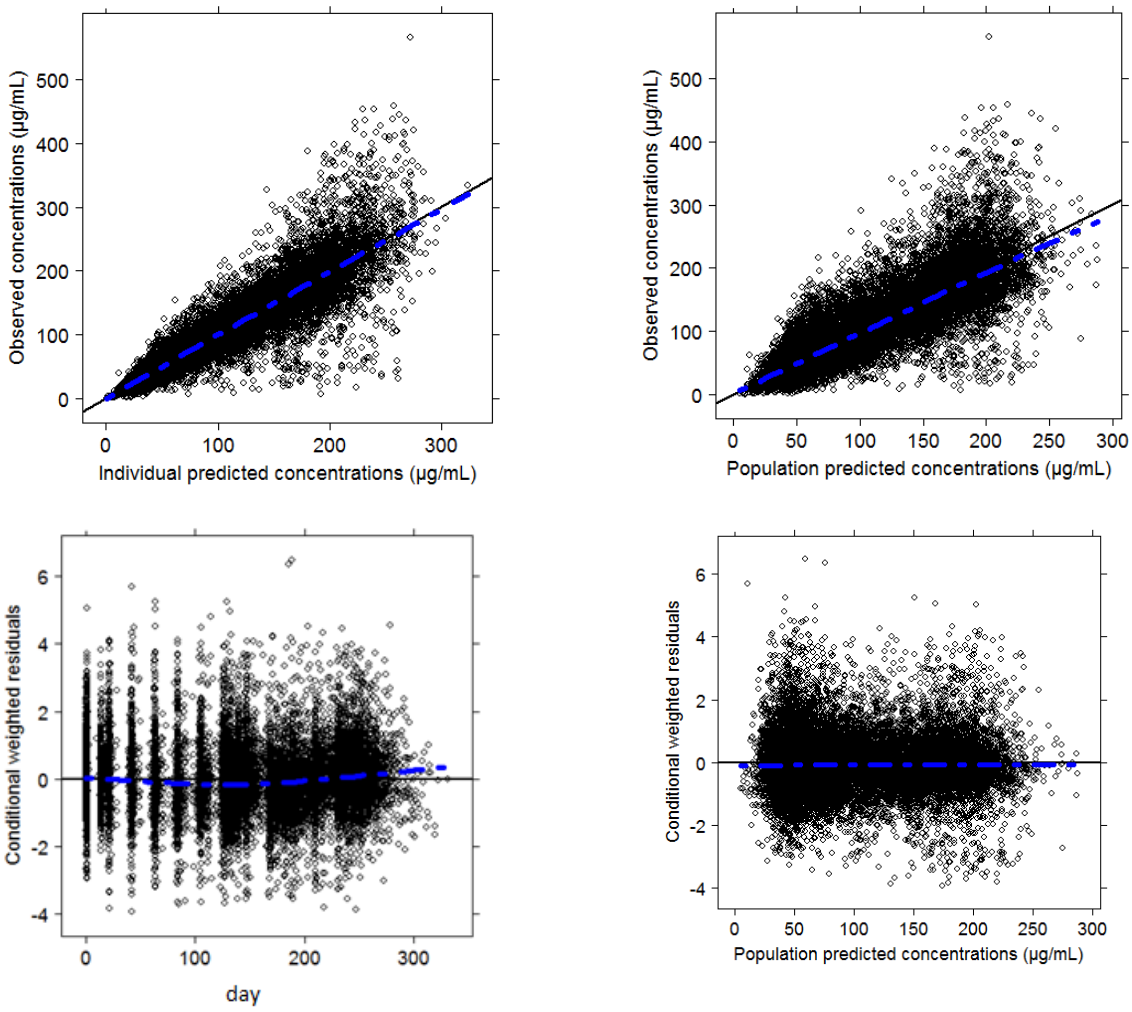
Table 61: Typical and 95% CIs for Population PK parameter Estimates from the Final Model and from the Bootstrap

