CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761091Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	Class 2 Resubmission of BLA, 351(k)
Application Number(s)	761091
Submit Date(s)	6/15/2017
Received Date(s)	6/15/2018
BSUFA Goal Date	12/15/2018
Division / Office	DOP1/OHOP
Reviewer Name(s)	Jennifer Gao, MD William Pierce, PharmD Sanjeeve Balasubramaniam, MD
Review Completion Date	12/13/2018
Established Name	Trastuzumab-pkrb
(Proposed) Trade Name	HERZUMA*
Therapeutic Class	HER2-binding humanized monoclonal antibody
Applicant	Celltrion
Formulation(s)	IV
Dosing Regimen	(b) (4) mg/kg IV loading dose, then (b) (4) mg/kg IV (b) (4) wks
Proposed Indication(s)	HERZUMA is a HER2/neu receptor antagonist indicated for: • the treatment of HER2 overexpressing breast cancer.
Recommended Indication	HERZUMA is a HER2/neu receptor antagonist indicated for: • the treatment of HER2 overexpressing breast cancer. Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.

*In this document, FDA generally refers to the applicant's proposed product by the applicant descriptor "CT-P6".

This biologics license application (BLA 761091) Class 2 Resubmission seeks approval of the product CT-P6 (proposed trade name Herzuma), which is a proposed biosimilar to US-licensed Herceptin (which will be referred to as US-Herceptin for the remainder of this review). The original BLA was submitted on May 30, 2017 and on March 29, 2018, a Complete Response letter was issued with facility inspection and product quality issues preventing approval. Refer to the clinical and statistical review dated February 13, 2018 of the original BLA 761091 submission and the review of the updated safety data dated August 13, 2018 with the Class 2 Resubmission.

The 4-letter suffix (b) (4) was conditionally accepted on July 19, 2017 with the applicant's original submission. FDA reassessed this proposed suffix with the Class 2 Resubmission. Given (b) (4) begins with the letters (b) (4) The applicant's fourth proposed suffix, -pkrb, is comprised of four distinct letters and is not too similar to any other products' suffix designation, does not look similar to the names of other currently marketed products, s devoid of meaning, does not include any abbreviations that could be misinterpreted, and does not make any misrepresentations with respect to safety or efficacy of this product. Refer to the review by DMEPA in DARRTs from September 20, 2018.

During this submission, the applicant has modified the requested indications for their product, (b) (4) The requested indications now include:

Adjuvant 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

Metastatic breast cancer (MBC):

- 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.

A teleconference was held with the applicant on December 6, 2018 to discuss the proposed USPI and information that is required to be removed and retained from the reference product to support the above proposed indications.

For the adjuvant treatment of breast cancer indication, FDA stated trastuzumab is not indicated and should not be used beyond 1 year in the adjuvant setting and this information must be included for the safe and effective use of the trastuzumab product.

FDA agreed with removing references to metastatic gastric cancer and Study 7 in the proposed USPI.

A summary of revisions made in the proposed USPI of BLA 761091 is discussed below:

Summary of Significant Labeling Changes		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling (As of December 11, 2018)**
1. Indications and Usage	HERZUMA is indicated for adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature *[see Clinical Studies (14.1)]*) 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 Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product *[see Dosage and Administration (2.1)]*. HERZUMA 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 a trastuzumab product *[see Dosage and Administration (2.1)]*.	FDA agrees with the applicant's proposed indication.

2. Dosage and Administration	**2.2 Recommended Doses and Schedules** *Adjuvant Treatment, Breast Cancer:* Administer according to one of the following doses and schedules for a total of 52 weeks of HERZUMA therapy: During and following paclitaxel, docetaxel, or docetaxel and carboplatin: • Initial dose of 4 mg/kg as an intravenous infusion over 90 minutes then at 2 mg/kg as an intravenous infusion over 30 minutes weekly during chemotherapy for the first 12 weeks (paclitaxel or docetaxel) or 18 weeks (docetaxel and carboplatin). • One week following the last weekly dose of HERZUMA, administer HERZUMA at 6 mg/kg as an intravenous infusion over 30–90 minutes every three weeks.	**2.2 Recommended Doses and Schedules** FDA agrees with removing information on single agent dosing regimen every 3 weeks. FDA disagrees with removing the following as it contains important safety information: "Extending adjuvant treatment beyond one year is not recommended [see Adverse Reactions (6.1)]."
5. Warnings and Precautions	**5.1 Cardiomyopathy** Applicant proposed removing information on (b) (4)	**5.1 Cardiomyopathy** FDA agrees with removing information regarding (b) (4) from the Warnings and Precautions (b) (4)
6. Adverse Reactions	(b) (4) **6.1 Clinical Trials Experience** • (b) (4)	FDA disagrees with including this information in the prescribing information, as (b) (4) **6.1 Clinical Trials Experience** • (b) (4)

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/s/

JENNIFER J GAO
12/13/2018

WILLIAM F PIERCE
12/13/2018

SANJEEVE BALASUBRAMANIAM
12/13/2018

CLINICAL REVIEW

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Division / Office	DOP1/OHOP
Reviewer Name(s)	Jennifer Gao, MD
Review Completion Date	8/13/18
Established Name	Trastuzumab-(b) (4)
(Proposed) Trade Name	HERZUMA*
Therapeutic Class	HER2-binding humanized monoclonal antibody
Applicant	Celltrion
Formulation(s)	IV
Dosing Regimen	(b) (4) mg/kg IV loading dose, then (b) (4) mg/kg IV (b) (4) wks
Proposed Indication(s)	HERZUMA is a HER2/neu receptor antagonist indicated for: • the treatment of HER2 overexpressing breast cancer. • the treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma.
Recommended Indication	HERZUMA is a HER2/neu receptor antagonist indicated for: • the treatment of HER2 overexpressing breast cancer. • the treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma. Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.

*In this document, FDA generally refers to the applicant's proposed product by the applicant descriptor "CT-P6".

This biologics license application (BLA 761091) Class 2 Resubmission seeks approval of the product CT-P6 (proposed trade name Herzuma), which is a proposed biosimilar to US-licensed Herceptin (which will be referred to as US-Herceptin for the remainder of this review). The original BLA was submitted on May 30, 2017 and on March 29, 2018, a Complete Response letter was issued with facility inspection and product quality issues preventing approval.

The original BLA submission contained data from study CT-P6 3.2 (which will be referred to as study 3.2 for the remainder of this review) to support the determination of no clinically meaningful differences between CT-P6 and US-Herceptin. This was a randomized, double-blind, parallel group, equivalence study in which patients received either CT-P6 or US-Herceptin with chemotherapy in the neoadjuvant setting. After completing neoadjuvant treatment and undergoing surgery, patients were able to continue with the same trastuzumab product as adjuvant monotherapy to complete 1 year of treatment. The primary endpoint of pathological complete response (pCR) ratio (the pCR rate with CT-P6 divided by the pCR rate with US-Herceptin) as assessed by local review of the per-protocol set (PPS) of 0.9282 (90% CI 0.7981-1.0796, 95% CI 0.7753-1.1113) was within the pre-specified equivalence margin of 0.74 to 1.35. Secondary endpoints of ORR, DFS, PFS, OS, breast conservation rate, and other pCR parameters were similar between both treatment arms. The safety findings of study 3.2 were reviewed, with special focus on cardiac, pulmonary, infusion reaction, and embryo-fetal toxicities and overall no clinically meaningful differences were found in the safety population.

Since August 11, 2017, CT-P6 has been marketed in South Korea under the name Herzuma. A total of 131 patients have received CT-P6 based on actual prescription count including 10 patients from a Korean post-marketing surveillance (PMS) study, which lasted from November 1, 2017 to January 14, 2018. As of November 30, 2017, 10 patients were enrolled (5 early breast cancer and 5 metastatic breast cancer). Only 1 patient had a TEAE hypersensitivity infusion related reaction and recovered. As of November 30, 2017, CT-P6 has not been marketed in other countries.

With the Class 2 Resubmission, no new patients have been treated with CT-P6 in clinical trials or as part of the clinical development of CT-P6 since the original submission. The applicant submitted an Additional Safety Update of the ongoing study 3.2 based on data available as of November 30, 2017. Deaths, serious treatment-emergent adverse events (TEAEs), and follow up information of TEAEs leading to treatment discontinuation are presented through March 30, 2018. AEs were assessed from signing of informed consent to 30 days after the last dose of study drug. Only related AEs and cardiac AEs were reported after 30 days and to the end of the study. Deaths were continuously monitored. The information presented in the Additional Safety Update was reviewed and no new safety signals identified. There was no new efficacy data presented.

Overall there are no new concerning clinical safety findings. Refer to the primary clinical and statistics review dated February 13, 2018 for a full analysis of clinical efficacy and safety.

Clinical Recommendation: The recommendation from the clinical reviewers is approval. The results of study 3.2 and Additional Safety Update support a demonstration of no clinically meaningful differences between CT-P6 and US-Herceptin.

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/s/

JENNIFER J GAO
08/13/2018

SANJEEVE BALASUBRAMANIAM
08/13/2018

Cross-Discipline Team Leader Review

Date	*Electronic Stamp Date*
From	Sanjeeve Balasubramaniam, M.D., M.P.H. (CDTL) Julia Beaver, M.D. (Division Director)
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	351(k) BLA 761091
Applicant	Celltrion
Date of Submission	5/30/2017
BsUFA Goal Date	3/30/2018
Proprietary Name / Established (USAN) names	HERZUMA/Trastuzumab-(b) (4) CT-P6[1] Lyophilized Powder for Intravenous Infusion
Dosage forms / Strength	lyophilized powder for injection/420 mg per vial
Proposed Indication(s)	HERZUMA is a HER2/neu receptor antagonist indicated for: 1. Adjuvant breast cancer: a. As part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel b. With docetaxel and carboplatin c. As a single agent following multi-modality anthracycline based therapy 2. Metastatic breast cancer (MBC): a. In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer b. As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease 3. Metastatic gastric cancer: a. In combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease
Recommended:	*Complete Response*
Recommended Indication (if applicable)	Not applicable

[1] For purposes of this review, the proposed product is referred to by the Sponsor's descriptor CT-P6, which was the name used to refer to this product during development. The proprietary name (Herzuma) and proper name (trastuzumab-(b) (4) for this proposed product have been conditionally accepted.

REVIEW TEAM

Product Quality (CMC) Review Team:

Drug Substance and Analytical Similarity: Riley Myers
Drug Product and Immunogenicity Assay: Shadia Zaman and Rachel Novak (TL)
Drug Substance Microbiology: Scott Nichols
Drug Product Microbiology: Candace Gomez-Broughton
Facility: Thuy Thanh Nguyen and Peter Qiu (Branch Chief)
Labeling: Vicky Borders-Hemphil
Product Quality Team Lead: Jennifer Swisher
Microbial QAL: Reyes Candau-Chacon
RBPM: Keith Olin
Application Team Lead: Jennifer Swisher and Kathleen Clouse (Branch Chief)

CMC Statistics: Chao Wang, Meiyu Shen

Pharm/Tox: Wei Chen and Haleh Saber (TL)

Clinical Pharmacology: Christy John and Sarah Schrieber (TL)

Clinical Reviewers: Jennifer Gao

Statistics: Erik Bloomquist and Shenghui Tang (TL)

OSI: Lauren Iacono-Connor and Susan Thompson

OSIS: Shieh Nkah (PM)

OSE/DMEPA: Tingting Gao and Chi-Ming (Alice) Tu (TL)

OSE/DEPI: Steven Bird and Carolyn Mccloskey (TL)

DDMAC: Kevin Wright

TBBS: Leah Christl, Sue Lim, Michele Dougherty, Tyree Newman, Neel Patel, Leila Hann

Safety: Christina Marshall (PM) and Kathy Fedenko (DDS)

RPM: Leyish Minie and Christie Cottrell (TL)

DOP1 Division Director: Julia Beaver

1. Introduction

On May 30, 2017, the applicant submitted a biologics license application (BLA) under Section 351(k) of the Public Health Service Act for CT-P6, a proposed biosimilar to US-licensed Herceptin (trastuzumab)[2]. The Applicant is seeking licensure of CT-P6 for the same indications as US-Herceptin:

Adjuvant breast cancer:

d. As part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
e. With docetaxel and carboplatin
f. As a single agent following multi-modality anthracycline based therapy

Metastatic breast cancer (MBC):

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

Metastatic gastric cancer:

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

Section 351(i) of the Public Health Service Act (PHS Act) defines the terms "biosimilar" or "biosimilarity" to mean that "the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the proposed biosimilar and the reference product in terms of the safety, purity, and potency of the product." Both parts of the statutory definition must be met to demonstrate biosimilarity, but the foundation of the data demonstrating biosimilarity is extensive structural and functional characterization to support a determination that the products are highly similar.

The applicant conducted an analytical comparison between the proposed biosimilar and US-licensed Herceptin (henceforth referred to as US-Herceptin) to support the demonstration that the products are highly similar. The applicant also conducted a head-to-head comparison of the non-clinical PK and toxicity profiles of CT-P6 and US-Herceptin via intravenous administration in cynomolgus monkeys. Further, the applicant conducted a PK similarity study, CT-P6 1.5, and a comparative clinical study, CT-P6 3.2 (henceforth referred to as study 3.2), to support the demonstration of no clinically meaningful differences between CT-P6 and US-Herceptin.

[2] In this document, any reference to "Herceptin" should be considered a reference to US-licensed Herceptin. References to unknown sources of trastuzumab (e.g., based on historical studies) will use "trastuzumab".

In the US, Herceptin is approved as a multi-dose vial containing 420 mg of lyophilized drug product and as a single-dose vial containing 150 mg of lyophilized drug product. (b) (4)

only seeking licensure of the 420 mg presentation.

The analytical data supports the determination that CT-P6 is highly similar to US-Herceptin notwithstanding minor differences in clinically inactive components. In addition, the data submitted from the clinical development program of CT-P6 support a demonstration of no clinically meaningful differences between CT-P6 and US-Herceptin. Together, the analytical and clinical data thus support the demonstration of biosimilarity of CT-P6 to US-Herceptin, as summarized below.

CT-P6 was evaluated and compared to US-Herceptin using multiple orthogonal physicochemical and functional methods. The analytical similarity data support the conclusion that the two products are highly similar, notwithstanding minor differences in clinically inactive components. The data indicate that the amino acid sequences of CT-P6 and US-Herceptin are the same. The results from the analysis of the secondary and tertiary structures and the biological activity analyses met the predefined analytical similarity acceptance criteria. Differences in the levels of some glycosylation species were identified; however, those differences did not impact biological activity in vitro and in vivo and do not preclude a finding that CT-P6 is highly similar to US-Herceptin.

However, the manufacturing and control data submitted in this application are not sufficient to support a conclusion that the manufacture of CT-P6 is well controlled and will lead to a product that is pure and potent for the duration of the shelf -life. Additional facility deficiencies have also been noted in the OPQ review.

The nonclinical pharmacokinetic and toxicity profile of CT-P6 was compared head-to-head with US-Herceptin via intravenous administration in cynomolgus monkeys. Overall, the animal studies provided in the BLA submission did not identify any safety concerns with CT-P6 or differences in the PK or toxicity profile of CT-P6 compared to US-Herceptin. The Pharmacology and Toxicology discipline has not identified any residual uncertainties.

The pharmacokinetic profiles of CT-P6 and US-Herceptin were evaluated in healthy male subjects in study CT-P6 1.5. The results of this pharmacokinetic similarity study support a demonstration of no clinically meaningful differences between CT-P6 and US-Herceptin. The results of this study also contribute to the totality of the data in support of a demonstration of biosimilarity of CT-P6 to US-Herceptin.

The results of study 3.2 support a demonstration of no clinically meaningful differences between CT-P6 and US-Herceptin. Specifically, the 90% confidence intervals for the pathologic complete response rate (pCR) ratio between CT-P6 and US-Herceptin are within the pre-specified statistical equivalence margins. The safety analyses in study 3.2 did not show any meaningful differences in safety between arms.

Anti-drug antibodies were measured in study 3.2 comparing CT-P6 to US-Herceptin. The data indicate that there is no increase in immunogenicity risk in terms of ADA development for CT-P6 when compared to US-Herceptin, which supports the demonstration of no clinically meaningful differences to US-Herceptin.

The applicant provided adequate scientific justification for extrapolation of data to support licensure of CT-P6 under Section 351(k) as a biosimilar for the conditions of use for which US-Herceptin has been previously approved.

In considering the totality of the evidence, the data submitted by the applicant show that CT-P6 is highly similar to US-Herceptin, notwithstanding minor differences in clinically inactive components, and support a demonstration that there are no clinically meaningful differences between CT-P6 and US-Herceptin in terms of safety, purity and potency (safety and efficacy); however, due to manufacturing and control deficiencies, described in further detail in section 3 of this review, the application is not recommended for approval.

2. Background

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

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

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

The "totality of the evidence" submitted by the applicant should be considered when evaluating whether an applicant has adequately demonstrated that a proposed product meets the statutory standard for biosimilarity to the reference product. Such evidence generally includes comparative

structural and functional characterization, animal study data, human PK and, if applicable, pharmacodynamics (PD) data, clinical immunogenicity data, and other clinical safety and effectiveness data.

In general, an applicant needs to provide information to demonstrate biosimilarity based on data directly comparing the proposed biosimilar product with the US-licensed reference product.

Regulatory History

December 19, 2013: Biosimilar Biological Product Development (BPD), Type 2 Meeting

- Discussed FDA's position that (b) (4) a 3-way scientific bridge between EU-Herceptin, US-Herceptin, and CT-P6 would not be needed if only US-Herceptin was used as the active comparator and there is no need to rely on any data generated using EU-Herceptin to support approval; FDA clarified that all patients who received neoadjuvant therapy should receive adjuvant HER2 therapy post-operatively; primary analysis should be based on pCR rate ratio and equivalence margins calculated based on this ratio; FDA clarified that an equivalence design should be used for study 3.2; clarification on scientific justification for extrapolation was provided.

March 21, 2017: BPD, Type 3 Meeting

- Discussed pre-specified equivalence margins and 90% CI for pCR; FDA agreed to exclusion of 13 patients from one GCP non-compliant site; FDA agreed with pCR definition and that the per-protocol set should be used as primary endpoint analysis; sensitivity analyses should be conducted on a subset of the intention-to-treat (ITT) population which excludes patients from the GCP non-compliant site; Celltrion will submit 1 year of clinical data in the initial application and 20 months median follow up for safety/immunogenicity at the Day 120 Safety Data Update.

May 30, 2017: BLA 761091 submitted to FDA.

3. CMC/Device

Source: CMC/Quality/Micro/Facilities Review Team, CMC Executive Summary dated February 8, 2018; OPQ Drug Product Microbiology Review dated January 19, 2018; OPQ Product Quality Microbiology Review and Evaluation dated February 21, 2018

Discipline	Reviewer	Branch/Division
Drug Substance	Riley Myers	OPQ/OBP/DBRR I
Drug Product	Shadia Zaman	OPQ/OBP/DBRR I
Drug Substance Microbiology Drug Product Microbiology	Scott Nichols Candace Gomez-Broughton	OPQ/OPF/DMA IV OPQ/OPF/DMA IV
Facility	Thuy Thanh Nguyen	OPQ/OPF/DIA

Immunogenicity assay	Shadia Zaman	OPQ/OBP/DBRR I
Analytical Similarity	Riley Myers	OPQ/OBP/DBRR I
Labeling	Vicky Borders Hemphill	OPQ/OBP
Product quality Team Lead Microbiology QAL Facility Branch Chief	Jennifer Swisher Reyes Candau-Chacon Peter Qiu	OPQ/OBP/DBRR I OPQ/OPF/DMA IV OPQ/OPF/DIA
CMC RPBM	Keith Olin	OPQ/OPRO
Application Team Lead	Jennifer Swisher	OPQ/OBP/DBRR I

Final Product Quality Team Recommendation: Complete Response

General product quality considerations

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

CT-P6 is a humanized IgG1κ monoclonal antibody produced in CHO cells. CT-P6 drug product is manufactured to the same strength and presentation as U.S.-licensed Herceptin at 420 mg/vial; the formulation is identical except for an increase in α,α-trehalose dihydrate (from 381 to 839 mg/vial), which is (b) (4). CT-P6 drug product is supplied at 420 mg/vial as a sterile, lyophilized powder for intravenous infusion; the 420 mg presentation is a multi-dose vial. CT-P6 is proposed as a treatment for HER2-overexpressing breast cancer and gastric cancer.

CT-P6 monoclonal antibody consists of two heavy chains that are each composed of 450 amino acids and two light chains that are each composed of 214 amino acids. Each heavy chain contains an N-linked glycan site at asparagine 300 (Asn300). The molecular weight of CT-P6 without C-terminal lysine is 148,055 Da. The theoretical extinction coefficient was calculated to be 1.48 (mg/mL) -1 cm-1, and it was determined experimentally to be 1.44 (mg/mL) -1 cm-1. The theoretical value has been used during development and will continue to be used to determine the CT-P6 protein concentration for commercial use.

CT-P6 is produced in genetically engineered CHO (b) (4) cells. The CT-P6 Master Cell Bank (MCB, CTC-06M-247) was developed (b) (4). The Working Cell Bank (WCB, MCB, CTC-06W-247) was created by the expansion of the MCB. This two-tiered cell banking system was implemented to ensure continued source of product. Non-animal derived materials were used in the manufacture of the WCB. The cell lines were appropriately tested to ensure product safety from adventitious and endogenous agents. Viability of both the MCB and WCB is monitored as part of a stability program.

