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APPLICATION NUMBER:

761073Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	Class 2 Resubmission of BLA, 351(k)
Application Number	761073
Resubmit Date	December 28, 2018
Received Date	December 28, 2018
BSUFA Goal Date	June 28, 2019
Division / Office	DOP1/OHOP
Reviewer Name(s)	Danielle Krol, MD Jennifer Gao, MD Joyce Cheng, PhD Lijun Zhang, PhD
Review Completion Date	April 18, 2019
Established Name	Trastuzumab-anms
Trade Name	Kanjinti*
Therapeutic Class	HER2-binding humanized monoclonal antibody
Applicant	Amgen
Formulation(s)	IV
Dosing	8mg/kg IV loading dose, then 6mg/kg IV q 3 weeks
Proposed Indication(s)	KANJINTI 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.
Recommended Indication	KANJINTI 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 "ABP-980".

This biologics license application (BLA 761073) Class 2 Resubmission seeks approval of the product ABP 980 (proposed trade name Kanjinti [trastuzumab-anns]), 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 July 28, 2017 and on May 25, 2018, a Complete Response Letter (CRL) was issued due to facility inspections. Amgen submitted a resubmission on December 28, 2019 which addresses all the deficiencies listed in the CRL.

The proprietary name KANJINTI was reviewed on September 9, 2016 under IND 115424, and on July 28, 2017 under BLA 761073. The Division of Medication Error and Prevention and Analysis (DMEPA) found the name conditionally acceptable under both IND 115424b and BLA 761073c.0F Amgen submitted the name, Kanjinti, for on December 28, 2018, as part of resubmission. DMEPA found this name to be acceptable during their review dated February 7, 2019. The 4-letter suffix -anns was conditionally accepted during the original submission by DMEPA. FDA reassessed this proposed suffix with the Class 2 Resubmission and determined the suffix is accepted.

The original BLA submission contained data results from the clinical program to support the determination of no clinically meaningful differences between ABP 980 and US-Herceptin. The applicant submitted data from the comparative clinical study 20120283 assessing ABP 980 when used as treatment in patients with HER2-positive early breast cancer in comparison to EU-approved Herceptin (hereafter referred to as EU-Herceptin). The study had co-primary efficacy endpoints of risk difference (RD) and risk ratio (RR) of the rate of pathologic complete response (pCR, defined as the absence of invasive tumor cells in the breast tissue and axillary lymph nodes regardless of ductal carcinoma in situ (DCIS) status as assessed by local review for those treated with ABP 980 as compared to EU-Herceptin. The FDA considered the RR of pCR to be the more appropriate metric for evaluating pCR. The RR of pCR in the ABP 980 arm as compared to the EU-Herceptin arm as assessed by local review was 1.1877 (90% CI: 1.0327, 1.3660), but the 90% CI was not contained within the pre-specified equivalence margin of (0.7586, 1.3182). Central blinded review, which the FDA considered to be more reliable, of the RR of pCR was 1.1419 (90% CI: 0.9934, 1.3124), and this 90% CI was entirely within pre-specified equivalence margin of (0.7586, 1.3182). The neoadjuvant setting for breast cancer used in study 20120283 is an acceptable, homogeneous, and sensitive patient population to evaluate for no meaningful differences between ABP 980 and EU-Herceptin. The patient population receiving HER2-based treatment is the same in the neoadjuvant and adjuvant settings, differing only in the timing of surgery. For this reason, the study population and primary endpoint used in study 20120283 is acceptable to support approval of ABP 980 for the indications for which US-Herceptin has been previously approved.

In addition, the applicant submitted data from study 20130119, a PK similarity study in healthy male volunteers comparing the PK of ABP 980, EU-Herceptin, and US-Herceptin. Based on the analytical data, a scientific bridge between EU-Herceptin, US-Herceptin, and ABP 980 has been established based in part on pharmacokinetic (PK) evaluation.