Parameter	Parameter Description	Final Model Point Estimate (95% CI)	Bootstrap Estimates Median (2.5th, 97.5th Percentiles)
θ_5	Bioavailability of SC formulation	0.771 (0.749 0.793)	0.773 (0.747, 0.797)
θ_6	First-order absorption rate, ka (day^{-1})	0.404 (0.381 0.427)	0.403 (0.381, 0.429)
θ_1	Linear Elimination clearance, CL (L/day)	0.111 (0.0887 0.133)	0.115 (0.094, 0.153)
θ_9	Vmax (mg/day)	11.9 (7.25 16.5)	11.0 (5.2, 16.3)
θ_{10}	Km (mg/L)	33.9 (8.22 59.6)	28.5 (5.69, 67.2)
θ_2	Volume of distribution, central compartment, Vc (L)	2.91 (2.84 2.98)	2.91 (2.85, 3.00)
θ_3	Distribution clearance, Q (L/day)	0.445 (0.353 0.537)	0.444 (0.314, 0.539)
θ_4	Volume of distribution, peripheral compartment, Vp (L)	3.06 (2.87 3.25)	3.08 (2.88, 3.40)
θ_7	Influence of WT on linear CL	1.04 (0.809 1.27)	0.99 (0.70, 1.26)
θ_8	Influence of WT on Vc	0.443 (0.345 0.541)	0.445 (0.336, 0.535)
θ_{12}	Influence of WT on Vp	0.5 (0.282 0.718)	0.481 (0.200, 0.735)
θ_{11}	Influence of SGPT on linear CL	0.144 (0.0852 0.203)	0.136 (0.085, 0.205)

Source: Table 8 on page 42 of Applicant's population PK report 12-0215v2

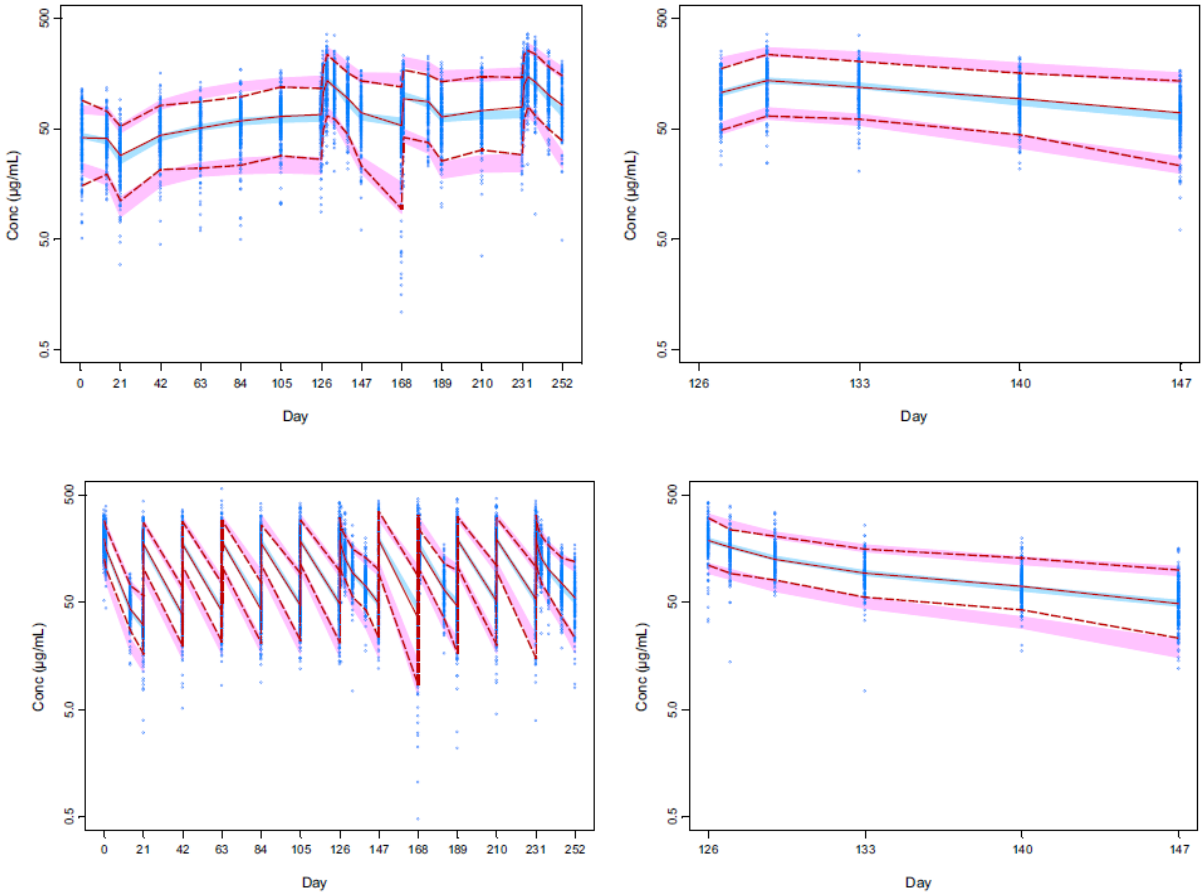
The final model was evaluated graphically by goodness-of-fit plots, visual predictive checks (VPCs) as well as bootstrap evaluation. The goodness-of-fit plots for the final model are displayed in Figure 17 and the VPCs plots are demonstrated in Figure 18, respectively.