CT-P6 drug substance is manufactured at Celltrion Inc., Incheon, Republic of Korea. (b) (4)

(b) (4)

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The CT-P6 drug substance manufacturing process development is based on minimal process characterization and process validation studies (see details in the CMC executive summary and specific discipline reviews). The overall adequacy of the control strategy cannot be assessed in the absence of a pre-license inspection, which could not take place during this review cycle.

CT-P6 drug product manufacturing includes (b) (4)

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CT-P6 drug product manufacturing process development is based on minimal process characterization and process validation studies. The control strategy is inadequate (see details in CMC Executive Summary and CR items below).

The bacteriostatic water for injection (BWFI) manufacturing process includes (b) (4)

The OPQ reviewers provided the following recommendations and conclusion:

- The data submitted in this application are not sufficient to support a conclusion that the manufacture of CT-P6 is well controlled and will lead to a product that is pure and potent for the duration of the shelf -life. From a CMC standpoint, OPQ is recommending a Complete Response letter be issued to Celltrion to describe the deficiencies noted and the information and data that will be required to support approval.

- Additionally, this application cannot be approved during this review cycle due to facility deficiencies. A pre-license inspection of CT-P6 drug substance and drug product manufacturing facility could not be conducted due to an Official Action Indicated (OAI) status associated with a Warning Letter (WL 320-18-28) issued to Celltrion following a post-approval inspection for another BLA. The Division of Inspectional Assessment, OPF, OPQ is recommending a withhold status, and a Complete Response letter be issued to Celltrion to describe the deficiencies noted.

- Pending the pre-license inspection that may include an on-site assessment of similarity data, the analytical similarity assessment is adequate to support the conclusion that the biological product, CT-P6, is highly similar to US-Herceptin.

Microbiology reviews

Dr. Scott Nichols (DS microbiology review) recommended approval of the BLA, as amended, from a microbial control and a microbiological product quality perspective.

Drs. Candace Gomez-Broughton (DP and BWFI microbiology review) recommended approval of the BLA from an assessment of sterility assurance and microbiology product quality perspective.

Facilities review/inspection

Facilities review was performed by Thuy T. Nguyen, OPF/DIA, with concurrence from branch chief Zhihao Peter Qiu. Adequate descriptions were provided for the CT-P6 DS and DP at the Celltrion facility but the Division of Inspectional Assessment, OPF, OPQ was unable to conduct a pre-license inspection in support of this BLA for the following reason. A surveillance inspection was conducted at the Celltrion, Inc. facility in Incheon, Republic of Korea, from May 22 – June 02, 2017 which resulted in an Official Action Indicated (OAI) status with Warning Letter Recommendation. The Warning Letter was issued to Celltrion on January 26, 2018. A pre-licensing inspection cannot be conducted until the OAI status is cleared by OMQ. Master Cell Bank and testing facilities for DS and DP are acceptable. The Celltrion Inc., Incheon, Republic of Korea facility is recommended for WITHHOLD from a facilities assessment standpoint.

Analytical similarity assessment

The analytical similarity assessment was performed to demonstrate that CT-P6 and US-Herceptin are highly similar, notwithstanding minor differences in clinically inactive components.

CT-P6 was evaluated and compared to US-Herceptin using a battery of biochemical, biophysical, and functional assays, including assays that addressed each major potential mechanism of action (see Section II A, CMC Executive Summary). The analytical data submitted support the conclusion that CT-P6 is highly similar to US-Herceptin. The amino acid sequences of CT-P6 and US-Herceptin are identical. A comparison of the secondary and tertiary structures and the impurity profiles of CT-P6 and US-Herceptin support the conclusion that the two products are highly similar.

Inhibition of proliferation, and ADCC activity, which reflect the presumed primary mechanisms of action of trastuzumab, were determined to be equivalent. HER2 binding is similar between CT-P6 and US-Herceptin. Some tests indicate that small shifts in low abundance glycan forms [e.g., sialic acid, high mannose, and non-glycosylated heavy chain (NGHC)] exist and are likely an intrinsic property of CT-P6 due to the manufacturing process. High mannose and sialic acid containing glycans can impact PK, while NGHC is associated with loss of effector function through reduced FcγRIIIa binding and reduced ADCC activity. However, ADCC activity was similar and FcγRIIIa binding was similar between CT-P6 and US-Herceptin. The minor differences related to the increase in total mannose forms and NGHC and decrease in sialic acid were addressed by the ADCC similarity and by the PK similarity between CT-P6 and US-

Herceptin as concluded by the clinical review team. Additional subtle differences in size and charge related variants were detected; however, these variants generally remain within the quality range criteria. Further, the data submitted by the applicant support the conclusion that CT-P6 and US-Herceptin can function through the same mechanisms of action for the indications for which US-Herceptin is currently approved, to the extent that the mechanisms of action are known or can reasonably be determined. Thus, based on the extensive comparison of the functional, physicochemical, protein and higher order structure attributes, CT-P6 is highly similar to US-Herceptin, notwithstanding minor differences in clinically inactive components. CT-P6 meets the statutory "same strength" requirement under section 351(k)(2)(A)(i)(IV) of the PHS Act.

Reviewer Comment: I concur with the CMC/OPQ review team's conclusion that the analytical data supports a determination that CT-P6 is highly similar to US-Herceptin. However, because of manufacturing and control deficiencies as well as facility deficiencies, this application is not recommended for approval. Refer to the finalized list of Complete Response comments in the CR Letter forwarded to the applicant on March 29, 2018.

CDRH

CDRH consultation was requested pertaining to the product label for BLA 761091, under sections 1.1, 1.2, and 1.3, regarding the statement for the companion diagnostic. Per CDRH reviewers (Drs. Jacob Richards, Eunice Lee, and Reena Philip), CDRH agreed with the CDER review team that the label should indicate the following: "Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product."

The applicant was requested to provide a rationale for why the approved companion diagnostics for trastuzumab could serve as companion diagnostics for CT-P6. The applicant provided a response on January 19, 2018. CDRH reviewers concluded that Celltrion's response explaining why it believes the approved companion diagnostics for trastuzumab could serve as companion diagnostics for CT-P6 is adequate. Moreover, for purposes of the HER-2 tests approved as companion diagnostics for trastuzumab, CDRH believes that reference to trastuzumab in the device labeling includes not only Herceptin but also products determined to be biosimilar to Herceptin.

4. Nonclinical Pharmacology/Toxicology

Source: Pharmacology and Toxicology primary Review dated February 20, 2018 (Drs. Wei Chen and Haleh Saber)

Final Pharmacology/Toxicology Team Recommendations: Approval.

A 4-week study with weekly administration of CT-P6 and US-licensed Herceptin were conducted in monkeys to compare the toxicity profiles and the toxicokinetic (TK) profiles of CT-P6 and US-licensed Herceptin. Monkey has been identified as a pharmacologically relevant

species. CT-P6 or US-licensed Herceptin was administered to cynomolgus monkeys at doses of 0 (Control), 14 and 42 mg/kg/week on Days 1, 8, 15 and 22. No apparent toxic response was observed in monkeys treated with CT-P6 or US licensed Herceptin at doses up to 42 mg/kg, which was consistent with published data for US-licensed Herceptin. TK evaluation showed that animals were continuously exposed to CT-P6 or US-licensed Herceptin for the duration of the study. Following repeated administration of CT-P6 and US licensed Herceptin at 14 and 42 mg/kg, similar systemic exposures were observed for both products. Accumulation of CT-P6 drug product and US-licensed Herceptin in serum was observed with repeated dosing over the 4-week dosing period. No immunogenic (anti-drug antibodies) responses to CT-P6 or US-licensed Herceptin were detected in samples taken from treated animals.

The pharmacology/toxicology review team recommended approval.

Reviewer Comment: I concur with nonclinical team's conclusion that the submitted pharmacology and toxicology data were adequate to demonstrate similarity in the toxicity and TK profiles of CT-P6 and US-Herceptin in cynomolgus monkeys.

5. Clinical Pharmacology

Source: Clinical Pharmacology Review (Drs. Christy S. John, Thiengi M. Thway, Sarah J. Schrieber and Nam Atiqur Rahman) and immunogenicity analysis from Dr. Shadia Zaman)

Final Clinical Pharmacology Team Recommendations: Approval

The objectives of the clinical pharmacology program were to demonstrate pharmacokinetic (PK) similarity between CT-P6 and US-Herceptin. The Applicant submitted study CT-P6 1.5 which evaluated the PK of CT-P6 and US-Herceptin.

Study CT-P6 1.5 was a single-dose, randomized, double-blind, 2-arm, parallel group study in 70 healthy male subjects designed to demonstrate PK similarity of CT-P6, and US-licensed Herceptin following a single 6 mg/kg intravenous dose infused over 90 minutes. The 90% confidence intervals (CI) for all pairwise comparisons of the PK endpoint (AUC0-inf) were within the limits of 80 to 125%. The results of the study established PK similarity between CT-P6 and US-licensed Herceptin. Overall, Study CT-P6 1.5 supports a demonstration of PK similarity between CT-P6 and US-licensed Herceptin.

Immunogenicity

The incidence of immunogenicity for CT-P6 and US-licensed Herceptin was compared in a multiple-dose, parallel-arm study in 562 patients with early HER2 positive breast cancer (CT-P6 3.2). The results indicate similar incidence and titers of anti-drug antibodies (ADA) for both products. These data indicate that there is no increase in immunogenicity risk for CT-P6 as compared to US-licensed Herceptin.

In conclusion, the PK and immunogenicity results support a demonstration of no clinically meaningful differences between CT-P6 and US-licensed Herceptin and add to the totality of the evidence to support a demonstration of biosimilarity of CT-P6 and US-licensed Herceptin.

Reviewer Comment: I concur with clinical pharmacology team's conclusion that the submitted clinical pharmacology study adequately demonstrated PK similarity between CT-P6 and US-Herceptin. The evidence of PK similarity supports a demonstration of no clinically meaningful differences between CT-P6 and US-Herceptin. The immunogenicity data indicate that there is no increase in immunogenicity risk for CT-P6 when compared to US-Herceptin, which supports a demonstration of no clinically meaningful differences between CT-P6 and US-Herceptin.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Source: Combined Clinical/Stat Review (Drs. Jennifer Gao, Erik Bloomquist and Shenghui Tang)

Final Clinical/Statistical Team Recommendations: Approval

The applicant also submitted study CT-P6 3.2 to support a determination of no clinically meaningful differences between CT-P6 and US-Herceptin.

Study 3.2 is a double-blind, randomized, parallel-group clinical study to compare the efficacy and safety of CT-P6 and US-Herceptin in the neoadjuvant and adjuvant treatment of patients with early HER2 positive breast cancer. In the neoadjuvant portion, patients were treated with 4 cycles of CT-P6 plus docetaxel or US-Herceptin plus docetaxel followed by 4 cycles of CT-P6 or US-Herceptin with 5-fluorouracil, epirubicin, and cyclophosphamide chemotherapy. In the adjuvant portion, CT-P6 or US-Herceptin was continued to complete 1 year of trastuzumab-based therapy (up to 10 cycles during the adjuvant portion). See Figure 1, below. Patients were randomized 1:1 and stratified by disease stage (stage I or II vs. IIIa), estrogen/progesterone receptor status (positive vs. negative); country of treatment was an additional geographic stratification factor.

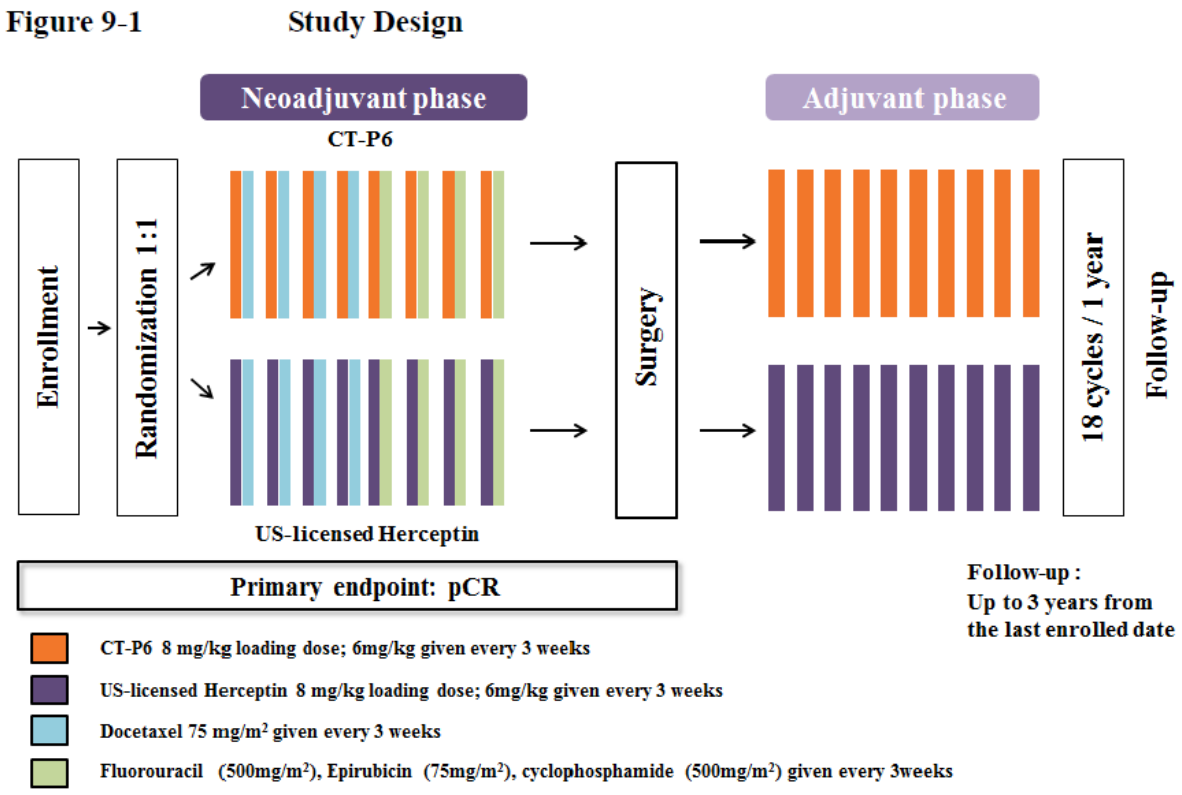

Figure 1. CT-P6 3.2 Study Schema
Source: CT-P6 3.2 Clinical Study Report

The primary efficacy endpoint of this trial was pathological complete response (pCR), defined as the absence of invasive tumor cells in the breast and in axillary lymph nodes, regardless of DCIS. The pCR was determined at the time of surgery, using hematoxylin and eosin evaluation of the resected breast specimen. The applicant used the 90% asymptotic confidence region of the ratio of pCR in the CT-P6 arm vs. the US-Herceptin arm as the primary analysis strategy. The primary analysis population was the per-protocol set (those without major protocol violations); the intention to treat population was used for supportive purposes.

The study was deemed positive if the 90% confidence region for the ratio was entirely contained with the interval (0.75, 1.35). To calculate this interval, the applicant reviewed six study control arms to obtain pCR rates for the control arm and four study treatment arms to obtain pCR rates for the treatment arms. The overall pCR rate for their control arm was estimated to be 15.9% (14 – 18%), and the overall pCR rate for their treatment arm was estimated to be 53.7% (38-70%). Using a 50% retention rate, the sponsor derived their equivalence margin for the ratio.

The applicant sized their study to achieve 80% power for the primary endpoint. The sponsor calculated that 266 patients per arm would provide sufficient power and account for a 10% dropout.

The primary pCR data were reviewed by a blinded central committee as a sensitivity analysis. Note that only pathology reports were sent to the blinded central committee, so the agreement was 100% between the local pathology and central pathology.

Key secondary endpoints included radiological endpoints such as overall response rate using RECIST v1.1 criteria and PFS. Overall survival was also a key secondary endpoint. For the radiological endpoints, scans were done in the neoadjuvant and adjuvant periods. The local investigator determined whether an individual had a response or progression event. A central review committee was used and reviewed the radiological images and made determinations of ORR and PFS for sensitivity purposes.

The statistical analysis plan had four versions. Significant changes include a change from the risk difference to risk ratio, the use of a 90% confidence interval instead of a 95% confidence interval for the primary analysis, and the use of the per protocol population for the primary analysis.

In summary, Study 3.2, together with other information in the application including Study 1.5, supports the demonstration of no clinically meaningful differences between CT-P6 and US-Herceptin. Specifically, the 90% confidence interval for the pCR ratio between CT-P6 and US-Herceptin in Study 3.2 is within the equivalence margin.

Reviewer Comment: I concur with clinical team's conclusion that the submitted clinical study demonstrated no differences in terms of efficacy between CT-P6 and US-Herceptin. Consequently, the results of study 3.2 support a demonstration of no clinically meaningful differences between CT-P6 and US-Herceptin.

8. Safety

Source: Combined Clinical/Stat Review dated February 13, 2018 (Dr. Jennifer Gao)

Final Clinical/Statistical Team Recommendations: Approval

The safety evaluation for this application is based on the neoadjuvant and adjuvant study portions of study 3.2. The safety assessments for 3.2 are adequate. There was particular attention to assessment of cardiac adverse events (AEs) due to the known cardiac effects of trastuzumab. The safety population consisted of 549 patients, 271 in the CT-P6 and 278 in the US-Herceptin arms and is defined as all patients who received at least 1 dose of study drug in any amount. The 13 patients from the non-GCP compliant site 2302 were excluded from the safety population as the actual treatment given to these patients could not be confirmed.

The frequency of TEAEs, serious events, and events leading to discontinuation of study drug had no meaningful differences between the treatment arms. Major events of interest which are listed as Black Box Warnings in the prescribing information for US-Herceptin include cardiomyopathy, infusion reactions, pulmonary toxicity, and embryo-fetal toxicity. There were

no reports of embryo-fetal toxicity in study 3.2. Most cardiac adverse events were grade 1-2 and most patients recovered in both groups. The safety results of study 3.2 showed no meaningful differences between CT-P6 and US-Herceptin.

Reviewer Comment: The comparative safety results obtained in study 3.2 support a demonstration of no clinically meaningful differences between CT-P6 and US-Herceptin. I concur with clinical team's conclusion that the submitted clinical study adequately supports a finding that there are no clinically meaningful differences in terms of safety between CT-P6 and US-Herceptin.

9. Considerations for Extrapolation of Biosimilarity

Source: Combined Clinical/Stat Review (Dr. Jennifer Gao)

The applicant seeks licensure for all indications for which US-Herceptin is licensed. The applicant has provided adequate justification for extrapolation of the data and information in the application, including comparative clinical efficacy and safety data from a clinical program in patients with early HER2 positive breast cancer, to support licensure of CT-P6 under Section 351(k) for the indications for which US-Herceptin is licensed.

The neoadjuvant setting for breast cancer used in study 3.2 is an acceptable, homogenous, and sensitive patient population to evaluate for no clinically meaningful differences between CT-P6 and US-Herceptin. The patient population receiving HER2-based treatment is the same in the neoadjuvant and adjuvant settings, differing only in the timing of surgery. The primary endpoint of pCR is an acceptable endpoint in breast cancer. The mechanism of action of trastuzumab in neoadjuvant breast cancer patients is expected to be the same as the mechanism of action for trastuzumab in the indications for which the applicant is seeking licensure. For these reasons, the study population and primary endpoint used in study 3.2 is acceptable to support approval of CT-P6 for the indications for which US-Herceptin has been previously approved.

The applicant has submitted the following scientific justifications for extrapolation of data to support licensure of CT-P6 as a biosimilar for the conditions of use for which US-Herceptin has been previously approved:

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

- PK results support a demonstration of no clinically meaningful differences between CT-P6 and US-Herceptin

- Immunogenicity was low and similar between CT-P6 and US-Herceptin

As described in the Guidance for Industry: "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009," if a biological product meets the statutory requirements for licensure as a biosimilar product under section 351(k) of the PHS Act based on, among other things, data derived from a clinical study or studies sufficient to demonstrate safety, purity, and potency in an appropriate condition of use, the potential exists for that product to be licensed for one or more additional conditions of use for which the reference product is licensed. The applicant has demonstrated that CT-P6 is highly similar to US-Herceptin with respect to analytical attributes, and that there are no clinically meaningful differences in safety, purity, and potency, which supports approval for all indications for which US-Herceptin was previously approved (adjuvant and metastatic breast cancer and metastatic gastric cancer). The clinical team consider extrapolation to be scientifically justified based on the bullets above.

Reviewer Comment: I concur with clinical team's conclusion that the evidence indicates that the extrapolation of data, including clinical data, to support licensure of CT-P6 for the indications for which US-Herceptin has previously been approved is scientifically justified.

10. Advisory Committee Meeting

An advisory committee meeting was not held for this application.

11. Pediatrics

Celltrion requested a full waiver of pediatric studies for the requested indications and submitted an agreed iPSP with the BLA. Breast and gastric cancers are included in FDA's September 2005 Guidance (How to Comply with the Pediatric Research Equity Act) for disease-specific waivers. The Oncology Center of Excellence Subcommittee of the Pediatric Review Committee met on January 31, 2018 and concurred with the applicant's request for a full waiver in HER-2 overexpressing breast and gastric cancers. The minutes were entered to DARRTS February 14, 2018.

12. Other Relevant Regulatory Issues

Application Integrity Policy (AIP)
The application contained statements from Celltrion that they certified that they did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Exclusivity or patent Issues

Not applicable.