Figure 17: Goodness-of-Fit Plots for the Final Population Pharmacokinetic Model



Source: Produced by reviewer with the output of the final model

Figure 18: Visual Predictive Checks Trastuzumab SC (top) and IV (bottom) for the Final Population PK Model



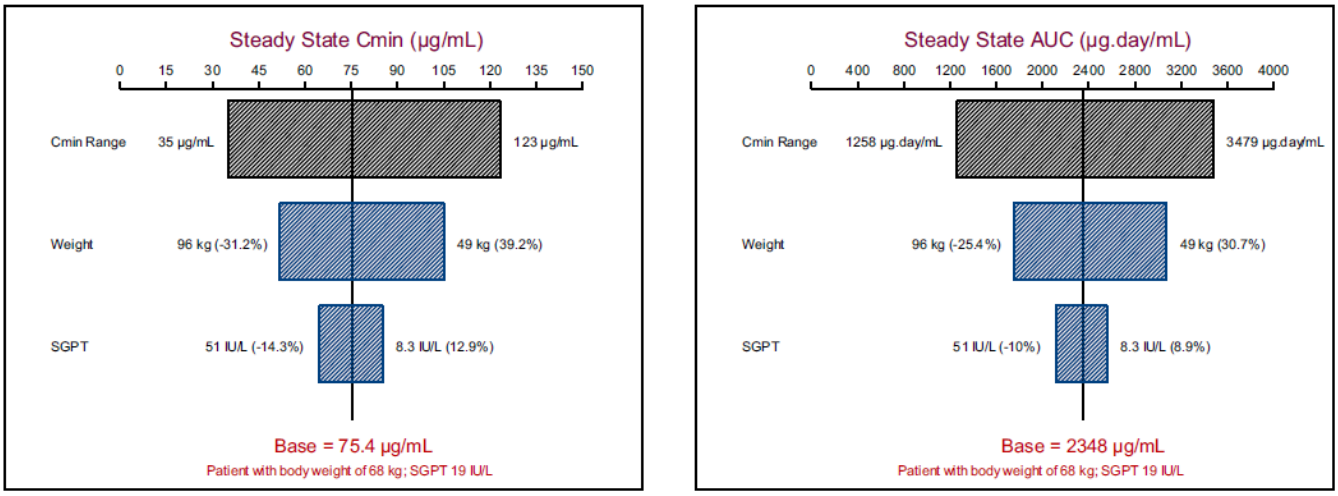
Note: Circles are observed trastuzumab serum concentrations, solid red lines represent the median observed value, and dashed lines represent 5%ile and 95%ile of the observed values. Blue shaded areas represent the median predicted values, and red shaded area represent the spread (5%ile and 95%ile) of the predicted concentrations. The width of the shaded areas indicates 95% confidence intervals. The left panel shows the entire time course, while right panel shows cycle 7.

Source: Adapted from Figure 9 and Figure 10 on page 48 of Applicant's population PK report 12-0215v2

Impact of Covariates on Trastuzumab Exposure: A sensitivity analysis was performed to examine the influence of covariates on the exposure of trastuzumab following 600 mg SC q3w. The influence of covariates on steady-state trough concentration (Cmin,ss) and average exposure (AUCss) is shown in **Figure 19**. Predicted steady-state trough concentrations (Cmin,ss) varied from 47 to 112 µg/mL (5th to 95th percentiles) across the overall patient population, representing a -38% to 48% change from the typical patient, while variability in body weight resulted in a -31% to +39% change. The 31% decrease in Cmin,ss value at the 95th percentile

body weight value was still well above the targeted efficacious concentration of 20 µg/mL, identified as having anti-tumor activity from nonclinical efficacy models. The extent of change caused by body weight on AUCss had a similar trend to that observed with Cmin,ss, within the range of -26% to +31%. The effect of SGPT on Cmin,ss and AUCss was modest, within the range of -15% to 15%, with no clinical relevance.

Figure 19: Sensitivity plot comparing the effect of covariates on model-predicted exposure measures (Cmin,ss and AUCss) for the 600 mg SC regimen (q3w)



Note: Each vertical reference line is the typical steady-state exposure value after 600mg SC q3w. The top bar of each plot shows the 5th to 95th percentile of exposure values across the entire population. The labels at each end of the lower bars indicate the 5th or 95th percentile of the covariate value, and the percent change from the typical value in exposure. The length of each bar describes the impact of that particular covariate on pharmacokinetics
Source: Figure 11 on page 51 of Applicant's population PK report 12-0215v2

Impact of Body Weight on Exposure for SC and IV Administration: The impact of baseline body weight on the predicted steady-state trough concentration (Cmin, ss) and total exposure (AUCss) after SC and IV administration is illustrated in Figure 20 and **Figure 21** respectively. Model-predicted exposures (Cmin,ss and AUCss) for 600 mg SC q3w or 8 mg/kg loading followed by 6 mg/kg IV q3w were generated using individual EBE's (post-hoc) PK parameters of the final PK model. The results are grouped by quartiles of the observed baseline body weight distribution. The exposures in IV patients with mg/kg dosing were comparable across body weight quartiles while the exposures in SC patients receiving a flat dose (mg) shows higher exposure for patients with lower body weight. In spite of the impact of body-weight on exposure, there is large overlap in the distribution of Cmin,ss and AUCss between the four body weight quartiles for both the SC and IV administration. The impact of body weight on Cmin,ss for flat SC regimen and weight-based IV regimen is further revealed by results of simulations (Figure 22**).**

Figure 20: Baseline Body Weight and Model-Predicted Exposures at Steady-state after 600 mg SC q3w Administration