Financial disclosures

In accordance with 21 CFR part 54 Financial Disclosures by Clinical Investigators, the applicant requested statements of financial interest from 114 principal investigators (PIs) and 449 sub-investigators for studies CT-P6 1.4, 1.5, and 3.2. All investigators were assessed for equity interest, significant payments of other sorts, and other compensation by the applicant and propriety interest. The applicant has stated that none of the clinical investigators involved with the CT-P6 studies have financial interests or arrangements to disclose as defined in 21 CFR 54.2(f).

Bioequivalence Inspections

In a review entered into DARRTS on August 21, 2018, Angel S. Jonson of the Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study
Integrity and Surveillance (OSIS) recommends accepting data without on-site inspection. The rationale for this approach was that OSIS had recently inspected two clinical and one analytical site, for which the inspectional outcomes were classified as No Action Indicated (NAI). The clinical sites previously inspected were th (b) (4) .
The analytical site previously inspected was (b) (4) .

Clinical Inspections

Lauren Iacono-Connors, Susan Thompson (Team Leader) and Kassa Ayalew (Branch Chief) from the Division of Clinical Compliance Evaluation, OSI, completed the clinical inspection summary (CIS) on December 8, 2017. FDA selected three clinical sites for audit. There were no significant inspectional findings for two of these three clinical investigators. There were no significant inspectional findings for clinical investigators Dr. Zanete Zvirbule, M.D., and Dr. Dmytro Boliukh, M.D. ORA recommended that the inspection of Dr. Vladimir Moiseenko, M.D. (Site 2816) be cancelled because as of December 1, 2017 the Russian Embassy had not yet responded to a visa request from ORA for the FDA field investigator. The inspection was cancelled on December 1, 2017. OSI review concluded that the data from study CT-P6 3.2

submitted to the Agency in support of BLA 761091, appear reliable based on available information.

Other Discipline Consultations

Tingting Gao and Chi-Ming (Alice) Tu from the Office of Medication Error Prevention and Risk Management (OMEPRM) completed a review dated August 14, 2017, that concluded that the proposed proprietary name, Herzuma, was conditionally acceptable. On February 14, 2018, the reviewers affirmed that the proprietary name was also conditionally acceptable (b) (4)

Tingting Gao and Lubna Merchant from OMEPRM completed a review dated July 19, 2017 that determined that the suffix (b) (4) derived from (b) (4) for the proper name is conditionally acceptable (trastuzumab- (b) (4)

Tingting Gao and Chi-Ming (Alice) Tu completed a review dated March 6, 2018 that defined recommendations relating to carton and container and product labeling. The recommendations were incorporated in revised product labeling.

Pediatric and Maternal Health

At the time of the submission of this BLA, a pregnancy registry and pharmacovigilance program was in place for US-Herceptin. Because the risks of oligohydramnios have been adequately characterized in the Herceptin labeling, FDA has determined that the Herceptin pregnancy registry and pregnancy pharmacovigilance program are no longer necessary for Herceptin and therefore, no registry or pharmacovigilance program is required for this biosimilar. Additional details may be found in the primary clinical review.

13. Labeling

Proposed labeling submitted by Celltrion was generally consistent with recommendations contained within FDA's draft Guidance for Industry "Labeling for Biosimilar Products" which recommends that the biosimilar product labeling incorporate relevant data and information from the reference product labeling, with appropriate product specific modifications. Some information in the labeling was revised to reflect CT-P6-specific information as well as to comply with current labeling practices. The review teams reserve final comment on the proposed labeling, container labels, and carton labeling until the application is otherwise adequate.

14. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

The applicant is seeking licensure for indications that are the same as those licensed for US-Herceptin. The applicant is seeking licensure for the adjuvant treatment of HER-2 overexpressing breast cancer, treatment of HER-2 overexpressing metastatic breast cancer, and treatment of HER-2 overexpressing metastatic gastric cancer indications. The data submitted to the BLA from the clinical development program of CT-P6 support a demonstration of no clinically meaningful differences between CT-P6 and US-Herceptin. These data also contribute to the totality of the data in support of a demonstration of biosimilarity of CT-P6 to US-Herceptin. The applicant provided adequate scientific justification for extrapolation of data to support licensure of CT-P6 for the breast cancer and metastatic gastric cancer indications. The applicant demonstrated that CT-P6 is highly similar to US-Herceptin based on extensive analytical data and that CT-P6 has no clinically meaningful differences from US-Herceptin in terms of safety, purity and potency. Accordingly, the data submitted support licensure of CT-P6 as biosimilar to US-Herceptin.

However, because of the inspectional and product quality deficiencies identified by OPQ, as summarized in section 3 of this review, the 351(k) BLA 761091 for CT-P6 will not be recommended for approval. Specifically, the data submitted in this application were not found to be sufficient to support a conclusion that the manufacture of CT-P6 is well controlled and will lead to a product that is pure and potent for the duration of the shelf -life. Additionally, this application cannot be approved during this review cycle due to facility deficiencies.

Risk Benefit Assessment

Section 351(i) of the PHS Act defines the terms “biosimilar” or “biosimilarity” to mean that “the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components” and that “there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.” Both parts of the statutory definition must be met to establish biosimilarity, but the foundation of the data demonstrating biosimilarity is extensive structural and functional characterization to support a demonstration that the products are highly similar.

As explained above, the data submitted to the 351(k) BLA support licensure of CT-P6 as biosimilar to US-Herceptin under section 351(k) of the PHS Act. Accordingly, CT-P6 is considered to have a favorable risk-benefit profile for all requested conditions of use.

However, because of the inspectional and product quality deficiencies identified by OPQ, as summarized in section 3 of this review, this application is not recommended for approval.

Recommendation for Postmarketing Risk Evaluation and Management Strategies

None.

Recommendation for other Postmarketing Requirements and Commitments

None.

Recommended Comments to Applicant

See Section 3, Chemistry, Manufacturing, and Controls for the list of CMC deficiencies and comments to be communicated to the applicant.

Recommended Regulatory Action

Complete Response.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SANJEEVE BALASUBRAMANIAM
03/29/2018

JULIA A BEAVER
03/29/2018

CLINICAL REVIEW

Application Type	BLA, Original 351(k)
Application Number(s)	761091
Priority or Standard	Standard
Submit Date(s)	5/30/2017
Received Date(s)	5/30/2017
BSUFA Goal Date	3/30/2018
Division / Office	DOP1/OHOP
Reviewer Name(s)	Jennifer Gao, MD Erik Bloomquist, PhD
Review Completion Date	2/12/18
Established Name	Trastuzumab-(b) (4)
(Proposed) Trade Name	HERZUMA*
Therapeutic Class	HER2-binding humanized monoclonal antibody
Applicant	Celltrion
Formulation(s)	IV
Dosing Regimen	(b) (4) mg/kg IV loading dose, then (b) (4) mg/kg IV (b) (4) wks
Proposed Indication(s)	HERZUMA is a HER2/neu receptor antagonist indicated for: • the treatment of HER2 overexpressing breast cancer. • the treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma.
Recommended Indication	HERZUMA is a HER2/neu receptor antagonist indicated for: • the treatment of HER2 overexpressing breast cancer. • the treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma. Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.

*In this document, FDA generally refers to the applicant's proposed product by the applicant descriptor "CT-P6".

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1. Recommendations/Risk Benefit Assessment

1.1. Recommendation on Regulatory Action

This biologics license application (BLA 761091) seeks approval of the product CT-P6 (proposed trade name Herzuma), which is a proposed biosimilar to US-licensed Herceptin (which will be referred to as US-Herceptin for the remainder of this review).

The biosimilar licensure pathway under section 351(k) of the Public Health Service Act (PHS Act) requires that the proposed biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between the proposed biosimilar and reference products in terms of safety, purity and potency. Both parts of the statutory definition need to be met to demonstrate biosimilarity, but the foundation of the data demonstrating biosimilarity is extensive structural and functional characterization to support a demonstration that the products are highly similar.

From a clinical standpoint, the data submitted to the 351(k) BLA from the clinical development program of CT-P6 support a demonstration of no clinically meaningful differences between CT-P6 and US-Herceptin. A demonstration that CT-P6 is highly similar to US-Herceptin, notwithstanding minor differences in clinically inactive components together with the clinical data discussed in this review, will support licensure of CT-P6 as a biosimilar to US-Herceptin under section 351(k) of the PHS Act.

1.2. Risk Benefit Assessment

Breast cancer is the number one cancer in women, with more than 200,000 women newly diagnosed in the United States and about 40,000 women dying of breast cancer annually. (1) HER2 is a tyrosine kinase transmembrane receptor that is amplified in about 20-30% of breast cancers. HER2-positive breast cancer is associated with a more aggressive phenotype.

Gastric cancer is much more common in less-developed countries than it is in the United States today. In 2017, about 28,000 new cases of gastric cancer and 11,000 deaths due to it are estimated in the United States, with about 7-34% of them overexpressing HER2. (2, 3) Known risk factors for gastric cancer are male sex, increasing age, ethnicity, geography, Helicobacter pylori infection, diet, and smoking, to name a few. As in breast cancer, HER2 positive gastric cancer has been associated with a more aggressive phenotype and resulting poorer prognosis. (3)

Treatment of HER2-positive breast and gastric cancer with targeted therapy such as trastuzumab has led to significant increases in response rates compared to chemotherapy alone. It is one of the key agents used to target these tumor subtypes

throughout the world and thus plays a central role in treatment of patients with breast and gastric cancer.

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

CT-P6 is a proposed biosimilar to trastuzumab (US-licensed Herceptin®). The applicant has submitted a BLA for CT-P6 with proposed indications the same as for US-Herceptin:

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

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

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

The clinical team recommends approval of CT-P6 for the following indications:
1. Adjuvant breast cancer:
    a. As part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
    b. With docetaxel and carboplatin
    c. As a single agent following multi-modality anthracycline based therapy

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

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

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

Study CT-P6 3.2 (which will be referred to as study 3.2 for the remainder of this review) supports the determination of no clinically meaningful differences between CT-P6 and US-Herceptin. This was a randomized, double-blind, parallel group, equivalence study in which patients received either CT-P6 or US-Herceptin with chemotherapy in the neoadjuvant setting. After completing neoadjuvant treatment and undergoing surgery, patients were able to continue with the same trastuzumab product as adjuvant monotherapy to complete 1 year of treatment. The primary endpoint of pathological complete response (pCR) ratio (the pCR rate with CT-P6 divided by the pCR rate with US-Herceptin) as assessed by local review of the per-protocol set (PPS) of 0.9282 (90% CI 0.7981-1.0796, 95% CI 0.7753-1.1113) was within the pre-specified equivalence margin of 0.74 to 1.35. Secondary endpoints of ORR, DFS, PFS, OS, breast conservation rate, and other pCR parameters were similar between both treatment arms.

The safety findings of study 3.2 were reviewed, with special focus on cardiac, pulmonary, infusion reaction, and embryo-fetal toxicities. Overall no clinically meaningful differences were found in the safety population.

The neoadjuvant setting for breast cancer used in study 3.2 is an acceptable, homogenous, and sensitive patient population to evaluate for no clinically meaningful differences between CT-P6 and US-Herceptin. The patient population receiving HER2-based treatment is the same in the neoadjuvant and adjuvant settings, differing only in the timing of surgery. The primary endpoint of pCR is an acceptable endpoint in breast cancer. The mechanism of action of trastuzumab in neoadjuvant breast cancer patients is expected to be the same as the mechanism of action for trastuzumab in the indications for which the applicant is seeking licensure. For these reasons, the study population and primary endpoint used in study 3.2 is acceptable to support approval of CT-P6 for the indications for which US-Herceptin has been previously approved.

The analytical data supports the demonstration that CT-P6 is highly similar to US-Herceptin, notwithstanding minor differences in clinically inactive components. The

clinical data which includes pharmacokinetics, efficacy, safety, and immunogenicity, supports the finding of no clinically meaningful differences between the two products. Thus, the totality of the evidence supports the biosimilarity of CT-P6 and US-Herceptin.

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

- The mechanism of action of trastuzumab is the same across all indications as the target receptor involved (HER2) is the same across indications
- The available safety data of the reference product does not indicate that there are any significant differences in expected toxicities for each condition of use and patient population
- There are no toxicities that are related to off-target activities in patients treated in the neoadjuvant setting compared with adjuvant/metastatic breast cancer or metastatic gastric cancer
- The dose of trastuzumab and route of administration is similar across all indications
- PK results support a demonstration of no clinically meaningful differences between CT-P6 and US-Herceptin
- Immunogenicity was low and similar between CT-P6 and US-Herceptin

The applicant has demonstrated high similarity of their product with respect to analytical attributes, and no clinically meaningful differences in efficacy and safety, which supports approval for all indications for which US-Herceptin was previously approved (adjuvant and metastatic breast cancer and metastatic gastric cancer). The reviewers consider extrapolation to be scientifically justified based on the bullets above.

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

- CT-P6 1.5 (PK similarity study, this study will be referred to as study 1.5 for the remainder of this review)
    - Study 1.5 was a randomized, controlled, two-arm, parallel-group, double-blinded, single-dose prospective study in healthy male subjects with a goal of demonstrating the similarity of PK in of CT-P6 and US-Herceptin after 6 mg/kg as a single dose administered as an IV infusion over 90 minutes. Study 1.5 enrolled 70 healthy male subjects.
- CT-P6 1.4 (pilot PK similarity study, this study will be referred to as study 1.4 for the remainder of this review)
    - Study 1.4 was a randomized, double-blind, two-arm, parallel-group, single-dose, pilot PK similarity study conducted in a single center in the Philippines and served to determine the initial PK and tolerability profile of CT-P6. Study 1.4 enrolled 70 healthy male subjects who received 6 mg/kg as a single dose administered as an IV infusion over 90 minutes.
- CT-P6 3.2 (comparative clinical study, this study will be referred to as study 3.2 for the remainder of this review)

- Study 3.2 is an ongoing randomized, double-blind, multicenter, parallel-group study comparing CT-P6 and US-Herceptin in the neoadjuvant and adjuvant treatment of patients with HER2 positive early breast cancer (EBC). This study enrolled 562 patients in 22 countries, with 278 patients randomly assigned to CT-P6 and 284 patients assigned to US-Herceptin. All patients were female.
- This was designed as an equivalence trial, with the primary endpoint of pathologic complete response (pCR) after 8 cycles of neoadjuvant treatment, defined as the absence of invasive tumor cells in the breast and axillary lymph nodes regardless of the ductal carcinoma in situ (DCIS) status, as identified at the time of surgery using hematoxylin and eosin evaluation of the resected specimens. If the 90% CI of the ratio in pCR proportions of responders was entirely bound by the interval 0.74 to 1.35, then therapeutic equivalence was met. The primary population for this analysis was the per-protocol set (PPS), with a supportive analysis also conducted using the intention to treat (ITT) patients. The PPS were all patients in the ITT set except for those excluded because of major protocol deviations and patients who withdrew from the study with confirmed progressive disease. Secondary endpoints included overall response rate (ORR), disease free survival (DFS), progression free survival (PFS), overall survival (OS), breast conservation rate (BCR), and other pCR parameters other than the primary endpoint.
- The safety findings of study 3.2 were reviewed, with special focus on cardiac, pulmonary, infusion reaction, and embryo-fetal toxicities. Overall no clinically meaningful differences were found in the safety population.
- The totality of the analytical data supports a demonstration that CT-P6 and US-Herceptin as highly similar, notwithstanding minor differences in clinically inactive components. The clinical data which includes pharmacokinetics, efficacy, safety, and immunogenicity, supports the finding of no clinically meaningful differences between the two products. Extrapolation of data to support approval for all of the proposed indications is justified. Thus, the totality of the evidence supports biosimilarity of CT-P6 and US-Herceptin.

1.3. Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No clinical postmarket risk evaluation and mitigation strategies are anticipated at this time.

1.4. Recommendations for Postmarket Requirements and Commitments

No PMRs or PMCs were requested.

Overall survival (OS) data should be provided post-approval. The OS data is important information to follow long term outcomes with CT-P6.

At the time of the submission of this BLA, a pregnancy registry and pharmacovigilance program was in place for Genentech's Herceptin. Because the risks of oligohydramnios have been adequately characterized in the Herceptin labeling, FDA has determined that the Herceptin pregnancy registry and pregnancy pharmacovigilance program are no longer necessary for Herceptin and therefore, no registry or pharmacovigilance program is needed for this biosimilar.

2. Introduction and Regulatory Background

2.1. Product Information

CT-P6 (proposed trade name Herzuma) is a proposed biosimilar to US-Herceptin (trastuzumab). Trastuzumab is a humanized IgG1 monoclonal antibody of the kappa isotype consisting of two identical glycosylated heavy chains and two identical light chains. The target of trastuzumab is the cell surface receptor human epidermal growth factor receptor 2 (HER2). HER2 is part of the HER family of transmembrane tyrosine kinases that have been shown to play a role in the regulation of cellular survival, proliferation, adhesion and differentiation.

2.2. Tables of Currently Approved Trastuzumab Products for Proposed Indications

Table 1 below lists the current FDA approved trastuzumab products.

Table 1: Summary of FDA Approved Trastuzumab Products

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

2.3. Availability of Proposed Active Ingredient in the United States

CT-P6 is not currently marketed in the United States.

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

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

2.4. Important Safety Issues With Consideration to Related Drugs

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

2.5. Summary of Presubmission Regulatory Activity Related to Submission

The major clinical regulatory activity with the FDA was as follows:

December 19, 2013: Biologics Product Development, Type 2 Meeting

- (b) (4), and that determination of analytical similarity will be a review issue; that a 3-way scientific bridge between EU-licensed Herceptin (which will be referred to as EU-Herceptin for the remainder of this review), US-Herceptin, and CT-P6 would not be needed if only US-Herceptin was used as the active comparator; FDA clarified that all patients who received neoadjuvant therapy should receive adjuvant HER2 therapy post-operatively; primary analysis should be based on pCR rate ratio and equivalence margins calculated based on this ratio; FDA clarified that an equivalence design should be used for study 3.2; clarification on scientific justification for extrapolation.

March 21, 2017: BPD, Type 3 Meeting

- Discussed pre-specified equivalence margins and 90% CI for pCR, FDA agreed to exclusion of 13 patients from one GCP non-compliant site, FDA agreed with pCR definition and that the PPS should be used as primary endpoint analysis, sensitivity analyses should be conducted on a subset of ITT population which excludes patients from the GCP non-compliant site, Celltrion will submit 1 year of clinical data in the initial application and 20 months median follow up for safety/immunogenicity at the Day 120 Safety Data Update

May 30, 2017: BLA 761091 submitted to FDA.

2.6. Other Relevant Background Information

None

3. Ethics and Good Clinical Practices

3.1. Submission Quality and Integrity

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

3.2. Compliance with Good Clinical Practices

The applicant stated that study 3.2 was conducted in accordance with the Declaration of Helsinki, International Council for Harmonization (ICH) Guidance for Industry E6 Good Clinical Practice (GCP), and all applicable regulations.

The applicant stated the investigators would conduct all aspects of the study in accordance with all national, state, and local laws or regulations and in accordance with ICH E6 (R1). The analytical assays would be conducted according to the general principles of the Organization for Economic Cooperation and Development Good Laboratory Practice for Testing of Chemicals C(81)30. All correspondence related to study 3.2 would be kept in appropriate file folders and records of patients, source documents, eCRFs, and drug inventory sheet would be kept on file. Essential files would be retained for a minimum of 2 years after the last approval of the marketing application. Study 3.2 would be monitored by an independent data safety monitoring board (DSMB) composed of a PK specialist, a statistician, a chairing physician, and an independent physician. An independent tumor review committee (ITRC) would be used to review the pathological reports and safety assessments. Study-related monitoring, audits, IRB/IEC review, and regulatory inspections would be permitted and direct access to all study records would be provided.

Site 2302 in Latvia violated GCP. This site enrolled thirteen patients which were subsequently not included in the efficacy or safety analyses.

3.3. Financial Disclosures

In accordance with 21 CFR part 54 Financial Disclosures by Clinical Investigators, the applicant requested statements of financial interest from 114 principal investigators (PIs) and 449 sub-investigators for studies CT-P6 1.4, 1.5, and 3.2. The applicant

stated none of the PIs or sub-investigators had financial information to disclose and all returned the financial disclosure information.

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

4.1. Product Quality

Please refer to Dr. Riley Myers's review for BLA 761091.

4.2. Clinical Microbiology

Please refer to Dr. Candace Gomez-Broughton's and Scott Nichols's review for BLA 761091.

4.3. Immunogenicity

Please refer to Dr. Shadia Zaman's review for BLA 761091.

4.4. Preclinical Pharmacology/Toxicology

Please refer to Dr. Wei Chen's review for BLA 761091.

4.5. Clinical Pharmacology

Please refer to Dr. Wento Fu's review for BLA 761091.

4.5.1. Mechanism of Action

Trastuzumab is a humanized $IgG_1\kappa$ monoclonal antibody directed against an epitope on the extracellular juxtamembrane domain of HER2. Multiple mechanisms of action have been proposed for trastuzumab, including inhibition of HER2 receptor dimerization, increased destruction of the endocytic portion of the HER2 receptor, inhibition of extracellular domain shedding, and activation of cell-mediated immune defenses such as ADCC activity. Trastuzumab has not been shown to inhibit the dimerization of HER2 with the other isoforms; therefore, signaling through the other three receptor isoforms is maintained in the presence of the antibody. Studies have supported a mechanism by which trastuzumab is bound to the HER2 receptor and taken up by the target cell through endocytosis and subsequently degrades the receptor leading to a downregulation of downstream survival signaling, cell cycle arrest and apoptosis. Trastuzumab has also been shown to block the cleavage/shedding of the HER2 receptor extracellular domain thereby preventing the formation of the activated truncated p95, which has been correlated with a poor prognosis based on the detection of the released extracellular domain of HER2 in the serum of metastatic breast cancer patients. (4, 5, 6)

Please refer to Dr. Wento Fu's review for BLA 761091 for further details.