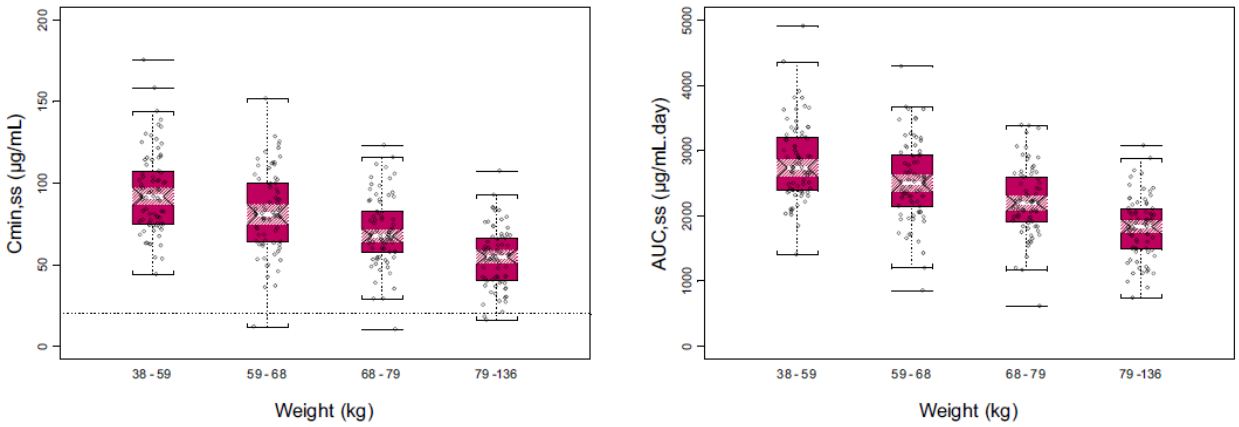
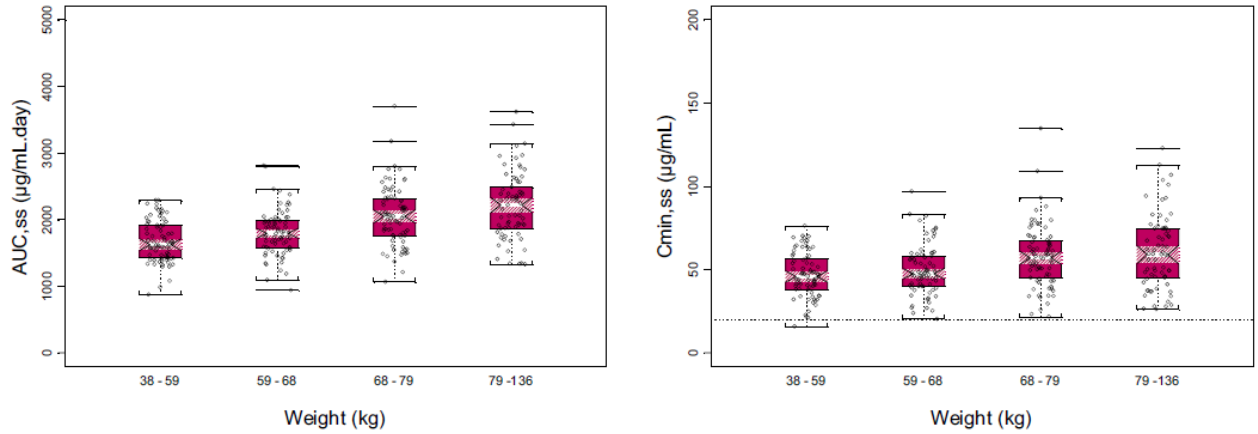


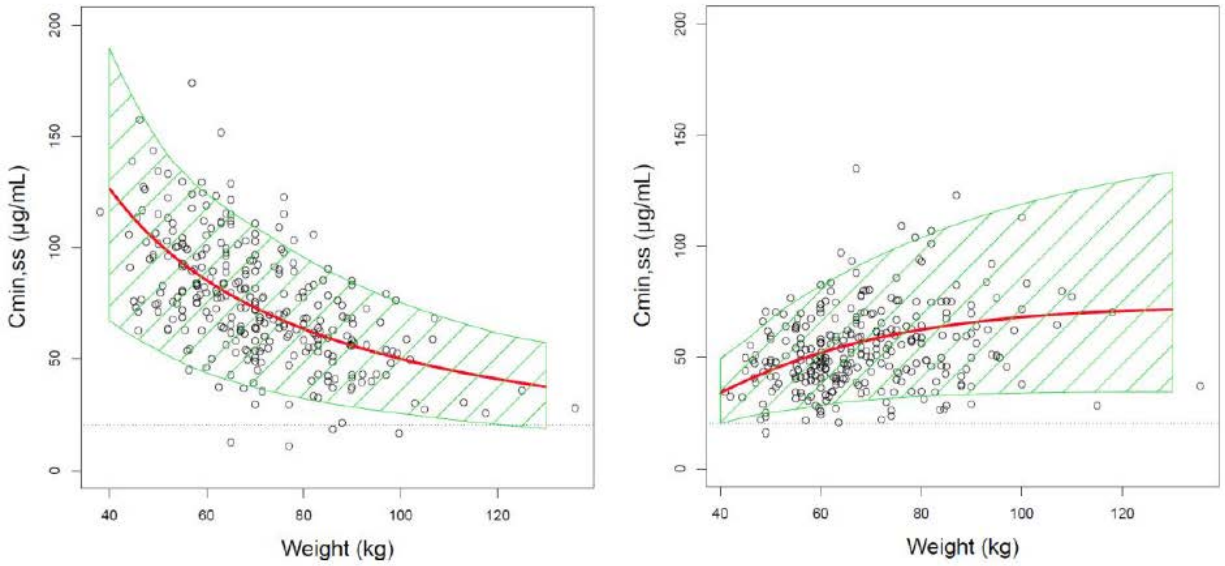
Figure 21: Baseline Body Weight and Model-Predicted Exposures at Steady-state after IV Q3W Administration



Note: The PK variables were calculated using empirical Bayes ("post hoc") PK parameters of the HANNAH nonlinear model for an IV administration of 8 mg/kg loading followed by 6 mg/kg q3w. PK parameters were grouped by quartiles of body weight distribution. The box (red area) shows the median, 25th and 75th percentile of the patients grouped by quartiles of the baseline body weight distribution. Shaded area represents the middle quartile and median. Lines outside of the upper and lower whisker indicate outliers. The horizontal line is the 20 µg/mL targeted treashold concentration for efficacy identified in preclinical xenograft models

Source: Figure 12 and Figure 13 on page 52-53 of Applicant's population PK report 12-0215v2

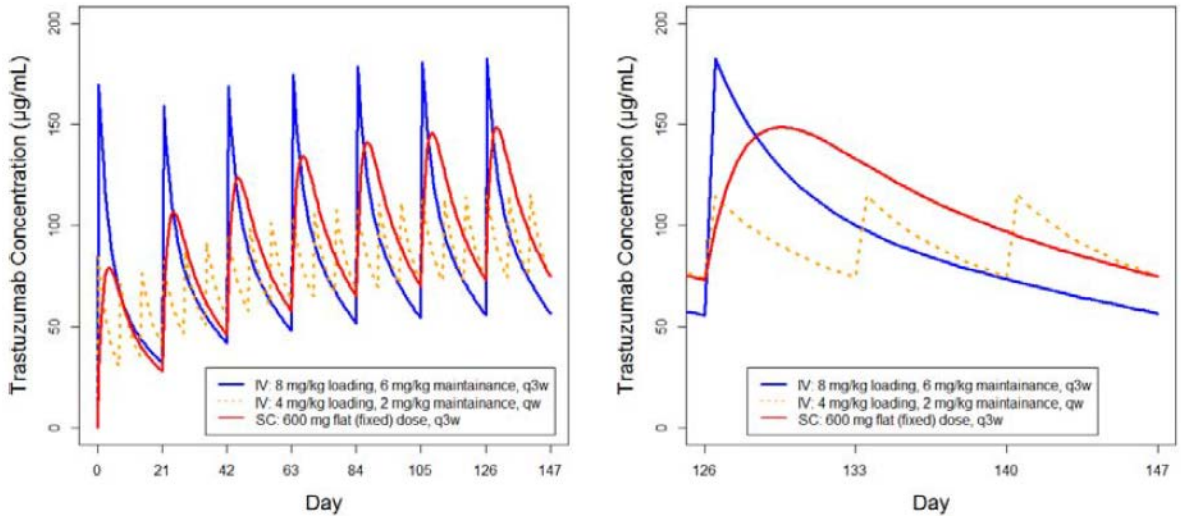
Figure 22: Impact of Body Weight on Cmin,ss for Flat SC Regimen (left) and Weight-based IV Regimen (right)



Note: Circles are the individual Cmin,ss calculated using empirical Bayes ("post hoc") PK parameters for a SC administration of 600 mg q3w (left) and for an IV administration of 8 mg/kg loading followed by 6 mg/kg q3w (right). The red line shows the impact of Cmin by body weight of patients with typical PK. The dashed area represents 90% predictive intervals based on simulations (n=300 for each weight value) including interindividual variability. The horizontal line is the 20 µg/mL targeted threshold concentration for efficacy identified in preclinical xenograft models
Source: Figure 14 on page 56 of Applicant's population PK report 12-0215v2

Impact of Regimen on PK: The typical predicted trastuzumab concentration versus time profiles after three regimens: 8 mg/kg loading dose followed by 6 mg/kg IV q3w, 4 mg/kg loading dose followed by 2 mg/kg IV qw, and flat 600 mg SC q3w. The simulation was done for typical patients with WT 68 kg and SGPT 19 IU/L At steady-state (cycle7, right panel), the SC regimen had greater trastuzumab concentrations than the IV regimen during the majority of the treatment cycle, while the IV regimen has a higher peak concentration. The peak concentration of the SC regimen was reached around 4 days post-dose at steady-state.