4.5.2. Pharmacodynamics

Please refer to Dr. Wento Fu's review for BLA 761091.

4.5.3. Pharmacokinetics

Please refer to Dr. Wento Fu's review for BLA 761091.

5. Sources of Clinical Data

5.1. Tables of Studies/Clinical Trials

A listing of clinical studies applicable to this BLA is provided below in Figure 1.

Figure 1: Listing of Clinical Studies

Type of Study	Study ID	Study Design and Type of Control	Test Product(s); Route of Administration; Dosage Regimen	Objective(s) of the Study	Study Population	Duration of Treatment	Healthy Subjects or Diagnosis of Patients	Study Status; Type of Report
Primary PK Similarity Study	CT-P6 1.5	Phase 1, randomized (1:1), controlled, 2-arm, parallel-group, double-blind, single-dose prospective study in healthy male subjects	Test product: CT-P6 - 6 mg/kg, IV infusion for 90 min (± 5 min) Reference product: US-licensed Herceptin® - 6 mg/kg, IV infusion for 90 min (± 5 min)	**Primary:** To demonstrate similarity of PK in terms of $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$ and C_{max} of CT-P6 to US-licensed Herceptin® over 71 days **Secondary:** To assess additional PK variables, safety and immunogenicity over 71 days	Randomized = 70 CT-P6: 35 US-licensed Herceptin®: 35	Up to Day 71 (Week 10)	Healthy male subjects	Final CSR CSR CT-P6 1.5
Pilot PK Similarity Study	CT-P6 1.4	Phase 1, randomized (1:1), controlled, 2-arm, parallel-group, double-blind, single-dose prospective study in healthy male subjects	Test product: CT-P6 - 6 mg/kg, IV infusion for 90 min Reference product: US-licensed Herceptin® - 6 mg/kg, IV infusion for 90 min	**Primary:** To demonstrate similarity of PK in terms of $AUC_{0\text{-last}}$ and C_{max} of CT-P6 to US-licensed Herceptin® over 42 days **Secondary:** To assess additional PK variables, safety, tolerability and immunogenicity over 42 days	Randomized = 70 CT-P6: 35 US-licensed Herceptin®: 35	Up to Day 42 (Week 6)	Healthy male subjects	Final CSR CSR CT-P6 1.4
Therapeutic Similarity Study	CT-P6 3.2	Phase 3, randomized (1:1), controlled, 2-arm, parallel-group, double-blind, multicenter, international, prospective study in patients with HER2-positive EBC	**Neoadjuvant Period:** Test product: CT-P6 - IV infusion for 90 min (± 5 min) - Loading dose of 8 mg/kg on Day 1 of Cycle 1, and then 6 mg/kg repeated every 3 weeks for 24 weeks (8 cycles) Reference product: US-licensed Herceptin® - IV infusion for 90 min (± 5 min) - Loading dose of 8 mg/kg on Day 1 of Cycle 1, and then 6 mg/kg repeated every 3 weeks for 24 weeks (8 cycles) Chemotherapy Regimen: Docetaxel: - 3-weekly for 12 weeks (Cycles 1-4)	**Primary:** To demonstrate similarity of efficacy in terms of pCR for CT-P6 and US-licensed Herceptin® during surgery after the Neoadjuvant Period (after Cycle 8) **Secondary:** To assess additional efficacy, PK, PD, safety, immunogenicity and biomarker (optional)	Randomized = 562 CT-P6: 278 US-licensed Herceptin®: 284	Until 3 years from the day of enrolment of the last patient	Female patients with a pathologically confirmed, newly diagnosed, operable early breast cancer (Stage I, II, or IIIa)	Ongoing US CSR CT-P6 3.2 (The analysis of PK, PD, efficacy, safety, biomarker and immunogenicity up to 1 year covering Neoadjuvant and Adjuvant Periods) Estimated Follow-up CSR completion date: 4Q 2019

Source: eCTD Module 5, Section 5.2

5.2. Review Strategy

The efficacy and safety review was conducted by Dr. Jennifer Gao and the statistical

review was conducted by Dr. Erik Bloomquist. The clinical review included the following:

1. Literature review of HER2-positive breast and gastric cancer
2. Research of the FDA data base for regulatory history of the CT-P6 IND 119650 and review of meeting minutes conducted during drug development
3. Review of applicant submitted CSR, protocol, protocol amendments, and selected datasets for Study CT-P6 3.2
4. Review of selected case report forms (CRFs) for CT-P6 3.2
5. Review of selected patient narratives for serious adverse events and deaths in CT-P6 3.2
6. Review of response to clinical and biostatistical queries sent to the applicant
7. Review of consultation reports from the Office of Scientific Investigations
8. Review of Herceptin label

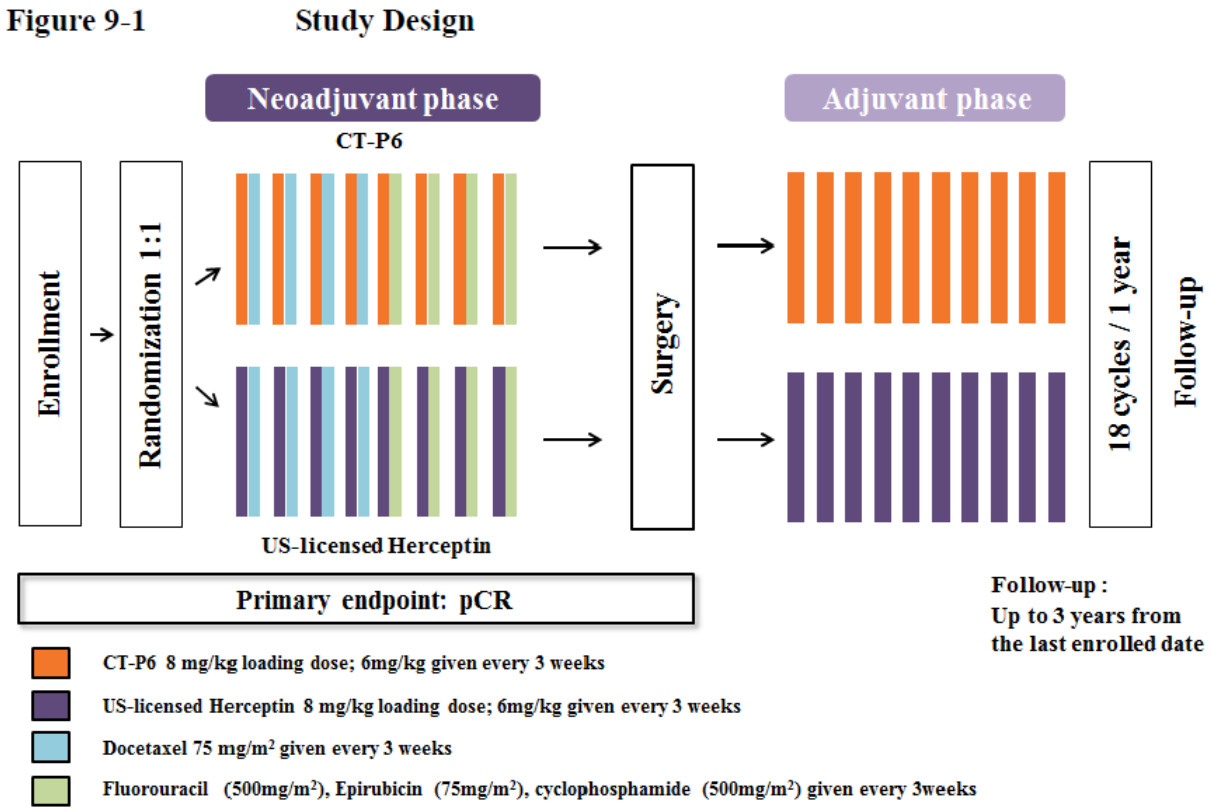
5.3. Discussion of Individual Studies/Clinical Trials

5.3.1. Study Design

Study 3.2 is a double-blind, randomized, parallel-group, clinicalstudy to compare the efficacy and safety of CT-P6 and US-Herceptin in the neoadjuvant and adjuvant treatment of patients with early HER2 positive breast cancer. In the neoadjuvant portion, patients receive 4 cycles of CT-P6 or US-Herceptin plus docetaxel followed by 4 cycles of CT-P6 or US-Herceptin with FEC chemotherapy. In the adjuvant portion, CT-P6 or US-Herceptin is continued to complete 1 year of trastuzumab-based therapy (up to 10 cycles during the adjuvant portion). Patients were randomized 1:1 and stratified by disease stage (stage I or II vs. IIIa), estrogen/progesterone receptor status (positive vs. negative) and country.

The study design is shown in Figure 2 below.

Figure 2: Study 3.2 Design



Source: CT-P6 3.2 Clinical Study Report

Reviewer comment: The design of the comparative clinical study is acceptable. The early breast cancer population studied and the efficacy endpoint of pCR after 8 cycles of neoadjuvant treatment is acceptable and previously agreed upon by the applicant and FDA.

The schedule of activities for study 3.2 is shown in Figure 3 below.

Figure 3: Study 3.2 Schedule of Events

Protocol Number CT-P6 3.2 Protocol Version 3.2 including Country-Specific Amendment 2

Table 12–1 Schedule of Events

Procedure	Screening Period	Neoadjuvant Period[1]					Adjuvant Period[1]				Post-treatment Follow-Up[2]		
		Each 3-week cycle		After Cycle 4	First EOT[3]	During Surgery	Each 3-week cycle		After Cycle 3 and Cycle 6	Second EOT[3]	Every 3 months	Every 6 months	Every 1 year
Evaluation (day)	–21 to 0	1	Before next cycle[4]				1	Before next cycle[4]					
Visit window (days)		±3[5]			±3		±3[5]			±3	±21	±21	±21
Informed consent	X												
Demographic data	X												
Medical history	X												
ECOG performance status	X	X			X		X			X			
Hormone receptor	X[6,7]					X[6,7]							
Tumor marker HER2	X[6,7]					X[6,7]							
Pathological diagnosis	X[8]												
Pregnancy test[9]	X				X		X[10]			X			
Hepatitis B, C and HIV infection	X[11]												
Vital sign and weight	X	X			X		X			X			
Physical examination	X			X[4]	X			X[113]		X			
Hematology[12]	X		X		X			X		X			
Clinical chemistry[12]	X		X		X			X		X			
Urinalysis[12]	X[12]				X								
Inclusion/exclusion criteria	X												
Randomization		X[13]											
Study drug (CT-P6 or US licensed Herceptin)		X					X[14]						
Docetaxel or FEC		X[15]											
Hypersensitivity monitoring[22]		X					X						
Breast surgery						X[16]							
Pathological response						X[17]							
Chest x-ray[18]	(X)				(X)			(X[10])		(X)		(X)	

Procedure	Screening Period	Neoadjuvant Period[1]					Adjuvant Period[1]				Post-treatment Follow-Up[2]		
		Each 3-week cycle		After Cycle 4	First EOT[3]	During Surgery	Each 3-week cycle		After Cycle 3 and Cycle 6	Second EOT[3]	Every 3 months	Every 6 months	Every 1 year
Evaluation (day)	–21 to 0	1	Before next cycle[4]				1	Before next cycle[4]					
Visit window (days)		±3[5]			±3		±3[5]			±3	±21	±21	±21
Sonogram	X			X	X								
Mammogram	X			X	X					X			X[30]
Physical examination on tumor site	X	X			X			X[10]	X[4]	X	X		
CT[19]	X			X	X								
Bone scans[19]	X				X								
Tumor response evaluation[20]				X	X			X[10]	X[4]	X	X		
Immunogenicity testing (central)[21]	X			X[4]	X			X[10]	X[4]	X	X		
PK testing (central)[22]		X			X								
HER2 shed antigen testing (central)[23]		X[31]		X	X								
12-lead electrocardiogram	X			X[4]	X			X[10]	X[4]	X		X[24]	
Echocardiogram or MUGA scan for LVEF	X			X[4]	X			X[10]	X[4]	X		X[24]	
NYHA class[25]	X		X		X			X		X		X[24]	
Concomitant medications[26]	X	X			X		X			X			
Adverse event monitoring[27]	X	X			X		X			X			
Salvage therapy, Survival status[28]					X					X	X		
Biomarker assessment (optional, central)		(X)[29]											

Abbreviations: CT, computerized tomography; FEC, 5-fluorouracil 500 mg/m^2, epirubicin 75 mg/m^2, and cyclophosphamide 500 mg/m^2; ECOG, Eastern Cooperative Oncology Group; EOT, End-of-Treatment, HER2, human epidermal growth factor receptor 2; HIV, human immunodeficiency virus; LVEF, left ventricular ejection fraction; MUGA, multiple-gated acquisition; NYHA, New York Heart Association; PK, pharmacokinetic.

Note: If a study center is not equipped to perform the specified tests, this will be discussed with the sponsor or the sponsor's designee and arrangements will be made to perform the tests centrally.

Note: assessments in parenthesis are optional.

1. The Neoadjuvant Period will have duration of 24 weeks (8 cycles). The Adjuvant Period will have duration of up to 1 year from the first day of study drug administration in the Neoadjuvant Period, excluding surgery (up to 10 cycles after surgery).
2. The Post-treatment Follow-Up Period will last until 3 years from the day of enrollment of the last patient.
3. The End-of-Treatment Visit will be performed 3 weeks after the last administration of study drug. In case of early discontinuation or discontinuation, EOT Visit will be performed 3 weeks after the last administration of study drug.
4. These assessments should be performed within 3 days before Day 1 of the next cycle.
5. Except Cycle 1
6. A biopsy performed within 6 weeks before study drug administration will be used for these assessments. Hormone receptor and HER2 overexpression will also be assessed using tissue obtained from the operation (after the Neoadjuvant Period).
7. HER2 overexpression will be assessed by local laboratory (defined as 3 + score by immunohistochemistry, or a positive fluorescence in situ hybridization or a chromogenic in situ hybridization result when IHC result is equivocal [defined as 2 + score]). Hormone receptor (estrogen and progesterone) status will be assessed by local laboratory. And HER2 overexpression and Hormone receptor status will be evaluated centrally for reporting purpose.
8. Pathological diagnosis will be performed using biopsy sample which will be obtained within 6 weeks before study drug administration. Regional lymph node involvement will be determined by radiograph. To confirm axillary node positivity, biopsy can be performed in certain case by investigator's discretion.
9. For females of childbearing potential only, a serum pregnancy test must be performed at Baseline (within 7 days before starting study drug), at the End-of-Treatment Visit, prior the start of the Adjuvant Period, or at any time if pregnancy is suspected. In the event of a positive serum pregnancy test, a urine pregnancy test should be performed 72 hours later.
10. Cycle 1 only, or if clinically indicated.
11. Hepatitis B surface antigen, Hepatitis B surface antibody, Hepatitis C virus antibody, and HIV-1 and -2 should be assessed at Screening in all patients (mandatory).
12. Hematology, clinical chemistry and urinalysis assessments must be completed within 21 days before Day 1 of Cycle 1 of Neoadjuvant period. Except Cycle 1 of Neoadjuvant period, all laboratory safety assessments must be completed within 3 days before Day 1 of each cycle. Urinalysis will be performed at the Screening Visit and at End-of-Treatment Visit of Neoadjuvant Period only, or if clinically indicated.
13. Randomization will be performed after eligibility is confirmed on Cycle 1, Day 1.
14. Study drug for adjuvant therapy will be administered between 3 to 6 weeks after operation. If a site practice has been established about trastuzumab monotherapy before and after surgery and if the practice has been notified to the sponsor or the sponsor's designee prior to the initiation of study treatment, the schedule of trastuzumab monotherapy could be decided upon investigator discretion.
15. Docetaxel for Cycles 1 to 4, and FEC for Cycles 5 to 8 during Neoadjuvant Period.
16. Breast surgery (lumpectomy or mastectomy) including axillary lymph node assessment (sentinel lymph node biopsy or axillary lymph node dissection) will be performed within 3 to 6 weeks after the last study drug administration of Neoadjuvant Period.
17. A pathological report will be issued locally and the report will be reviewed by the central reviewer for reporting purpose only.
18. Chest x-ray assessments will only be performed at investigator's discretion.
19. Chest and abdomen CT (including adrenal) and bone scan, will be performed within 4 weeks before the start of study drug (to determine stage at Baseline and measurable lesion). CT will be performed after 4th cycle and at the Neoadjuvant Period End-of-Treatment Visit (3 weeks after the start of the last study drug, to make a decision regarding surgery and to assess the response to neoadjuvant treatment). Additionally, bone scan will be performed at EOT_1 if clinically indicated. CT and bone scans will be obtained within 7 days before the next visit.When bone scan is not available at baseline, CT image can replace bone scan image.
20. Tumor response evaluation will be performed until disease progression or recurrence. If a patient has signs/symptoms of central nervous system metastases, a brain CT or magnetic resonance imaging scan should be performed at any time. Chest CT scan, bone scan, thyroid function test, or other radiologic test will be ordered if required according to the clinical symptoms/signs, or biochemical alterations.
21. Immunogenicity test will be performed at Screening, after Cycle 4, and End-of-Treatment Visit in the Neoadjuvant. For Adjuvant Period, immunogenicity test will be done at Cycle 1, Day 1, after Cycle 3, after Cycle 6, and End-of-Treatment Visit. For Follow-up Period, it will be done every 3 months up to 1 year (maximum 4 times). Immunogenicity sample will be transferred to central laboratory.
22. Pharmacokinetic samples will be collected before study drug (CT-P6 or US-licensed Herceptin) administration (within 15 minutes prior to the beginning of the study drug infusion) and within 15 minutes after the end of the study drug infusion for each cycle during the Neoadjuvant Period. After the completion of treatment, an additional PK sample will be collected at the End-of-Treatment Visit. Testing will be performed at the central laboratory.
23. Blood samples for pharmacodynamic assessment will be taken at pre-dose of cycle 1, pre-dose of cycle 5 (within 15 minutes prior to the beginning of the study drug infusion) and the first EOT visit.
24. Up to 2 year (maximum 4 times) during Follow-Up Period. Additional assessments should be performed if clinically indicated (in case of suspicion of reduced LVEF).
25. If a patient has a symptomatic cardiac problem during study period, ECHO or MUGA test will be done by investigator discretion.
26. All medications used during the study, as well as all medications taken within 30 days of Day 1 of Cycle 1 and until 30 days after the last dose of study treatment.
27. Adverse events will be assessed from the date the informed consent form is signed until up to 30 days from last dose of study drug, regardless of the relationship to the study drug. The related adverse events will be followed until one of the following: resolution or improvement from Baseline, relationship reassessed as unrelated, death, start of new anti-cancer regimen, confirmation from the investigator that no further improvement can be expected, end of collection of clinical or safety data, or final database closure.
28. Patients who discontinued early before surgery or discontinued during the Adjuvant Period, or who completed adjuvant treatment will be followed up for disease progression or recurrence, survival status and any salvage treatment (e.g., including chemotherapy, immunotherapy, surgery, radiotherapy, or hormone therapy).
29. Only for patients who sign a separate informed consent form for the biomarker assessment (genotypes). Blood samples for FcγR genotype (FcγRIIa, IIIa, and/or any necessary genotypes) will be collected after enrollment and before study treatment administration on Day 1 of Cycle 1 during the Neoadjuvant Period only. FcγR genotyping will be performed at the central laboratory.
30. During the Post-treatment Follow-Up Period, mammogram will be performed at every 1-year if patients are eligible for measurement.
31. Cycle 1 only.
32. Additional vital signs including systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature will be assessed to monitor for possible hypersensitivity reactions. Hypersensitivity monitoring should be done during first infusion as; before beginning the study drug infusion (within 15 minutes before the beginning of the study drug infusion), at the end of study drug infusion, and every 60 minutes (±15 minutes) until 6 hours after the start of the study drug infusion. In subsequent infusion, it should be monitored as; before beginning the study drug infusion, at the end of study drug infusion, and every 60 minutes over 2 hours after the start of the study drug infusion.

Source: Study 3.2 Protocol Version 3.2 with Country Specific Amendment 2

Reviewer comments: The schedule of activities is appropriate. Cardiac assessment was performed at baseline, after cycles 4 and at end of treatment in the neoadjuvant portion, at the end of cycle 1, 3, 6, and end of treatment at during

the adjuvant portion, and every 6 months during post-treatment follow up. Laboratory, EKG, AE, and PK assessments are also appropriate.