Figure 23: Model-predicted Typical Concentration versus Time Profiles for SC and IV Regimens



Note: Simulated using estimated population PK parameters for a patient with WT 68 kg, and SGPT 19 IU/L. Left panel shows the profile from cycle 1 to 7, Right panel shows cycle 7 only.

Source: Figure 15 on page 57 of Applicant's population PK report 12-0215v2

Simulations: Simulations for trastuzumab SC treatment for patients with EBC respective dosing were performed using the updated non-linear popPK model developed from Study HANNAH. The summary of predicted exposure following treatment with trastuzumab IV and SC doses are shown in Table 62 and Table 63, respectively.

Table 62: Summary of Model Predicted Concentrations and Exposures at Various Cycles Following Treatment with Trastuzumab IV 8/6°mg/kg q3w (typical [5th -95th Percentiles])

Dose Regimen	PK Parameter	BC (EBC and MBC)	AGC
8/6 mg/kg IV q3w IV	**N**	**1195**	**274**
Cycle 1	C_{max} (µg/mL)	178 (116.5 - 290.5)	131.9 (84.2 - 225.2)
	C_{min} (µg/mL)	29.4 (5.8 - 59.5)	23.1 (6.1 - 50.3)
	AUC (day*µg/mL)	1372.5 (735.8 - 2245)	1108.5 (588.2 - 1937.9)
Cycle 2	C_{max} (µg/mL)	162.2 (102.1 - 261.2)	121.5 (71.9 - 211.3)
	C_{min} (µg/mL)	36.7 (4.5 - 78.1)	27.6 (6 - 65.9)
	AUC (day*µg/mL)	1500.6 (658.4 - 2631)	1182.3 (548.3 - 2235)
Cycle 3	C_{max} (µg/mL)	169.5 (104.8 - 276.5)	125.9 (72.1 - 223.1)
	C_{min} (µg/mL)	41.2 (4.9 - 90.8)	30.1 (6 - 75.5)
	AUC (day*µg/mL)	1624.9 (665 - 2981.6)	1255.1 (555 - 2503.2)
Cycle 4	C_{max} (µg/mL)	174 (105.8 - 290.8)	128.4 (72.3 - 232.8)
	C_{min} (µg/mL)	44.0 (5 - 100.3)	31.5 (6.1 - 81.1)
	AUC (day*µg/mL)	1701 (667.6 - 3211.9)	1295.6 (557.7 - 2652.4)
Cycle 5	C_{max} (µg/mL)	176.7 (106.9 - 299.3)	129.8 (72.4 - 241.2)
	C_{min} (µg/mL)	45.7 (5.1 - 106.2)	32.3 (6.1 - 85.2)
	AUC (day*µg/mL)	1747.7 (672.2 - 3417.9)	1318.3 (557.2 - 2761.1)
Cycle 6	C_{max} (µg/mL)	178.4 (107.2 - 303.9)	130.5 (72.4 - 247.9)
	C_{min} (µg/mL)	46.8 (5 - 110.5)	32.7 (6.1 - 86.9)
	AUC (day*µg/mL)	1776.5 (673.1 - 3527.9)	1331 (557 - 2832.5)
Cycle 7	C_{max} (µg/mL)	179.4 (107.3 - 308.8)	131 (72.5 - 250.5)
	C_{min} (µg/mL)	47.4 (5 - 114.7)	32.9 (6.1 - 88.9)
	AUC (day*µg/mL)	1794.2 (673 - 3618.4)	1338.2 (557 - 2875.4)
Cycle 12	C_{max} (µg/mL)	181 (107.5 - 317.8)	131.5 (72.5 - 253)
	C_{min} (µg/mL)	48.4 (5.1 - 124)	33.2 (6.1 - 93.3)
	AUC (day*µg/mL)	1820.3 (673 - 3730.3)	1346.8 (557 - 2955.4)

BC; Breast cancer (EBC early breast cancer, and MBC metastatic breast cancer)
AGC; Advanced gastric cancer
Cmax (µg/mL); maximum serum trastuzumab concentration
Cmax (µg/mL); minimum serum trastuzumab concentration
AUC (day*µg/mL); area under the serum trastuzumab concentration-time curve
Cmax,ss (µg/mL); maximum serum trastuzumab concentration at steady state
Cmax,ss (µg/mL); minimum serum trastuzumab concentration at steady state
AUCss (day*µg/mL); area under the serum trastuzumab concentration-time curve at steady state
Covariates for a typical MBC/EBC or AGC patient: WT of 66 kg, SGOT of 24 IU/L, ALBU of 4.0 g/dL and without LMET.