5.3.2. Protocol Amendments

The original protocol (Version 1.0) was dated Nov 11, 2013 and was amended 10 times during the course of the study. Notable amendments and protocol changes pertinent to the United States are briefly summarized below:

- Global protocol amendment Jan 20, 2014 (Version 2.0)
  Trastuzumab monotherapy allowed by investigator discretion, tumor assessments in the adjuvant portion to be optional on C1D1/C3/C6, drug-switching design in adjuvant portion was removed, eligibility for post-treatment follow-up was updated, visit windows for safety assessments specified, cardiac ejection fraction data to be reported to DSMB for independent review
- Country-specific protocol amendment (US) March 18, 2014 (Version 2.2)
  All changes from Global Amendment Version 2.0
- Global protocol amendment Dec 24, 2014 (Version 3.0)
  Inclusion criterion 4 updated to specify breast cancer type, biopsy portion updated, MI added as an example of serious cardiac illness and exclusion criterion, patients with pre-existing peripheral neuropathy excluded, ITT set definition updated to include patients regardless whether or not any study treatment dosing was completed, safety assessments including echo and MUGA added to the data to be reviewed by the ITRC, hypersensitivity monitoring time points added, central assessment of HER2 and hormone receptor status added, pregnancy reporting duration expanded to 7 weeks from last administration of study drug from 6 weeks
- Country-specific protocol amendment (US) December 24, 2014 (Version 3.2)
  All changes from Global Amendment Version 3.0

Reviewer comments: The protocol amendments and changes appear reasonable with no concerning changes. No patients received trastuzumab monotherapy on Study 3.2.

5.3.3. Study Objectives

Primary Objective
To demonstrate similarity of CT-P6 and US-Herceptin in combination with docetaxel (cycles 1-4) followed by 5-fluorouracil, epirubicin and cyclophosphamide (FEC, cycles 5-8) in terms of efficacy as determined by pCR in patients with HER2 positive operable early breast cancer.

Secondary Objectives

- Overall response rate (ORR)
- Disease-free survival (DFS)
- Progression-free survival (PFS)
- Overall survival (OS)

- Breast conservation rate
- pCR of the breast only regardless of DCIS status
- pCR of breast and axillary nodes with absence of DCIS

Reviewer comments: The objectives are appropriate, with pCR after 8 cycles of neoadjuvant treatment an appropriate endpoint and agreed upon by the FDA.

5.3.4. Eligibility Criteria

Inclusion Criteria

1. Patient was a female 18 years of age or older
2. Patient had Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1
3. Patient had histologically confirmed and newly diagnosed breast cancer
4. Patient had clinical Stage I, II, or IIIa operable breast adenocarcinoma according to the American Joint Committee on Cancer (AJCC) Breast Cancer Staging 7th edition
5. At least 1 measurable lesion by RECIST Version 1.1
    a. Tumor lesions: ≥10 mm in long axis by computerized tomography (CT) scan
    b. Malignant lymph nodes: ≥15 mm in short axis when assessed by CT scan
6. Patient had HER2-positive status confirmed locally, defined as 3+ score by immunohistochemistry (IHC). When the IHC result was equivocal (defined as 2+ score), patient had a positive fluorescence in situ hybridization (FISH) or a chromogenic in situ hybridization (CISH) result.
7. Patient had a normal left ventricular ejection fraction (LVEF) (≥55%) at baseline, as determined by either 2-dimensional echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan. If the patient was randomized, the same method of LVEF assessment, ECHO or MUGA, was required to be used throughout the study
8. Patient had known estrogen receptor and progesterone receptor status
9. Patient had adequate bone marrow function, defined as:
    a. Absolute neutrophil count ≥1500/μL
    b. Hemoglobin ≥10.0 g/dL
    c. Platelets ≥100000/μL
10. Patient had adequate hepatic and renal function, defined as:
    a. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × upper limit of normal (ULN)
    b. Total bilirubin ≤1.5 × ULN
    c. Alkaline phosphatase ≤2.5 × ULN
    d. Serum creatinine ≤1.5 mg/dL
11. Patient had the ability to comprehend the full nature and purpose of the study, including possible risks and side effects, to cooperate with the investigator, to understand verbal and/or written instructions, and to comply with the requirements of the entire study.
12. Patient was required to voluntarily sign an IRB/IEC-approved ICF before any study specific procedures.

Exclusion Criteria

1. Patient had bilateral breast cancer
2. Patient was pregnant or lactating
3. Patient had received prior treatment for breast cancer, including chemotherapy, biologic therapy, hormone therapy, immunotherapy, radiation, or surgery, with the exception of diagnostic biopsy for primary breast cancer
4. Patient had received any prior therapy with anthracyclines
5. Patient had other concomitant active malignancy or history of malignancy in the past 5 years except treated basal cell carcinoma of the skin or carcinoma in situ of the cervix
6. Serious cardiac illness or medical conditions that could preclude the use of trastuzumab, specifically: New York Heart Association (NYHA) class ≥2, history of documented congestive heart failure (CHF), myocardial infarction (MI), high-risk uncontrolled arrhythmias, angina pectoris requiring medication, clinically significant valvular disease, evidence of transmural infarction on electrocardiogram (ECG), poorly controlled hypertension
7. Patient had a current history of infection with hepatitis B, hepatitis C, or infection with human immunodeficiency virus, or had a positive result to the screening test for those infections
8. Patient had any recent infection requiring a course of systemic anti-infectives that were completed ≤14 days before randomization (with the exception of uncomplicated urinary tract infection)
9. Patient was a woman of childbearing potential who did not consent to use highly effective methods of birth control (e.g., intra-uterine device, barrier methods including condom and diaphragm, also in conjunction with spermicidal jelly, or total abstinence; oral, injectable, or implant hormonal contraceptives were not acceptable) during treatment and for an additional 7 months after the last administration of the protocol-specified treatment
10. Patient was currently receiving treatment with another investigational device or medical product, or less than 30 days or 5 half-lives, whichever was longer, spanned since ending treatment with another investigational device or medical product.
11. Patient had known sensitivity to any of the products to be administered during the study, including mammalian cell derived drug products, trastuzumab, and murine proteins, or to any of the excipients
12. Patient had previously participated in this study
13. Patient was likely not to be available to complete all protocol-required study visits or procedures
14. Patient had history or evidence of any other clinically significant disorder, condition, or disease (with the exception of those outlined above) that, in the opinion of the investigator, would pose a risk to patient safety or interfere with the study evaluation, procedures, or completion
15. Patient had pre-existing, clinically significant (>Grade 1 by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Version 4.03) peripheral neuropathy.

Reviewer comments: The inclusion and exclusion criteria are appropriate.

5.3.5. Drug Administration

Neoadjuvant Portion
CT-P6 or US-Herceptin: loading dose of 8 mg/kg body weight on C1D1, and then 6 mg/kg body weight every 3 weeks from cycles 2-8. The drug was administered as a 90 minute IV infusion with an infusion pump.

Docetaxel: given immediately after the study drug on day 1 of each cycle and repeated every 3 weeks for a total of 4 cycles (cycles 1-4) at a dose of 75 mg/m2 as a 1 hour IV infusion using a single injection using an infusion bag containing 250 mL of 5% glucose solution or 0.9% sodium chloride solution. Patients were pre-medicated with oral corticosteroids.

FEC: was given immediately after study drug on day 1 of each cycles from cycles 5-8 every 3 weeks. Fluorouracil was administered at 500 mg/m2 as a 3-5 min IV bolus or as an infusion over 30 minutes using an infusion bag containing 500 mL of 5% glucose solution or 0.9% sodium chloride solution. Epirubicin was administered at 75 mg/m2 as a 3-5 min IV bolus or as an infusion over 30 min using an infusion bag containing 5% glucose solution or 0.9% sodium chloride solution. Cyclophosphamide was administered at 500 mg/m2 as an IV bolus over 3-5 min dissolved in 25mL of 0.9% sodium chloride solution.

Adjuvant Portion
CT-P6 or US-Herceptin was administered every 3 weeks at 6 mg/kg for up to 10 cycles after surgery to complete 1 year of a trastuzumab product.

5.3.6. Dose Modifications

- Trastuzumab: for infusion reactions, the infusion rate should be decreased or the infusion should be temporarily interrupted. For cardiac dysfunction, trastuzumab might either be held or discontinued and consultation with a cardiologist might be warranted.
- Docetaxel and/or FEC: dose reductions to 50% or 75% of the previous dose were permitted for neutropenia, thrombocytopenia, and febrile neutropenia. Dose reductions for non-hematologic toxicities were to be managed as per local practice.

5.3.7. Statistical Analysis Plan

The primary efficacy endpoint of this trial was pCR, defined as the absence of invasive tumor cells in the breast and in axillary lymph nodes, regardless of DCIS. The pCR was determined at the time of surgery, using hematoxylin and eosin evaluation of the resected breast specimen. The applicant used the 90% asymptotic confidence region of the ratio of pCR in the CT-P6 arm vs. the US-Herceptin arm as the primary analysis

strategy. The primary analysis population was the per-protocol set (those without major protocol violations); the intention to treat population was used for supportive purposes.

The study was deemed successful if the 90% confidence region for the ratio was entirely contained with the interval (0.75, 1.35). To obtain this interval, the applicant reviewed 6 study control arms to obtain pCR rates for the control arm and 4 study treatment arms to obtain pCR rates for the treatment arms. The overall pCR rate for their control arm was estimated to be 15.9% (14 – 18%), and the overall pCR rate for their treatment arm was estimated to be 53.7% (38-70%). Using a 50% retention rate, the sponsor derived their equivalence margin for the ratio.

The applicant sized their study to achieve 80% power for the primary endpoint. The sponsor found that 266 patients per arm would provide sufficient power and account for a 10% dropout.

The primary pCR data was reviewed by a blinded central committee as a sensitivity analysis. Note that only pathology reports were sent to the blinded central committee, so the agreement was 100% between the local pathology and central pathology.

Key secondary endpoints included radiological endpoints such as overall response rate using RECIST v1.1 criteria and PFS. Overall survival was also a key secondary endpoint. For the radiological endpoints, scans were done in the neoadjuvant and adjuvant periods. The local investigator determined whether an individual had a response or progression event. A central review committee was used a reviewed the radiological images and made determinations of ORR and PFS for sensitivity purposes.

The statistical analysis plan had four versions. Significant changes include a change from the risk difference to risk ratio, the use of a 90% confidence interval instead of a 95% confidence interval for the primary analysis, and the use of the per protocol population for the primary analysis.

Reviewer Comments: The applicant's equivalence margin is acceptable to demonstrate equivalence. The statistical analysis plan and sample size is appropriate. The changes to the statistical analysis plan are acceptable.

5.3.8. Charter and SOP Review

Blinding

The applicant confirmed in their response to the July 24, 2017 IR that study site personnel, including local pathologists, were blinded to the treatments in study 3.2 and the randomization codes. Treatment group information will not be revealed to patients, investigators, local pathologists, or any other blinded site staff until all final clinical data from the neoadjuvant, adjuvant, and post-treatment follow-up portions have been entered into the database and the databased is locked and released for analysis.

Imaging Review Charter

(b) (4) worked in conjunction with Celltrion for contracting with the sites to provide imaging and clinical data. (b) (4) provided the imaging analysis and specifically, imaging protocol recommendations development, imaging charter development, image site qualification, image site initiation, image site management, image processing services, project management, radiological consultation, image analysis, and quality control. The Imaging Review Charter (IRC) discusses the CT, MRI, echo/MUGA scans that were conducted for study 3.2 and the standardized processes for image acquisition, transfer, receipt, and evaluation that (b) (4) followed. (b) (4) received image data sent by imaging sites via AG Mednet or courier. Tumor assessments were performed using RECIST version 1.1 criteria using a dual reader with adjudication paradigm. Echo/MUGA images were performed using single reader paradigm. An independent (b) (4) pathologist reviewed the pathology report generated by the site local pathologist of the resected breast tissue for determination of pCR. The independent (b) (4) pathologist did not review the slides themselves. Image interpretation was carried out by trained reviewers such as radiologists, nuclear medicine physicians, and cardiologists.

6. Review of Efficacy

Efficacy Summary

Study 3.2, together with other information in the application, supports the determination of no clinically meaningful differences between CT-P6 and the US-Herceptin (discussed in Section 5.3). Specifically, the 90% confidence interval for the pCR ratio between CT-P6 and EU-Herceptin in Study 3.2 is within the equivalence margin.

6.1. Indication

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

6.2. Methods

Similarity in clinical efficacy was assessed in Study 3.2 comparing CT-P6 with US-Herceptin in patients with early breast cancer. The primary efficacy analysis population is the per protocol set (PPS) as agreed upon with the FDA at the March 21, 2017 meeting. The primary efficacy analysis was based on the pCR rate at the time of surgery, as assessed locally, after completing 8 cycles of neoadjuvant treatment in the PP population. Sensitivity analyses were performed as appropriate. Recalculating of the primary and secondary efficacy endpoints was conducted from the submitted datasets. Analyses of the primary endpoint, secondary endpoints, and safety are included in this review.

6.3. Demographics

This was an international study with a total of 504 patients in the PPS population enrolled in 22 different countries (Table 2).

Table 2: Study 3.2 Enrollment by Country, PPS Population

Country	CT-P6 n=248	US-Herceptin n=256
Argentina	1	2
Bosnia and Herzegovina	0	1
Belarus	25	26
Chile	6	2
Spain	0	1
France	0	1
Georgia	26	28
Hungary	2	1
India	13	10
Italy	1	2
Japan	14	14
Latvia	3	2
Mexico	2	3
Peru	3	3
Philippines	17	16
Poland	11	14
Portugal	1	0
Romania	17	14
Russia	72	77
Taiwan	4	3
Ukraine	26	31
South Africa	4	5

Source dataset: adsl.xpt

Reviewer Comments: The top five countries for enrollment were Russia, Belarus, Ukraine, Georgia, and Philippines. There were no patients enrolled from the United States.

The demographic characteristics of the PPS population are shown in Table 3 below.

Table 3: Study 3.2 Demographic Characteristics, PPS Population

	CT-P6 n=248	US-Herceptin n=256
Age		
Mean	51.75	51.9
SD	10.9	10.2
Median	53	52
Range	28-78	24-74
Age Range		
<50	98	106
≥50	150	150
ECOG		
0	218	231
1	30	25
Race		
American Indian or Alaskan Native	1	1
Asian	48	44
Black or African American	1	4
White	189	198
Unknown	9	9
Region		
America	12	10
Asian	48	43
EMEA	188	203
ER		
Positive	143	143
Negative	105	113
PR		
Positive	105	101
Negative	143	155
Disease Stage		
Stage I	20	30
Stage IIA	69	78
Stage IIB	101	94
Stage IIIA	58	54

Source dataset: adsl.xpt

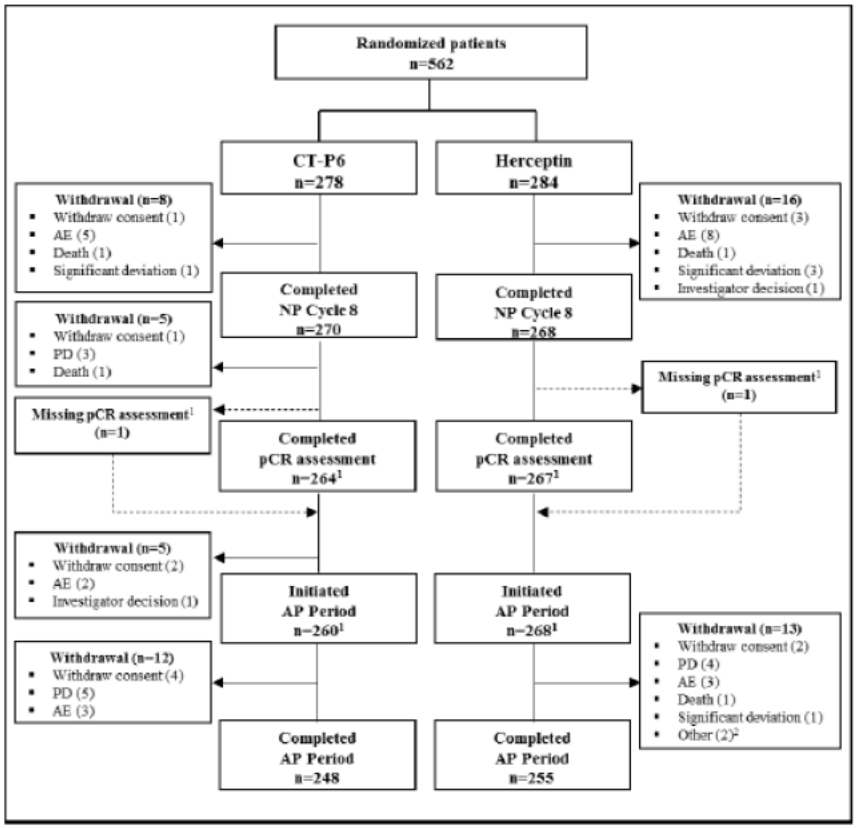
Reviewer Comments: Baseline patient demographics were well balanced

between the two arms. All patients were female and a majority of patients were Caucasian and had stage IIB disease at baseline. African American patients represent ~ 15% of the US population and are underrepresented in this study. However, this does not impact our conclusion that the study supports a finding of no clinically meaningful differences.

6.4. Subject Disposition

A total of 562 patients were randomized, 278 to CT-P6 and 284 to US-Herceptin. A total of 264 patients in the CT-P6 arm and 267 patients in the US-Herceptin arm completed pCR assessment. A total of 248 patients in the CT-P6 and 255 patients in the US-Herceptin arm completed treatment in the adjuvant portion. The overall patient disposition for study 3.2 is shown below in Figure 4.

Figure 4: Study 3.2 Overall Patient Disposition



Abbreviations: AE, adverse event; AP, Adjuvant Period; LVEF, left ventricular ejection fraction; NP, Neoadjuvant Period; pCR, pathological complete response; PD, progressive disease.

1. Patients (b) (6) in the US-licensed Herceptin treatment group and (b) (6) in the CT-P6 treatment group performed the surgery and initiated the Adjuvant Period. However, pCR assessments were not available due to lost pathological samples, therefore, they were not counted as they completed pCR assessment.
2. Patient (b) (6) permanently discontinued the study treatment as she relocated and was no longer able to visit the site. Patient (b) (6) delayed the study drug administration due to low LVEF and recovered LVEF (50%), however, was permanently discontinued the study treatment as she was not able to visit the site within the visit window due to family reasons.

Source: Study 3.2 CSR Page 119

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

Table 4 below lists the patient disposition for the PPS, which was the primary population set used for the primary endpoint of pCR. Of note patients with major protocol deviations were excluded from the PPS as per the statistical analysis plan (SAP).

Table 4: Study 3.2 Per-Protocol Set Patient Disposition

	CT-P6 (N=248)	US-licensed Herceptin® (N=256)	Total (N=504)
	Number (%) of patients		
Total number of patients			
Screened[1]			781
Screening failure reason[2]			219
Inclusion/exclusion criteria not met			199 (90.9)
Patient withdrew consent			12 (5.5)
Other			8 (3.7)
Randomized	248 (100.0)	256 (100.0)	504 (100.0)
Initiated Neoadjuvant Period	248 (100.0)	256 (100.0)	504 (100.0)
Completed Neoadjuvant Period (including pCR assessment)	248 (100.0)	256 (100.0)	504 (100.0)
Discontinued Neoadjuvant Period	0	0	0
Missing pCR assessment	0	0	0
Did not initiate Adjuvant Period after surgery	5 (2.0)	0	5 (1.0)
Initiated Adjuvant Period	243 (98.0)	256 (100.0)	499 (99.0)
Completed Adjuvant Period	233 (94.0)	243 (94.9)	476 (94.4)
Discontinued Adjuvant Period	10 (4.0)	13 (5.1)	23 (4.6)
Initiated Follow-up Period	2 (0.8)	3 (1.2)	5 (1.0)
Primary reason for treatment discontinuation after surgery (Did not initiate Adjuvant Period after surgery)			
Patient withdrew consent to continue study treatment	2 (0.8)	0	2 (0.4)
Adverse event that, in the opinion of the investigator, precludes further participation in the study[3]	2 (0.8)	0	2 (0.4)
Investigator's decision[4]	1 (0.4)	0	1 (0.2)
Primary reason for treatment discontinuation (Adjuvant Period)			
Patient withdrew consent to continue study treatment	4 (1.6)	2 (0.8)	6 (1.2)

	CT-P6 (N=248)	US-licensed Herceptin® (N=256)	Total (N=504)
	Number (%) of patients		
Progressive disease	5 (2.0)	4 (1.6)	9 (1.8)
Adverse event that, in the opinion of the investigator, precludes further participation in the study[5]	1 (0.4)	3 (1.2)	4 (0.8)
Patient died[6]	0	1 (0.4)	1 (0.2)
Significant deviation from the treatment plan specified in the protocol[7]	0	1 (0.4)	1 (0.2)
Other[8]	0	2 (0.8)	2 (0.4)
Reason for ending study participation			
Patient withdrew consent to continue study participation including follow-up assessments	3 (1.2)	0	3 (0.6)
Death	0	2 (0.8)	2 (0.4)

Abbreviations: pCR, pathological complete response.

1. This included screening failures and randomized patients. If a patient was screened, randomized and included in the PPS, the treatment assignment was displayed in the "randomized" row.
2. Number of patients who failed screening was used as a denominator.
3. Patients (b) (6) and (b) (6) in the CT-P6 treatment group did not initiate the Adjuvant Period due to adverse events (1 case each of ejection fraction decreased).
4. Patient (b) (6) in the CT-P6 treatment group did not initiate the Adjuvant Period as the investigator evaluated that tumor response was not sufficient.
5. Patient (b) (6) in the CT-P6 treatment group were discontinued due to adverse events (1 case of ejection fraction decreased). Patients (b) (6) in the US-licensed Herceptin® treatment group were discontinued due to adverse events (1 case each of humerus fracture, ejection fraction abnormal, and congestive cardiomyopathy).
6. Patient (b) (6) in the US-licensed Herceptin® treatment group died due to aortic dissection.
7. Patient (b) (6) in the US-licensed Herceptin® treatment group was discontinued as Adjuvant Period Cycle 8 was administrated out of window visit.
8. Patient (b) (6) in the US-licensed Herceptin® treatment group was discontinued as she relocated and was no longer able to visit the site. Patient (b) (6) in the US-licensed Herceptin® treatment group delayed the study drug administration due to low LVEF and recovered LVEF (50%), however, was permanently discontinued as she was not able to visit the site within the visit window due to family reasons.

Note: Unless otherwise stated, percentage denominator was number of patients in the PPS.

Source: IR Response 8/14/17

Reviewer Comments: The PPS was the population used for efficacy analysis for the primary endpoint as agreed upon with the FDA. All patients completed the neoadjuvant portion. The majority of patients initiated and completed the adjuvant portion. The patients that discontinued prior to end of the adjuvant portion are few and unlikely to impact the overall efficacy analysis results.

Table 5 below lists the number of patients for each of the different analysis populations for Study 3.2.

Table 5: Analysis Populations for Study 3.2

	CT-P6 n=278	US-Herceptin n=284
All randomized patients	278 (100)	284 (100)
ITT population	278 (100)	284 (100)
PPS population	248 (89.2)	256 (90.1)
Safety population	271 (97.5)	278 (97.9)

Source: information from Study 3.2 Adjuvant CSR Synopsis Page 4
ITT=intent-to-treat; PPS=per protocol set

Reviewer Comments: As agreed upon with the FDA, the primary efficacy analysis was performed using the PPS population.

Protocol Violations/Deviations

The PPS population excluded all patients with major protocol deviations. Major protocol deviations for the ITT set are listed below in Table 6. The majority were due to patients who did not receive all doses of study treatment during the neoadjuvant portion or discontinued treatment early. One patient in the CT-P6 arm and 3 patients in the US-Herceptin arm discontinued early as they did not fully meet all the eligibility criteria.

Table 6: Study 3.2 ITT Set Major Protocol Deviations

Table 10-2 Major Protocol Deviations: Intent-to-Treat Set

	CT-P6 (N=278)	US-licensed Herceptin (N=284)	Total (N=562)
	Number (%) of patients		
Patients with at least 1 major protocol deviation	**30 (10.8)**	**28 (9.9)**	**58 (10.3)**
Misrandomizations	1 (0.4)	0	1 (0.2)
Patients who do not fully comply with inclusion or exclusion criteria[1]	4 (1.4)	4 (1.4)	8 (1.4)
Patients who have a missing primary efficacy assessment during surgery	5 (1.8)	3 (1.1)	8 (1.4)
Patients who have not received all doses of study treatment during Neoadjuvant Period or discontinued early[1]	13 (4.7)	18 (6.3)	31 (5.5)
Patients who have received any prohibited therapies	2 (0.7)	0	2 (0.4)
Patients with nonadherence to regulatory regulations or ICH E6(R1) guidelines (ICH 1996)	7 (2.5)	6 (2.1)	13 (2.3)

Abbreviation: ICH, International Conference for Harmonisation.
1. One patient (Patient (b) (6)) in the CT-P6 treatment group and 3 patients (Patients (b) (6) (b) (6)) in the US-licensed Herceptin treatment group were discontinued early as inclusion or exclusion criteria were not fully complied.

Source: Study 3.2 Adjuvant Portion CSR Page 126

Reviewer Comments: Few patients from the ITT set had major protocol deviations and these patients were all excluded in the PPS, which was the primary population used for efficacy analyses as agreed upon with the FDA.

6.5. Analysis of Primary Endpoint

Pathological complete response (pCR), assessed locally, was the primary analysis endpoint for this trial. The sponsor estimated the 90% confidence interval of the pCR rate ratio (CT-P6 to US-Herceptin.) The results of the primary analysis are shown in Table 7. The results demonstrate that the 90% confidence interval for the pCR response rate ratio fell entirely inside the pre-defined equivalence margin (0.75, 1.35), thus Study 3.2 met its primary endpoint. As a sensitivity analysis, the 95% confidence interval also fell within the pre-defined equivalence margin. In addition, the risk difference fell within the interval (-15%, 15%), which was an earlier equivalence margin used by the sponsor.

The results of the primary endpoint in the ITT population are shown in Table 8. The results are very similar to those seen in the per-protocol population. Note that the risk ratio confidence interval (both the 90% and 95%) fell within the predefined equivalence margins.

Reviewer Comment: The trial met its primary objective of showing equivalence of the pCR rates. Additional sensitivity analyses further support the equivalence of the pCR rates.

Table 7: Study 3.2 Pathological Complete Response (pCR) in Per Protocol Population

	CT-P6 N=248	**US-Herceptin N=256**
Responders	116	129
Response rate	46.8%	50.4%
95% CI	40.4% - 53.2%	44.1% - 56.7%
Response rate difference (CT-P6 – US-Herceptin)	-3.6%	
95% CI	(-12.7% - 5.5%)	
Response rate ratio (CT-P6/US-Herceptin)	0.928	
90% CI*	(0.798 – 1.080)	
95% CI	(0.775 – 1.111)	

**The 90% CI for the response rate ratio served as the primary analysis strategy. The predefined equivalence margin was that the 90% CI would be entirely contained within (0.75, 1.35). The other results are presented to support the primary analysis strategy. Source CSR Table 11-7.*

Table 8: Study 3.2 Pathological Complete Response (pCR) in ITT Population

	CT-P6 N=278	**US-Herceptin N=284**
Responders	120	134
Response rate	43.2%	52.8%
95% CI	(37.2% - 49.2%)	(41.2% - 53.2%)
Response rate difference (CT-P6 – US-Herceptin)	-4.0%	
95% CI	(-12.6% - 4.6%)	
Response rate ratio (CT-P6/US-Herceptin)	0.915	
90% CI	(0.785 – 1.066)	
95% CI	(0.762 – 1.098)	

Source: CSR Table 11-9

Secondary Endpoints

Key secondary endpoints include overall response rate, progression-free survival (PFS), and overall survival (OS). Overall response rate data is presented in Table 9. The results demonstrate that the two arms have very similar response rates, i.e. within 1-2% of each other. PFS and OS data are presented in Table 10. Since this is a non-metastatic setting, progression and death events are very limited. Nevertheless, the data do not show a difference in either progression rate or overall survival rate.

Table 9: Study 3.2 Overall Response Rate in per-protocol population

	CT-P6 N=248	US-Herceptin N=256
Local Investigator		
Responders (PR + CR)	209	215
Response rate	84.2%	84.0%
95% CI	(79.1% - 88.6%)	(78.9% - 88.3%)
Central Review Committee		
Responders (PR + CR)	219	229
Response Rate	88.3%	89.5%
95% CI	83.6% - 92.0%	85.0% - 92.9%

CR = complete response, PR = partial response. Source: CSR Table 11-7

Table 10: Study 3.2 Progression and Survival Events in per-protocol population

	CT-P6 N=248	US-Herceptin N=256
Progression Events	6 (2.4%)	5 (2.0%)
Deaths since randomization	2 (0.8%)	2 (0.7%)

Source: Reviewer's analysis

Reviewer Comments:

The secondary endpoints are very similar between the two arms. The results further support the equivalence of CT-P6 to US-Herceptin.

6.6. Subpopulations

Subgroup analyses of ORR

Subgroup analyses of pCR were done in demographic subgroups and important clinical subgroups. As shown in Table 11, the 90% CIs of the pCR ratio include 1.

Table 11: FDA Subgroup Analyses of pCR in the Per-Protocol Population

	CT-P6	EU-Herceptin	pCR Ratio (90% CI)
Age			
<65 (N=441)	46.3%	49.8%	0.93 (0.79 – 1.10)
≥65 (N=63)	50.0%	54.3%	0.92 (0.62 – 1.38)
Region			
EMEA (N=391)	47.9%	51.7%	0.93 (0.78 – 1.09)
Asia (N=91)	43.7%	44.2%	0.99 (0.67 – 1.46)
Race			
White (N=387)	47.6%	52.0%	0.915 (0.77-1.08)
Asian (N=92)	43.7%	43.2%	1.01 (0.68-1.50)
Disease Stage			
Stage I (N=50)	65.0%	46.7%	1.39 (0.92 – 2.12)
Stage IIA/IIB (N=342)	48.2%	56.4%	0.86 (0.72 – 1.01)
Stage IIIA/IIIB (N=112)	36.2%	33.3%	1.09 (0.71 – 1.66)
Menopausal Status			
Post- (N=275)	47.3%	52.8%	0.90 (0.74 – 1.09)
Pre-[a] (N=205)	46.1%	46.5%	0.99 (0.77 – 1.27)
Progesterone/Estrogen Receptor Status			
Positive[b] (N=299)	39.6%	40.7%	0.97 (0.77 – 1.23)
Negative[c] (N=205)	57.6%	64.2%	0.90 (0.74 – 1.08)

[a] *Pre-menopausal was defined as the ability to potentially bear children.* [b] *Positive was ER+ or PR+.* [c]*Negative was both PR- and ER-. Source: Reviewer's analysis, dataset: adbspr.xpt*

Reviewer Comments:
In the exploratory subgroup analyses, there is not strong evidence that any subgroup differs from the overall results.

6.7. Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable to this application.

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

With only 6 events in the CT-P6 arm and 5 progression events in the US-Herceptin arm, there does not appear, at this point, to be any difference in disease progression between CT-P6 and US-Herceptin. Longer follow-up data (3-5 years) on overall survival should be provided post-approval.

6.9. Additional Efficacy Issues/Analyses

No additional issues.

7. Review of Safety

Safety Summary

Study 3.2., along with other information in the application, support a determination of no clinically meaningful differences between CT-P6 and US-Herceptin. The safety analyses in Study 3.2, which compared CT-P6 and US-Herceptin in HER2 positive breast cancer patients treated in the neoadjuvant and adjuvant settings, did not show any meaningful differences in safety between arms.

7.1. Methods

7.1.1. Studies/Clinical Trials Used to Evaluate Safety

The safety evaluation for this application is based on the neoadjuvant and adjuvant study portions of study 3.2. Details of the design for 3.2 are presented in Section 5. Key features of two additional PK similarity studies utilizing CT-P6 (study 1.4 and 1.5) are summarized in Section 5.1. Efficacy results for 3.2 are presented in Section 6.

The applicant is seeking approval of CT-P6 for the same indications as US-Herceptin: 1) adjuvant and metastatic treatment of patients with HER2 positive breast cancer and 2) HER2 positive metastatic gastric adenocarcinoma.

Study 3.2 is the primary study used for the overall safety assessment of CT-P6. There is no pooling of safety data.

The safety assessments for 3.2 are adequate. There was particular attention to assessment of cardiac adverse events (AEs) due to the known cardiac effects of trastuzumab. Echocardiography or MUGA to assess for LVEF was performed at baseline. During the neoadjuvant portion, LVEF assessment was done after cycle 4 and at the first end of treatment visit at the conclusion of the neoadjuvant portion. During the adjuvant portion, LVEF was assessed at the end of cycle 1, after cycle 3 and cycle 6, and at the second end of treatment visit at the conclusion of the adjuvant portion. During the post-treatment follow up, LVEF was assessed every 6 months. Patients also received LVEF assessments if they developed signs and/or symptoms of left ventricular dysfunction. Echo or MUGA images were transmitted to independent reviewers, who evaluated LVEF, LV end-systolic diameters, LV end-diastolic diameter, and wall motion abnormalities. A patient was withdrawn from the study if LVEF decreased by 10% from baseline and had an absolute value below 50% if a repeat assessment done within 3 weeks of the first assessment using the same method confirmed the findings.

Patients were assessed using New York Heart Association criteria (NYHA) at screening, end of cycle 1 in both the neoadjuvant and adjuvant portions, and at the end of treatment visit at the neoadjuvant and adjuvant portions. During the post-treatment follow up portion, patients were assessed every 6 months. Patients were taken off study if they developed NYHA class III or IV cardiac dysfunction. Patients were excluded if they had class II or greater cardiac condition at screening.

7.1.2. Categorization of Adverse Events

The applicant defined an adverse event as any untoward medical occurrence in a patient enrolled (i.e. when the ICF was signed) into study 3.2 regardless of its causal relationship to the study treatment.

A treatment-emergent adverse event (TEAE) was defined as any event not present before exposure to the study drug or any event already present that worsened in intensity or frequency after exposure to the study drug. Only clinically significant cases of laboratory test abnormalities were considered TEAEs, defined as resulting in discontinuation from the study, requiring any therapeutic intervention, required further diagnostic evaluation (excluding a repetition of the same procedure to confirm the abnormality), dose modification or delay, associated with clinical signs/symptoms judged by the investigator to have a significant clinical impact.

A serious adverse event (SAE) was defined as any untoward medical occurrence that at any dose resulted in death, is life-threatening, resulted in persistent or significant disability/incapacity, is a congenital anomaly, is an important medical event, or requires inpatient hospitalization or prolongation of existing hospitalization.

AEs were assessed from the date the ICF was signed until 30 days from the last dose of study drug. Between 30 days after the last study drug and the end of the study, only related AEs and cardiac AEs were reported.

Adverse events of special interest include heart failure during the study and up to 12 months after the last administration of study drug, symptomatic LV systolic dysfunction, and all infusion related reactions.

Patients were asked non-leading questions at each study visit to elicit any changes in their well-being. AEs were documented in the AE page of the eCRF. The Medical Dictionary for Regulatory Activities Version 18.1 was used to code all AEs. AEs were graded for severity using the National Cancer Institute Common Terminology criteria for Adverse Events (NCI CTCAE) version 4.03. Medical history and AEs were summarized by MedDRA primary system organ class (SOC) and preferred term (PT).

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

There was no pooling as there was only one comparative clinical study.

7.2. Adequacy of Safety Assessments

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

The safety population consisted of 549 patients, 271 in the CT-P6 and 278 in the US-Herceptin arms and is defined as all patients who received at least 1 dose of study drug in any amount. The 13 patients from the non-GCP compliant site 2302 were excluded from the safety population as the actual treatment given to these patients could not be confirmed.

Table 12 below lists the exposure to the study drug for the neoadjuvant and adjuvant portions of study 3.2. The study drug was given as a 8 mg/kg loading dose and then 6 mg/kg every 3 weeks.

Table 12: Safety Population Study Drug Exposure for Study 3.2

	CT-P6 n=271	US-Herceptin n=278
Neoadjuvant Portion		
Mean	441.2	446.3
SD	103.1	101.8
Median	426	436.8
Range	239.4-992	258-960
Adjuvant Portion		
Mean	421.6	427.5
SD	85.9	86
Median	409.8	420
Range	252-737.1	250.2-720

Source dataset: ADEX.xpt

Reviewer Comments: The exposure was well balanced between the two arms in the neoadjuvant and adjuvant portions.

The safety population consisted of all patients who received at least 1 dose of CT-P6 or US-Herceptin in any amount. Thirteen patients who enrolled in site 2302 which violated GCP were excluded because actual treatment could not be confirmed. An overview of the demographics of this population is presented in Table 13 below.

Table 13: Safety Population Demographic Overview for Study 3.2

		CT-P6 n=271	US-Herceptin n=278
Age			
	Mean	51.8	52.1
	SD	11	10.5
	Median	53	53
	Range	24-78	22-74
Age Range			
	<50	108 (39.9)	112 (40.3)
	≥50	163 (60.1)	166 (59.7)
ECOG			
	0	239 (88.2)	250 (89.9)
	1	32 (11.8)	28 (10.1)
Race			
	American Indian or Alaskan Native	1 (0.4)	1 (0.4)
	Asian	51 (18.8)	48 (17.3)
	Black or African American	2 (0.7)	5 (1.8)
	White	207 (76.4)	214 (77.0)
	Unknown	10 (3.7)	10 (3.6)
Region			
	America	12 (4.4)	10 (3.6)
	Asian	50 (18.5)	46 (16.5)
	EMEA	209 (77.1)	222 (79.9)
ER Status			
	Positive	154 (56.8)	154 (55.4)
	Negative	117 (43.2)	124 (44.6)
PR Status			
	Positive	112 (41.3)	108 (38.8)
	Negative	159 (58.7)	170 (61.2)
Disease Stage			
	Stage I	23 (8.5)	31 (11.2)
	Stage IIA	75 (27.7)	86 (30.9)
	Stage IIB	105 (38.7)	98 (35.3)
	Stage IIIA	64 (23.6)	61 (21.9)
	Stage IIIB	1 (0.4)	0 (0.0)
	Stage IIIC	3 (1.1)	1 (0.4)
	Stage IV	0 (0.0)	1 (0.4)

Source dataset: ADSL.xpt

Reviewer Comments: The demographics for the safety population are well balanced. There were 13 patients excluded from the safety analysis population because their actual treatment could not be confirmed, as agreed upon with the FDA.

7.2.2. Explorations for Dose Response

Not applicable.

7.2.3. Special Animal and/or In Vitro Testing

Not applicable.

7.2.4. Routine Clinical Testing

The schedule of safety evaluations for study 3.2 was described in Appendix 12.1 Schedule of Events (page 111-114) of study 3.2 protocol version 3.2 including country-specific amendment 2 (Dec 24, 2014) (refer to Figure 3 above). The frequency of monitoring was considered adequate within the context of the study. Cardiac assessments were adequate

7.2.5. Metabolic, Clearance, and Interaction Workup

Not applicable.

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

Not applicable.

7.3. Major Safety Results

Table 14 below is a summary of the treatment-emergent adverse events (TEAEs). TEAEs occurred in both arms and in both the neoadjuvant and adjuvant portions of the trial. More TEAEs occurred during the neoadjuvant portion with concomitant chemotherapy than during the monotherapy adjuvant portion.

Table 14: Summary of TEAEs for Study 3.2

	Neoadjuvant Portion		Adjuvant Portion	
	CT-P6 n=271	US-Herceptin n=278	CT-P6 n=271	US-Herceptin n=278
All grade TEAEs	255 (94.1)	264 (95.0)	139 (51.3)	147 (52.9)
All grade TEAEs related to study drug	112 (41.3)	129 (46.4)	50 (18.5)	63 (22.7)
Grade 3-5 TEAEs	98 (36.2)	106 (38.1)	10 (3.7)	17 (6.1)
Serious TEAEs	19 (7.0)	22 (7.9)	3 (1.1)	12 (4.3)
Permanent study drug discontinuation	7 (2.6)	9 (3.2)	2 (0.7)	4 (1.4)
Deaths	2 (0.7)	1 (0.4)	0 (0.0)	1 (0.4)

Source dataset: adae.xpt

Reviewer Comments: More TEAEs were reported during the neoadjuvant portion compared to the adjuvant, which is likely attributable to concomitant chemotherapy. The TEAEs were well balanced overall between the two arms in each portion with no concerning safety findings.

7.3.1. Deaths

The number of deaths in each treatment group during the neoadjuvant and adjuvant portions are shown in Table 15 below. Deaths that occurred during the post-treatment portion are discussed in Section 7.7.

Table 15: Deaths on Study 3.2

Neoadjuvant Portion			
Subject ID	Treatment Arm	Study Drug Action	Study Drug Relation
(b) (6)	US-Herceptin	Permanently Discontinued	Possible
	CT-P6	Permanently Discontinued	Unrelated
	CT-P6	Permanently Discontinued	Unrelated
Adjuvant Portion			
Subject ID	Treatment Arm	Study Drug Action	Study Drug Relation
(b) (6)	US-Herceptin	Permanently Discontinued	Unrelated

Source dataset: adae.xpt, adsl.xpt

The narratives for these patients were reviewed and showed the following:

- (b) (6): 67-year-old white female assigned to US-Herceptin. She was diagnosed with breast cancer (b) (6). She only received one dose of study drug on (b) (6). On (b) (6) (neoadjuvant portion C1D10), she experienced an acute MI, with presenting complaints of chest pain, abdominal

pain, nausea, and vomiting. The admission echo showed LVEF 70%. Autopsy showed transmural myocardial infarction with concomitant diagnoses of hypertension stage III, LV hypertrophy, atherosclerosis of the arteries of the brain, cardiosclerosis, dilation of heart cavities, and hypertensive encephalopathy.

- [(b) (6)]: 61-year-old female (race: other) assigned to CT-P6. She was diagnosed with breast cancer [(b) (6)]. She received the first dose of study drug on [(b) (6)]. On [(b) (6)] (neoadjuvant portion C1D7) she experienced grade 2 neutropenia. On [(b) (6)] she experience grade 3 stomatitis and was hospitalized and ultimately discharged after AEs resolved on [(b) (6)] On [(b) (6)] (C3D11), the patient experienced sudden onset SOB and dyspnea and died the same day after experiencing cardiac arrest. Autopsy was not carried out due to religious beliefs. She had an ongoing medical history of DVTs, pulmonary hypertension, and pulmonary emboli documented since [(b) (6)]. INR on [(b) (6)] was 3.32-4.32 and the patient was on warfarin.
- [(b) (6)]: 57-year-old white female assigned to CT-P6. She was diagnosed with breast cancer [(b) (6)]. Her first dose of study drug was [(b) (6)]. On [(b) (6)] (neoadjuvant C8D12), the patient suddenly died. Two days prior to her death, the patient reported no complaints to the investigator. Autopsy showed liver metastases and left mammary gland tumor. The investigator learned of the death from the patient's relative but was not able to communicate with the hospital where the patient died directly. After cycle 4, CT scans showed partial response. LVEF was 64% at screening and 57% after cycle 4. EKG was normal. The investigator suspected thromboembolism as a possible cause of death given the complaints of pain rolling up the body while the patient was being transported to the hospital. The role of metastases could not be ruled out as contributing to the cause of death.
- [(b) (6)]: 59-year-old white female assigned to US-Herceptin. She was diagnosed with breast cancer [(b) (6)]. She received her first dose of study drug on [(b) (6)] and last dose on [(b) (6)]. On [(b) (6)] (adjuvant portion C9D22), the patient experienced impaired speech, confusion, weakness, slurred speech and fell. The patient was hospitalized for possible stroke. Imaging tests were not performed on admission. Autopsy reports showed the patient died of dissection of the ascending aorta with rupture, with concomitant hypertension and atherosclerosis.