Source: Table 2 on page 23 from Applicant's response to the information request from the clinical pharmacology review team dated on September 12, 2018.

Table 63: Summary of Model Predicted Concentrations and Exposures at Various Cycles Following Treatment with Trastuzumab SC 600mg/5mL q3w (Typical [5th -95th Percentiles])

Dose Regimen	PK Parameter	EBC
600mg/5mL q3w SC	N	297
Cycle 1	C_{max} (µg/mL)	79.3 (56.1 - 109.1)
	C_{min} (µg/mL)	28.2 (14.8 - 40.9)
	AUC (day*µg/mL)	1064.9 (717.6 - 1503.8)
Cycle 2	C_{max} (µg/mL)	106.6 (71.6 - 149)
	C_{min} (µg/mL)	46.2 (23.2 - 66.1)
	AUC (day*µg/mL)	1564.2 (963.9 - 2177.9)
Cycle 3	C_{max} (µg/mL)	123.6 (77.9 - 169.3)
	C_{min} (µg/mL)	57.6 (28.1 – 85.0)
	AUC (day*µg/mL)	1875.3 (1082.5 - 2633.4)
Cycle 4	C_{max} (µg/mL)	134.4 (81.1 - 185.7)
	C_{min} (µg/mL)	65 (30.3 - 95.7)
	AUC (day*µg/mL)	2073.3 (1161.9 - 2897.7)
Cycle 5	C_{max} (µg/mL)	141.4 (84.1 – 199.0)
	C_{min} (µg/mL)	69.8 (32.4 - 105.6)
	AUC (day*µg/mL)	2200.9 (1199.5 - 3146.2)
Cycle 6	C_{max} (µg/mL)	145.9 (84.9 - 205.8)
	C_{min} (µg/mL)	72.9 (34.4 - 115.5)
	AUC (day*µg/mL)	2283.5 (1207.7 - 3314.6)
Cycle 7	C_{max} (µg/mL)	148.8 (86.1 - 213.6)
	C_{min} (µg/mL)	75.0 (35.1 - 123.4)
	AUC (day*µg/mL)	2337.3 (1257.7 - 3478.1)
Cycle 12	C_{max} (µg/mL)	153.7 (90.5 - 230.1)
	C_{min} (µg/mL)	78.3 (35.6 - 141)
	AUC (day*µg/mL)	2426.5 (1292.5 - 3830.6)

EBC; Early breast cancer
Cmax (µg/mL); maximum serum trastuzumab concentration
Cmax (µg/mL); minimum serum trastuzumab concentration
AUC (day*µg/mL); area under the serum trastuzumab concentration-time curve
Cmax,ss (µg/mL); maximum serum trastuzumab concentration at steady state
Cmax,ss (µg/mL); minimum serum trastuzumab concentration at steady state
AUCss (day*µg/mL); area under the serum trastuzumab concentration-time curve at steady state
Covariates for a typical EBC patient: WT of 68 kg and SGPT of 19 IU/L.

Source: Table 3 on page 25 from Applicant's response to the information request from the clinical pharmacology review team dated on September 12, 2018.

Reviewer's comments: The Applicant's population PK analysis is acceptable. Overall, the final population PK model is adequate to characterize the PK profile of trastuzumab IV and SC formulations as indicated in the reviewer and applicant's goodness-of-fit plots and the VPC plots. The reviewer was able to repeat and verify the Applicant's analysis.

Information request was submitted to the Applicant for simulation of exposure at each cycle. Simulations results as demonstrated in Figure 7 indicate that the trough concentration achieved

in SC formulation was higher than IV almost in every treatment circle. Higher or comparable exposure is achieved by the SC dosing regimen of 600 mg q3w relative to the IV dosing regimen.

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LALEH AMIRI KORDESTANI
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