Reviewer Comments:
Overall there are no concerning safety findings in the patients who died.

- ***Patient [(b) (6)] only received 1 dose of study drug and had an autopsy that showed underlying heart disease and hypertension. Her cause of death was an MI likely due to comorbidities and less likely due to study drug.***
- ***Patient [(b) (6)] had an ongoing history of DVTs and PEs. While her INR was supratherapeutic on [(b) (6)] DVT/PE cannot be ruled out as a possible cause of death, especially given her past medical history.***

- ***Patient (b) (6) died of unclear causes. Her LVEF after cycle 4 was within normal limits and CT at the time had shown partial response. At the time of death, the patient had grade 1 hepatic cyst and grade 2 alopecia. No laboratory results were reported at the time of death. Given the sudden nature of the death and the patient reporting no symptoms 2 days before she died, DVT/PE is a possible cause of death.***
- ***Patient (b) (6) had underlying hypertension and died after completing 1 year of US-Herceptin of an aortic dissection. The dissection is likely due to hypertension and unlikely to be due to US-Herceptin.***

7.3.2. Nonfatal Serious Adverse Events

Serious TEAEs from study 3.2 neoadjuvant and adjuvant portions are listed below in Table 16, Table 17, and

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Table 18 below.

Table 16: Serious TEAEs from Study 3.2 in the Neoadjuvant Portion

MedDRA Term	CT-P6 n=271	US-Herceptin n=278
Anaemia	1 (0.4)	3 (1.1)
Febrile neutropenia	6 (2.2)	3 (1.1)
Leukocytosis	0 (0.0)	1 (0.4)
Neutropenia	2 (0.7)	3 (1.1)
Acute myocardial infarction	0 (0.0)	1 (0.4)
Angina pectoris	0 (0.0)	1 (0.4)
Abdominal pain	1 (0.4)	0 (0.0)
Gastritis	0 (0.0)	1 (0.4)
Haemorrhoidal haemorrhage	0 (0.0)	1 (0.4)
Stomatitis	1 (0.4)	0 (0.0)
Upper gastrointestinal haemorrhage	0 (0.0)	1 (0.4)
Incarcerated hernia	1 (0.4)	0 (0.0)
Sudden death	1 (0.4)	0 (0.0)
Drug hypersensitivity	1 (0.4)	0 (0.0)
Appendicitis	1 (0.4)	0 (0.0)
Bronchitis	0 (0.0)	1 (0.4)
Device related infection	0 (0.0)	1 (0.4)
Endocarditis	0 (0.0)	1 (0.4)
Pneumonia	2 (0.7)	1 (0.4)
Postoperative abscess	1 (0.4)	0 (0.0)
Septic embolus	0 (0.0)	1 (0.4)
Subcutaneous abscess	0 (0.0)	1 (0.4)
Complications of transplant surgery	1 (0.4)	0 (0.0)
Infusion related reaction	0 (0.0)	1 (0.4)
Overdose	0 (0.0)	1 (0.4)
Seroma	0 (0.0)	1 (0.4)
Thermal burn	1 (0.4)	0 (0.0)
Dehydration	1 (0.4)	0 (0.0)
Hypokalaemia	0 (0.0)	1 (0.4)
Ovarian germ cell teratoma benign	0 (0.0)	1 (0.4)
Cerebral infarction	0 (0.0)	1 (0.4)
Dyspnoea	1 (0.4)	0 (0.0)
Pulmonary embolism	1 (0.4)	0 (0.0)
Neurodermatitis	0 (0.0)	1 (0.4)

Deep vein thrombosis	0 (0.0)	1 (0.4)

Source dataset: adae.xpt

Table 17: Serious TEAEs in Study 3.2 in the Adjuvant Portion

MedDRA Term	CT-P6 n=271	US-Herceptin n=278
Congestive cardiomyopathy	0 (0.0)	1 (0.4)
Gastritis	0 (0.0)	1 (0.4)
Pancreatitis acute	1 (0.4)	0 (0.0)
Implant site extravasation	1 (0.4)	0 (0.0)
Incarcerated hernia	1 (0.4)	0 (0.0)
Cholecystitis acute	0 (0.0)	1 (0.4)
Appendicitis	0 (0.0)	1 (0.4)
Device related infection	0 (0.0)	1 (0.4)
Humerus fracture	0 (0.0)	1 (0.4)
Multiple fractures	0 (0.0)	1 (0.4)
Pneumothorax traumatic	0 (0.0)	1 (0.4)
Scar	0 (0.0)	1 (0.4)
Breast cancer	0 (0.0)	2 (0.7)
Ovarian cancer	0 (0.0)	1 (0.4)
Calculus urinary	0 (0.0)	1 (0.4)
Aortic dissection	0 (0.0)	1 (0.4)

Source dataset: adae.xpt

Table 18: Total Serious TEAEs in Study 3.2 in the Neoadjuvant and Adjuvant Portions Combined

MedDRA Term	CT-P6 n=271	US-Herceptin n=278
Anaemia	1 (0.4)	3 (1.1)
Febrile neutropenia	6 (2.2)	3 (1.1)
Leukocytosis	0 (0.0)	1 (0.4)
Neutropenia	2 (0.7)	3 (1.1)
Acute myocardial infarction	0 (0.0)	1 (0.4)
Angina pectoris	0 (0.0)	1 (0.4)
Congestive cardiomyopathy	0 (0.0)	1 (0.4)
Abdominal pain	1 (0.4)	0 (0.0)
Gastritis	0 (0.0)	1 (0.4)
Haemorrhoidal haemorrhage	0 (0.0)	1 (0.4)
Pancreatitis acute	1 (0.4)	0 (0.0)
Stomatitis	1 (0.4)	0 (0.0)
Upper gastrointestinal haemorrhage	0 (0.0)	1 (0.4)
Implant site extravasation	1 (0.4)	0 (0.0)
Incarcerated hernia	1 (0.4)	0 (0.0)
Sudden death	1 (0.4)	0 (0.0)
Cholecystitis acute	0 (0.0)	1 (0.4)
Drug hypersensitivity	1 (0.4)	0 (0.0)
Appendicitis	1 (0.4)	1 (0.4)
Bronchitis	0 (0.0)	1 (0.4)
Device related infection	0 (0.0)	2 (0.7)
Endocarditis	0 (0.0)	1 (0.4)
Pneumonia	2 (0.7)	1 (0.4)
Postoperative abscess	1 (0.4)	0 (0.0)
Septic embolus	0 (0.0)	1 (0.4)
Subcutaneous abscess	0 (0.0)	1 (0.4)
Complications of transplant surgery	1 (0.4)	0 (0.0)
Humerus fracture	0 (0.0)	1 (0.4)
Infusion related reaction	0 (0.0)	1 (0.4)
Multiple fractures	0 (0.0)	1 (0.4)
Overdose	0 (0.0)	1 (0.4)
Pneumothorax traumatic	0 (0.0)	1 (0.4)
Scar	0 (0.0)	1 (0.4)
Seroma	0 (0.0)	1 (0.4)
Thermal burn	1 (0.4)	0 (0.0)

Dehydration	1 (0.4)	0 (0.0)
Hypokalaemia	0 (0.0)	1 (0.4)
Breast cancer	0 (0.0)	2 (0.7)
Ovarian cancer	0 (0.0)	1 (0.4)
Ovarian germ cell teratoma benign	0 (0.0)	1 (0.4)
Cerebral infarction	0 (0.0)	1 (0.4)
Calculus urinary	0 (0.0)	1 (0.4)
Dyspnoea	1 (0.4)	0 (0.0)
Pulmonary embolism	1 (0.4)	0 (0.0)
Neurodermatitis	0 (0.0)	1 (0.4)
Aortic dissection	0 (0.0)	1 (0.4)
Deep vein thrombosis	0 (0.0)	1 (0.4)

Source dataset: adae.xpt

Reviewer Comments: Overall there are no concerning safety findings for serious TEAEs. Serious TEAEs were infrequent and primarily occurred during the neoadjuvant portion with concomitant chemotherapy. There were very few serious TEAEs during the adjuvant portion.

7.3.3. Dropouts and/or Discontinuations

The pre-specified safety withdrawal criteria are reasonable and included infusion reacted reaction that precluded further participation (tachypnea, bronchospasm, hypotension, hypoxia), cardiotoxicity by opinion of the investigator, NYHA class III/IV cardiac dysfunction, cycle delay by more than 3 weeks, or pregnancy.

Table 19 below lists patients on each treatment arm and during the neoadjuvant and adjuvant study portions who had TEAEs leading to permanent withdrawal from the study and the associated MedDRA term and grade.

Table 19: TEAEs Leading to Permanent Discontinuation From Study 3.2

MedDRA Term	Grade	Treatment Arm	Patient ID
Neoadjuvant Portion			
Infusion related reaction	Grade 2	CT-P6	17046004
Infusion related reaction	Grade 2	CT-P6	22056001
Infusion related reaction	Grade 2	CT-P6	28186003
Infusion related reaction	Grade 2	CT-P6	28186007
Dyspnoea	Grade 5	CT-P6	30046005
Sudden death	Grade 5	CT-P6	34066008
Neutrophil count decreased	Grade 2	CT-P6	58056003
Hepatitis C	Grade 1	US-Herceptin	17046003
Ejection fraction decreased	Grade 2	US-Herceptin	20016001
Infusion related reaction	Grade 4	US-Herceptin	22066001
Infusion related reaction	Grade 2	US-Herceptin	28046005
Acute myocardial infarction	Grade 5	US-Herceptin	28096027
Overdose[a]	Grade 4	US-Herceptin	32026002
Endocarditis	Grade 3	US-Herceptin	51066002
Hyponatraemia	Grade 3	US-Herceptin	53036010
Cerebral infarction[b]	Grade 4	US-Herceptin	58056002
Adjuvant Portion			
Infusion related reaction	Grade 2	CT-P6	25016008
Ejection fraction decreased	Grade 2	CT-P6	51126004
Humerus fracture	Grade 2	US-Herceptin	25036005
Ejection fraction abnormal	Grade 1	US-Herceptin	28046013
Congestive cardiomyopathy	Grade 2	US-Herceptin	28166019
Aortic dissection	Grade 5	US-Herceptin	34096010
Follow-Up Portion			
Ejection fraction decreased	Grade 2	CT-P6	17046001[c]
Ejection fraction decreased	Grade 2	CT P6	25016006[d]

Source dataset: ADAE.xpt

[a] Patient (b) (6) received an overdose of docetaxel (729 mg administered, screening weight 59 kg, screening height 159 cm, BSA 1.61 m2) during the neoadjuvant portion C1D1. The patient, based on screening height and weight, had a calculated BSA around 1.61 m2, with docetaxel 75 mg/m2 the patient should have received approximately 120 mg. However, 729 mg was administered (overdose by 609 mg). The overdose was coded as resolved a month later with sequelae of peripheral neuropathy (grade 2-3), chemical conjunctivitis, keratitis, and mixed sensorimotor polyneuropathy.

[b] Patient (b) (6) experienced cerebral infarction on C1D28 during the neoadjuvant portion, confirmed by head CT showing right MCA occlusion. The patient had a past medical history of hypertension on atenolol and amlodipine. A carotid artery plaque was

also reported. The patient had no history of thromboembolic event. The event of cerebral infarction was resolved with sequelae. It was felt this was possibly related to the study drug as uncontrolled blood pressure increases the risk of stroke and the study drug was used with docetaxel and drug-drug interaction causing the venous thromboembolism could not be excluded.
[c] *Patient (b) (6) completed the neoadjuvant phase and had asymptomatic LVEF decrease from 61%at screening to 44% at EOT1.*
[d] *Patient (b) (6) was discontinued from study after the neoadjuvant phase when her LVEF dropped from 62% at screening to 50% at EOT1. She was asymptomatic.*

Reviewer Comments: The majority of patients who experienced TEAEs leading to permanent discontinuation from the study were during the neoadjuvant portion (7 CT-P6, 9 US-Herceptin) when chemotherapy was also given. During the adjuvant portion there were 2 CT-P6 and 4 US-Herceptin patients who had TEAEs leading to permanent study discontinuation. These were well balanced between the two arms. Please refer to Section 7.3.1 for details regarding the patients with grade 5 TEAEs. Overall there were no concerning safety findings.

7.3.4. Submission Specific Primary Safety Concerns

7.3.4.1 Treatment-Related TEAEs

Table 20 below lists a summary of treatment-related TEAEs by grade, which was balanced between the two study arms. The majority occurred during the neoadjuvant portion during concomitant chemotherapy administration and were grade 1-2 in severity.

Table 20: Summary of Treatment-Related TEAEs for Study 3.2

	Neoadjuvant Portion		Adjuvant Portion	
AE Grade	CT-P6 n=271	US-Herceptin n=278	CT-P6 n=271	US-Herceptin n=278
Grade 1	96 (35.4)	103 (37.1)	35 (12.9)	49 (17.6)
Grade 2	59 (21.8)	72 (25.9)	27 (10.0)	23 (8.3)
Grade 3	16 (5.9)	18 (6.5)	2 (0.7)[b]	1 (0.4)[c]
Grade 4	6 (2.2)	13 (4.7)	0 (0.0)	0 (0.0)
Grade 5	0 (0.0)	1 (0.4)[a]	0 (0.0)	0 (0.0)

Source dataset: ADAE.xpt
[a] Patient (b) (6): acute MI, possibly due to study drug (see section 7.3.1 above)
[b] Patient (b) (6): pruritus, possibly due to study drug; Patient (b) (6): acute pancreatitis, possibly due to study drug
[c] Patient (b) (6): ALT increase, definitely due to study drug

Reviewer comments: The treatment-related TEAEs were well balanced between the two arms and the majority occurred during the neoadjuvant portion and are

likely attributable to chemotherapy. The majority were grade 1-2 in severity. One patient who received US-Herceptin died of an acute MI with underlying comorbidities (refer to section 7.3.1 above). Of the 3 patients who experienced grade 3 treatment-related TEAEs during the adjuvant portion, the two patients who received CT-P6 experienced pruritus and acute pancreatitis felt possibly due to the study drug, and the patient who received US-Herceptin had ALT increase felt definitely due to the study drug. All three patients had resolution of their AEs. Overall no safety concerns noted in the treatment-related TEAEs.

7.3.4.2 Adverse Events of Special Interest

Major events of interest which are listed as Black Box Warnings in the prescribing information for US-Herceptin include cardiomyopathy, pulmonary toxicity, infusion reactions, and embryo-fetal toxicity. There were 2 pregnancies reported on study 3.2, both with voluntary abortions. There were no embryo-fetal toxicities reported. Cardiac toxicities, pulmonary toxicities, and infusion reactions are discussed below.

7.3.4.2.1 Cardiac Toxicity

Table 21 below lists the cardiac TEAEs during the neoadjuvant and adjuvant portions of study 3.2. There were 18 patients (6.6%) on the CT-P6 and 9 patients (3.2%) on the US-Herceptin arm who experienced ejection fraction decrease. The majority were grade 1-2 in severity and most patients had resolution of their AEs (includes Day 120 Safety Update AE resolution status).

Table 21: Cardiac Toxicities for Study 3.2 During the Neoadjuvant and Adjuvant Portions

MedDRA Term	CT-P6 N=271 Total	CT-P6 N=271 Resolved	CT-P6 N=271 Grade 3+	US-Herceptin N=278 Total	US-Herceptin N=278 Resolved	US-Herceptin N=278 Grade 3+
Acute myocardial infarction	0	0	0	1	0	1
Cardiac disorder	0	0	0	1[k]	1	0
Cardiac failure	1	0	0	0	0	0
Cardiac hypertrophy	1[j]	0	0	0	0	0
Cardiomyopathy	1	0	0	5	3	0
Cardiotoxicity	1	1	0	1	1	0
Congestive cardiomyopathy	0	0	0	1	1	0
Coronary artery disease	2	0	0	0	0	0
Diastolic dysfunction	0	0	0	1	0	0
Ejection fraction abnormal	0	0	0	1	1	0
Ejection fraction decreased	18[a,b]	14	2[a,c]	9[d,e,f,k]	8	0
Left atrial hypertrophy	0	0	0	1	0	0
Left ventricular dysfunction	0	0	0	1[g]	0	0
Left ventricular hypertrophy	0	0	0	1	0	0
Metabolic cardiomyopathy	0	0	0	1[g]	0	0
Myocardial ischaemia	1[j]	0	0	0	0	0
Right ventricular failure	0	0	0	2[h]	1	0
Ventricular hyperkinesia	1	1	0	1	1	0

Source dataset: ADAE.xpt

[a] Patient (b) (6) experienced grade 2 and grade 3 ejection fraction decreased, both resolved

[b] Patient (b) (6) experienced 2 instances of grade 2 and grade 3 ejection fraction decreased, both resolved

[c] Both patients had ejection fraction decreased resolved

[d] Patient (b) (6) experienced 2 instances of grade 2 RV failure, one resolved and one not resolved

[e] Patient (b) (6) experienced 2 instances of grade 1 ejection fraction decreased, one resolved and one not resolved

[f] Patient (b) (6) experienced 2 instances of grade 2 ejection fraction decreased, both resolved and one with sequelae
[g] Patient (b) (6) experienced metabolic cardiomyopathy (grade 1) and LV dysfunction (grade 2), both not resolved
[h] Patient (b) (6) experienced 2 instances of grade 2 RV failure, one resolved and one not resolved
[j] Patient (b) (6) experienced grade 1 cardiac hypertrophy and grade 2 myocardial ischemia, both not resolved
[k] Patient (b) (6) experienced grade 1 cardiac disorder and ejection fraction decreased, both resolved

Reviewer Comments: More patients in the CT-P6 arm experienced ejection fraction decrease and more patients on the US-Herceptin arm experienced cardiomyopathy, but both were within the expected incidence of cardiotoxicities based on the US-Herceptin label. The majority of all cardiac TEAEs were grade 1-2 and most patients had resolution of their TEAEs. Overall the differences do not impact our conclusion that the study supports a finding of no clinically meaningful differences.

7.3.4.2.2 Pulmonary Toxicity and Infusion Reactions

Table 22 below lists the frequency of treatment-emergent pulmonary toxicities and infusion reactions. The majority were grade 1-2, all patients had resolution of their infusion related reaction, and most occurred during the neoadjuvant portion.

Table 22: Pulmonary Toxicities and Infusion Reactions on Study 3.2

	CT-P6 n=271			US-Herceptin n=278		
Neoadjuvant Portion	**Total**	**Resolved**	**Grade 3+**	**Total**	**Resolved**	**Grade 3+**
Drug hypersensitivity	1	1	0	0	0	0
Idiopathic pulmonary fibrosis	0	0	0	1	0	0
Infusion related reaction	23	23	1	25	25	1
Respiratory disorder	1	1	0	0	0	0
	CT-P6 n=271			**US-Herceptin n=278**		
Adjuvant Portion	**Total**	**Resolved**	**Grade 3+**	**Total**	**Resolved**	**Grade 3+**
Drug hypersensitivity	1	0	0	0	0	0
Infusion related reaction	11	11	0	5	5	0
Interstitial lung disease	1	1	0	0	0	0

Source dataset: ADAE.xpt

Reviewer Comments: ***There are no safety concerns noted for pulmonary toxicities and infusion reactions.***

Patient (b) (6) ***was randomized to US-Herceptin and had a grade 4 infusion related reaction which resolved in the neoadjuvant portion. Patient was permanently discontinued from the study. The patient was 40 yo and received first dose of US-Herceptin on*** (b) (6) ***and last dose on*** (b) (6) ***On*** (b) (6) ***the patient had cutaneous rash, dyspnea, wheezing, hypoxemia, throat irritation, flushing, swollen lips, BP 150/80, HR 78, O2 sat 94% after completing US-Herceptin and 5 minutes after docetaxel administration. She received IV steroids. This was felt to be due to docetaxel.***

Patient (b) (6) ***was randomized to CT-P6 and had three separate grade 3 infusion related reaction which all resolved and manifested as exacerbation of underlying hypertension with otherwise normal vital signs. The patient went on to complete the rest of the study.***

7.4. Supportive Safety Results

7.4.1. Common Adverse Events

Common TEAEs seen in ≥5% of patients in any group during the neoadjuvant portion of study 3.2 are shown in Table 23 below with similar MedDRA terms combined by this reviewer. Adverse events of special interest were discussed in Section 7.3.4.2 above.

Table 23: TEAEs in ≥5% of Patients During the Neoadjuvant Portion of Study 3.2

MedDRA Terms	CT-P6 n=271	US-Herceptin n=278	Total n=549
Anaemia/Haemoglobin decreased/ Red blood cell count decreased	56 (20.7)	64 (23.0)	120 (21.9)
Febrile neutropenia	17 (6.3)	19 (6.8)	36 (6.6)
White blood cell count decreased/Lymphocyte count decreased/Neutrophil count decreased/Lymphopenia/Neutropenia/ Leukopenia	142 (52.4)	178 (64.0)	320 (58.3)
Neutrophil count decreased/Neutropenia	108 (39.9)	124 (44.6)	232 (42.3)
Alopecia	195 (72.0)	213 (76.6)	408 (74.3)
Nausea	99 (36.5)	91 (32.7)	190 (34.6)
Diarrhoea	52 (19.2)	48 (17.3)	100 (18.2)
Fatigue/Asthenia	91 (33.6)	96 (34.5)	187 (34.1)
Mucosal inflammation/Stomatitis	47 (17.3)	37 (13.3)	84 (15.3)
Pyrexia	29 (10.7)	28 (10.1)	57 (10.4)
Arthralgia	28 (10.3)	33 (11.9)	61 (11.1)
Vomiting	27 (10.0)	26 (9.4)	53 (9.7)
Muscle rigidity/Muscle spasms/ Musculoskeletal chest pain/Myalgia/ Back pain/Musculoskeletal pain/ Pain in extremity/Neck pain/Pain	43 (15.9)	50 (18.0)	93 (16.9)
Constipation	24 (8.9)	18 (6.5)	42 (7.7)
Decreased appetite	21 (7.7)	18 (6.5)	39 (7.1)
Headache/Tension headache	20 (7.4)	19 (6.8)	39 (7.1)
Eye discharge/Lacrimation increased	17 (6.3)	16 (5.8)	33 (6.0)
Eyelid rash/Neurodermatitis/Dermatitis atopic/Hand dermatitis/Dermatitis/Dermatitis allergic/Pruritus/Rash generalised/Rash papular/Acne/Dermatitis contact/Eczema/Rash pruritic/Pruritus generalised/Rash maculo-papular/Rash macular/Dermatitis acneiform/Rash/Genital rash	52 (19.2)	40 (14.4)	92 (16.8)
Hypertension/Blood pressure increased	18 (6.6)	5 (1.8)	23 (4.2)
Alanine aminotransferase increased	15 (5.5)	23 (8.3)	38 (6.9)
Aspartate aminotransferase increased	11 (4.1)	20 (7.2)	31 (5.6)

Peripheral sensory neuropathy/Peripheral motor neuropathy/Neuropathy peripheral/Sensory loss/Hypoaesthesia	15 (5.5)	25 (9.0)	40 (7.3)
Epistaxis/Haematuria/Metrorrhagia/ Vaginal haemorrhage	15 (5.5)	11 (4.0)	26 (4.7)
Respiratory disorder/Upper respiratory tract inflammation/Viral infection/Respiratory tract infection viral/Influenza/Influenza like illness/Chills/Cough/Productive cough/ Upper respiratory tract infection/ Rotavirus infection	29 (10.7)	27 (9.7)	56 (10.2)
Nasopharyngitis/Pharyngitis/Rhinitis/Sinusitis/Gingivitis/Laryngitis/Oral candidiasis/Otitis media acute/Conjunctivitis/Oral herpes/Tonsillitis/Angular cheilitis/Otitis media/Portionontitis/Mumps/ Oral candidiasis/Rhinorrhoea	33 (12.2)	35 (12.6)	68 (12.4)
Abdominal pain upper/Abdominal pain/ Gastrointestinal pain/Abdominal tenderness	13 (4.8)	21 (7.6)	34 (6.2)
Gastrointestinal disorder/Chronic gastritis/ Dyspepsia/Gastritis/Abdominal discomfort	9 (3.3)	16 (5.8)	25 (4.6)
Bone pain	11 (4.1)	17 (6.1)	28 (5.1)
Procedural pain/Wound infection/Post procedural infection/Skin infection/Subcutaneous abscess/ Postoperative abscess/Device related infection	11 (4.1)	17 (6.1)	28 (5.1)
Nail discolouration/Dermatophytosis of nail/Nail disorder/Onychomadesis/ Onychoclasis/Nail bed tenderness/Nail dystrophy/Nail ridging/ Nail bed disorder/Onychomycosis	25 (9.2)	16 (5.8)	41 (7.5)
Palpitations/Tachycardia/Bundle branch block right/Sinus tachycardia/Supraventricular extrasystoles/Supraventricular tachycardia/ Tachyarrhythmia/Electrocardiogram QT prolonged/Heart rate increased	16 (5.9)	17 (6.1)	33 (6.0)

Oedema peripheral/Peripheral swelling/ Generalised oedema	10 (3.7)	16 (5.8)	26 (4.7)

Source dataset: ADAE.xpt

Reviewer Comments: TEAEs seen in ≥5% in any arm during the neoadjuvant portion are well balanced with no meaningful differences. The majority of TEAEs are likely attributable to chemotherapy.

Common TEAEs seen in ≥5% of patients in any group during the adjuvant portion of study 3.2 are shown in Table 24 below with similar MedDRA terms combined by this reviewer. Adverse events of special interest were discussed in Section 7.3.4.2 above. There were no reported cases of febrile neutropenia during the adjuvant portion.

Table 24: TEAEs in ≥5% of Patients During the Adjuvant Portion of Study 3.2

MedDRA Terms	CT-P6 n=271	US-Herceptin n=278	Total n=549
Radiation skin injury	30 (11.1)	32 (11.5)	62 (11.3)
Fatigue/Asthenia	26 (9.6)	17 (6.1)	43 (7.8)
Anaemia	11 (4.1)	19 (6.8)	30 (5.5)
Upper respiratory tract infection/Respiratory tract infection/Respiratory tract infection viral/Upper respiratory tract inflammation/Viral infection/Viral upper respiratory tract infection/Influenza/Influenza like illness/Cough/Upper-airway cough syndrome/Viral pharyngitis	24 (8.9)	14 (5.0)	38 (6.9)
Neutropenia/White blood cell count decreased/Lymphopenia/Leukopenia/Neutrophil count decreased	18 (6.6)	23 (8.3)	41 (7.5)
Nasopharyngitis/Pharyngitis/Nasal congestion/Rhinitis/Nasal dryness/Sinusitis/Gingivitis/Oropharyngeal pain/Otitis media/Oral herpes/Tonsillitis/Rhinorrhoea	18 (6.6)	12 (4.3)	30 (5.5)

Source dataset: ADAE.xpt

Reviewer Comments: TEAEs seen in ≥5% in any arm during the adjuvant portion are well balanced with no meaningful differences.

7.4.2. Laboratory Findings

Trastuzumab is not known to cause significant laboratory abnormalities, but chemotherapy is. The reported changes in laboratory values for study 3.2 were reviewed and overall well balanced between the treatment arms in hematology labs and chemistries for the safety population in the neoadjuvant and adjuvant portions.

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

7.4.3. Vital Signs

Changes in vital signs for the safety population reported were reviewed and overall well balanced between the treatment arms for temperature, blood pressure, heart rate, and respiratory rate for the neoadjuvant and adjuvant portions of study 3.2.

Reviewer Comments: No safety concerns noted.

7.4.4. Electrocardiograms (ECGs)

Trastuzumab is not known to cause clinically significant ECG changes. The reported ECG findings for study 3.2 were reviewed. One patient who received CT-P6 had both ejection fraction decrease and supraventricular tachycardia after neoadjuvant portion cycle 4. Overall there were very few patients with abnormal, clinically significant ECG results post-baseline in the neoadjuvant portion (3 CT-P6 and 2 US-Herceptin. During the adjuvant portion, few patients had clinically significant ECG abnormalities (2 CT-P6 and 4 US-Herceptin).

Reviewer Comments: Very few patients experienced ECG changes post-baseline during the neoadjuvant and adjuvant portions. No safety concerns.

7.4.5. Special Safety Studies/Clinical Trials

No special safety studies were conducted.

7.4.6. Immunogenicity

Immunogenicity results were reviewed for study 3.2. Twelve patients had positive ADA results at baseline (4 CT-P6 and 8 US-Herceptin) but neutralizing antibody results were negative for all. None of these 12 patients had previous trastuzumab exposure and all samples were collected prior to study drug administration. During the neoadjuvant and adjuvant portions, there were no positive ADA results at post-baseline visits. After the applicant generated the first CSR for study 3.2, three additional patients (2 CT-P6 and 1 US-Herceptin) were found to also have baseline ADA positivity with negative samples for the remainder of the neoadjuvant and adjuvant portions.

Please refer to Dr. Shadia Zaman's review for BLA 761091 for further details.

Reviewer Comments: No safety concerns.

7.5. Other Safety Explorations

None

7.6. Additional Safety Evaluations

7.6.1. Human Carcinogenicity

Trastuzumab is not known to cause secondary malignancies. During the neoadjuvant portion, one patient who received US-Herceptin had a benign ovarian germ cell teratoma. During the adjuvant portion, two patients who received US-Herceptin had breast cancer and one patient who received US-Herceptin had ovarian cancer. No malignancies were reported for patients who received CT-P6.

Reviewer Comments: No safety concerns noted.

7.6.2. Human Reproduction and Pregnancy Data

Two women were reported as having pregnancies while on study 3.2 during the adjuvant portion and both had voluntary abortions:

- Patient (b) (6) was randomized to US-Herceptin and reported a pregnancy during the adjuvant portion C4D15 and had a positive serum pregnancy test adjuvant portion C4D16. A voluntary abortion for an 8-week pregnancy was carried out during C4D17 without complications. The patient completed 10 cycles of adjuvant treatment without complication. There were no TEAEs reported after the abortion.
- Patient (b) (6) was randomized to US-Herceptin and reported a pregnancy with positive serum pregnancy test on adjuvant portion C1D25. The patient terminated a 4-week pregnancy voluntarily with misoprostol administered to induce abortion on C1D42 with no reported complications. The patient went on to complete 10 cycles of adjuvant treatment without complications.

Three women did not have a documented negative serum pregnancy test at baseline.

- Patient (b) (6) had a negative urine pregnancy test at baseline. No pregnancy was reported during the study portion and the patient completed adjuvant portion cycle 10
- Patient (b) (6) did not have a serum or urine pregnancy test at screening but had a negative serum pregnancy test at the end of the neoadjuvant portion.
- Patient (b) (6) had a positive serum pregnancy test at screening, with a negative urine pregnancy test on neoadjuvant portion C1D1. This patient had

another positive serum pregnancy test at the end of the neoadjuvant portion but had a negative urine pregnancy test 4 days later.

There have been no reported embryo-fetal toxicities.

Reviewer comments: Trastuzumab products are known to cause embryo-fetal toxicity. No cases of embryo-fetal toxicities were reported for study 3.2. The two patients who had voluntary abortions while on study were within the first trimester and had no documented complications from the abortion and both went on to complete 10 cycles of adjuvant treatment. Patient (b) (6) had a positive serum pregnancy test at screening yet was still randomized and enrolled in the study. Only a urine pregnancy test was performed on C1D1 of the neoadjuvant portion. She had another positive serum pregnancy test at the end of the neoadjuvant portion and again only a urine pregnancy test to confirm. Urine pregnancy tests are less sensitive compared to serum and it is unclear why a confirmatory serum pregnancy test was not performed.

7.6.3. Pediatrics and Assessment of Effects on Growth

There has been no CT-P6 exposure in pediatric patients in study 3.2.

Reviewer Comments: No safety concerns noted.

7.6.4. Overdose, Drug Abuse Potential, Withdrawal and Rebound

Refer to section 7.3.3 above regarding patient (b) (6) who received an overdose of docetaxel and was withdrawn from the study.

Reviewer Comments: Only one patient experienced a drug overdose due to a pharmacy mistake with docetaxel. This patient was withdrawn from the study. No other patient experienced a drug overdose.

7.7. Additional Submissions / Safety Issues

The Day 120 Safety Update was submitted on September 25, 2017 for study 3.2 (the estimated final CSR completion will be quarter 4 of 2019 for study 3.2). TEAEs from the post-treatment follow-up period were included through February 28, 2017. Deaths and serious TEAEs were included through July 15, 2017. No patients were treated with CT-P6 or US-Herceptin as part of the clinical development of CT-P6 since the original BLA submission. The original BLA submission contained data through the adjuvant period completion or at least 1 year for each patient on study 3.2 (last patient last visit January 6, 2017). Safety data from the post-treatment follow-up period were submitted for 6 patients on the CT-P6 and 12 patients from the US-Herceptin treatment arms who discontinued/were withdrawn from the study before completing the adjuvant period.

At the time of clinical data cut-off, patient had been followed up for a median of 19.3

months in the CT-P6 arm and 19.6 months in the US-Herceptin arm. Related and cardiac AEs were collected from 30 days after the last dose of study drug until the end of study. Deaths were continuously monitored for all patients.

Reviewer Comments: Overall, there were no clinically significant safety findings in the Day 120 Safety Update.

Deaths

As of July 15, 2017, there were a total of 7 deaths on the CT-P6 arm and 6 deaths on the US-Herceptin arm (Table 25).

Table 25: Total Deaths on Study 3.2

Treatment group	Subject ID	Age/ Race	Study Period	Reason for Death
Deaths summarized in the original submission				
CT-P6	(b) (6)	61/O	NP	Dyspnea
		57/W	NP	Sudden death
US-licensed Herceptin®		67/W	NP	Acute myocardial infarction
		59/W	AP	Aortic dissection
		32/A	FU	Disease progression
Deaths recorded since the original submission				
CT-P6	(b) (6)	64/W	FU	Disease progression
		63/W	FU	Disease progression
		58/W	FU	Disease progression

Treatment group	Subject ID	Age/ Race	Study Period	Reason for Death
	(b) (6)	64/W	FU	Disease progression
		31/A	FU	Disease progression
US-licensed Herceptin®		60/W	FU	Unknown
		67/W	FU	Disease progression
		66/W	FU	Pulmonary embolism

Source: BLA 761091 4-Month Safety Update CSR Table 6

Deaths that occurred during the neoadjuvant and adjuvant periods of the study are discussed in Section 7.3.1 above. Narratives for deaths that occurred during the follow-up period were reviewed:

- Patient (b) (6): 64F randomized to CT-P6 with stage IIB disease at screening. She completed the neoadjuvant portion and had pCR of breast and axillary nodes with absence of DCIS at surgery. She went on to receive 8 cycles of adjuvant treatment, but was discontinued from the study when progression was noted with new brain lesions confirmed on MRI. She died about 5 months later.
- Patient (b) (6): 60F randomized to US-Herceptin with stage IIIA disease at screening. At surgery she had pCR of the breast only. She completed 10 cycles

of adjuvant treatment and about a year later, the investigator was informed she died. The cause of death is unknown.

- Patient (b) (6): 63F randomized to CT-P6 with stage IIIC disease at screening. She was a pCR non-responder after the neoadjuvant period. She completed all 10 cycles of adjuvant treatment and approximately 2 months after completing the adjuvant period, she had progression at the postsurgical suture area which was assessed by phone and not by imaging or physical exam. The patient died shortly thereafter.
- Patient (b) (6): 67F randomized to US-Herceptin with stage IIIA disease at screening. She had pCR of the breast and axilla with absence of DCIS at surgery and completed 10 cycles of adjuvant treatment. She progressed about 8 months later and died within the month.
- Patient (b) (6): 66F assigned to US-Herceptin. First dose of study drug was on (b) (6). On (b) (6) (22 days after adjuvant period cycle 5), the patient had grade 2 congestive cardiomyopathy with DOA that started (b) (6). LVEF on (b) (6) was 36%. She was medically managed and LVEF (b) (6) was 30%. She was discontinued from the study. LVEF recovered to 55% by (b) (6). On (b) (6) (380 days after adjuvant period cycle 5), the patient died due to bilateral PE.
- Patient (b) (6): 58F randomized to CT-P6 with stage IIB disease at diagnosis. She was sap CR non-responder and received 8 cycles of adjuvant treatment. She was discontinued from the study with progressive disease with new axillary lymph nodes found on physical exam. She died ~14 months later.
- Patient (b) (6): 64F randomized to CT-P6 with stage IIIA disease at screening. At surgery she had pCR of the breast only. She completed 3 cycles of adjuvant treatment and was discontinued when new brain lesions were found on imaging. The patient died about a year later.
- Patient (b) (6): 32F randomized to US-Herceptin with stage IIIA disease at screening. She completed the neoadjuvant portion and was a pCR non-responder. After Adjuvant Period Cycle 1, she had PD with new lesions on the breast, supraclavicular lymph node, axillary lymph node, and bone and was discontinued from the study. She died approximately 2 months later.
- Patient (b) (6): 31F randomized to CT-P6 with stage IIA disease at screening. At surgery she had pCR of the breast only and received 9 cycles of adjuvant treatment, when she had progressive disease with new lesions on the breast, axillary and subpectoral lymph nodes, and bone confirmed on imaging. She died ~ 6 months later.

Reviewer Comments: Narratives for death were reviewed for all patients and discussed above. Progressive disease was confirmed either by physical exam or by imaging for the majority of patients. Overall, 5 (1.8%) patients who received CT-P6 and 2 (0.7%) who received US-Herceptin died of progressive disease. These values are within the expected survival rate for patients with early breast cancer treated in the adjuvant setting.

Serious TEAEs

Two patients had serious TEAEs during the follow-up period. Patient (b) (6) received CT-P6 and 148 days after completing adjuvant period cycle 10, she experienced grade 3 Adams Stokes syndrome. She had known underlying second degree AV block at the time of study enrollment. She received a pacemaker. Patient (b) (6) received US-Herceptin and 261 days after adjuvant period cycle 10, the patient had grade 3 dacryostenosis. Patient was treated with surgery, although the exact type of surgery is not known.

Reviewer Comments:
Serious TEAEs for these two patients both occurred well after the last dose of study drug. Patient (b) (6) had underlying 2nd degree AV block at the time of study enrollment and patient (b) (6)'s dacryostenosis is likely due to docetaxel.

Cardiac Toxicities

At follow-up visits 2 and 4, the mean change from baseline in LVEF was assessed and found to be similar between the two arms:

- Follow Up Visit 2: CT-P6 -1.81% vs. US-Herceptin -1.55%
- Follow Up Visit 4: CT-P6 -1.42% vs. US-Herceptin -1.57%

Patients with significant LVEF decrease was reported for 2 patients in each arm:

- CT-P6
  - (b) (6): 45F who received first dose of study drug on (b) (6) On (b) (6) (21 days after neoadjuvant period cycle 8), she had asymptomatic grade 2 ejection fraction decrease to 44% from 61% at baseline. Repeat LVEF was still 44% on (b) (6) and the patient was discontinued from the study. On (b) (6) her LVEF was 60%.
  - (b) (6): 58F who received first dose of study drug on (b) (6). On (b) (6) (118 days after neoadjuvant period cycle 8 and the day she was supposed to start adjuvant period cycle 1), the patient experienced asymptomatic grade 2 ejection fraction decrease from 48% from 62% at baseline. Patient was discontinued from study and follow up LVEF on (b) (6) was 50%
- US-Herceptin
  - (b) (6): 45F who received first dose of study drug on (b) (6) On (b) (6) (21 days after adjuvant period cycle 3), the patient had asymptomatic grade 1 ejection fraction decrease of 43% from 56% at screening. She was discontinued from the study and on (b) (6) her LVEF was 43%. And on (b) (6) her LVEF was 52%.
  - (b) (6): 66F who received first dose of study drug on (b) (6). On (b) (6) (21 days after adjuvant period cycle 5), the patient had DOE and grade 2 congestive cardiomyopathy. The DOE started on (b) (6). Echo showed LVEF 33% and she was seen by cardiology and medically managed. On (b) (6) LVEF was 55%.

One patient ((b) (6)) who received CT-P6 had asymptomatic NYHA Class II heart failure (ventricular bigeminy and LVH) at follow-up visit 2, which subsequently resolved by follow-up visit 4 with normal EKGs and no NYHA class.

Reviewer Comments: Cardiac toxicities updates were reviewed and no clinically significant findings found.

8. Postmarket Experience

CT-P6 is not marketed in any country. There is no postmarket safety data.

9. Appendices

9.1. Literature Review/References

1: NCI: SEER, Cancer Stat Facts: Breast Cancer, https://seer.cancer.gov/statfacts/html/breast.html, Accessed June 30, 2017.

2: NCI: SEER, Cancer Stat Facts: Stomach Cancer, https://seer.cancer.gov/statfacts/html/stomach.html, Accessed June 30, 2017.

3: Bang, et al., The Lancet, 2010, 376, 687-697

4: Nahta, et al., Oncogene, 2007, 26, 3637-3643

5: Pupa, et al., Oncogene, 1993, 8, 2917-2923

6: Hayes, et al., Clinical Cancer Research, 2001, 7, 2701-2711

7: Arnould, et al., British Journal of Cancer, 2006, 94, 2559-2267

8: Wen, et al., Oncogene, 2006, 25, 6986-6996

9: Gasparini, et al., Breast Cancer Research and Treatment, 2007, 101, 355-365

10: Marty, et al., Journal of Clinical Oncology, 2005, 4265-4274

11: Slamon, et al., New England Journal of Medicine, 2001, 365, 783-792

9.2. Labeling Recommendations

The following changes were made to the Herzuma label:

1. Per guidance for biosimilars, throughout the label:
    a. “trastuzumab” refers to US-Herceptin
    b. “trastuzumab product(s)” refers to US-Herceptin and biosimilars
    c. “Herzuma” refers to CT-P6
2. Highlights of Prescribing Information
    a. Product name changed to “HERZUMA”
    b. Full product title changed to “HERZUMA (trastuzumab-(b) (4)
    c. Added description of biosimilar and biosimilarity of Herzuma
3. Section 1 Indications and Usage wording changed to: *“Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.”*
4. Section 8 Use in Specific Populations
    a. (b) (4)” section removed.

9.3. Advisory Committee Meeting

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

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/s/

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02/13/2018

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