The safety evaluation for this application is based off study 20120283, which was completed during the original submission. The findings were reviewed, with special focus on cardiac dysfunction, infusion-related reactions, hematotoxicity, embryo-fetal toxicity and pulmonary

adverse reactions and no clinically meaningful differences were found in the safety population.

With the Class 2 Resubmission, the applicant submitted a Safety Update Report which covered the period from May 16, 2018 until September 24, 2018. During this period, no new patients were enrolled or randomized into study 20120283 since the original BLA submission. During the reporting period, no new benefit data became available, and there was no significant change in the risk profile of KANJINTI. There are no ongoing clinical trials with ABP 980.

Overall there are no new concerning clinical safety findings. Refer to the primary clinical and statistics review dated July 28, 2017 for a full analysis of clinical efficacy and safety.

Clinical Recommendation: The recommendation from the clinical and statistics reviewers is approval. The results from the PK similarity study 20130119 and the efficacy and safety study 20120283 support the determination of no clinically meaningful differences between ABP 980 and US-Herceptin.

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

/s/

DANIELLE N KROL
06/05/2019 09:25:12 AM

JENNIFER J GAO
06/05/2019 09:26:59 AM

JOYCE H CHENG
06/05/2019 09:37:40 AM

LIJUN ZHANG
06/05/2019 10:02:09 AM

Cross-Discipline Team Leader Review

Date	<i>Electronic Stamp Date</i>
From	Laleh Amiri-Kordestani, M.D. (CDTL and Acting Associate Director)
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	351(k) BLA 761073
Applicant	Amgen
Date of Submission	July 28, 2017
BsUFA Goal Date	May 28, 2018
Proprietary Name / Established (USAN) names	KANJINTI / Trastuzumab-anns (ABP 980) ¹
Dosage forms / Strength	Lyophilized powder for injection/420 mg per vial
Proposed Indication(s)	KANJINTI 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:	<i>Complete Response</i>
Recommended Indication (if applicable)	Not applicable

¹ The proposed proprietary name, Kanjinti, and the proposed proper name, trastuzumab-anns, are conditionally accepted until such time that the application is approved. In this document, we refer to Amgen's proposed product by the descriptor "ABP 980", which was the name Amgen used to refer to this product during development.

REVIEW TEAM

Discipline	Reviewer	Office/Division
Cross-disciplinary Team Lead	Laleh Amiri Kordestani	OND/OHOP/DOP1
RPM	Amy Tilley	OND/OHOP/DOP1
Clinical Medical Officer	Lynn Howie, Jennifer Gao,	OND/OHOP/DOP1
Pharm/Tox	Kimberly Ringgold/Tiffany Ricks (TL)	OND/OHOP/DHOT
Clinical Pharmacology	Olanrewaju Okusanya/ Sarah Schrieber (TL)	OTS/OCP
Statistics	Joyce Cheng/ Shenghui Tang (TL)	OTS/OB/DBV
CMC Statistics	Yu-Yi Hsu/ Meiyu Shen (TL)	OTS/OB/DBIV
Drug Substance	Chen Sun	OPQ/OBP/DBRRII
Analytical Similarity	Chen Sun	OPQ/OBP/DBRRII
Drug Product	Chih-Jung Hsu	OPQ/OBP/DBRRII
Immunogenicity Assays	Chih-Jung Hsu	OPQ/OBP/DBRRII
Labeling	Vicky Borders-Hemphill	OPQ/OBP
Facilities	Wayne Seifert	OPQ/OPF/DIA
Facilities Team Lead	Zhihao Peter Qui	OPQ/OPF/DIA
Microbiology Drug Substance	Kathleen Jones	OPQ/OPF/DMA
Microbiology Drug Product	Jessica Hankins	OPQ/OPF/DMA
Microbiology QAL	Reyes Candau-Chacon	OPQ/OPF/DMA
Application Technical Lead	Patrick Lynch	OPQ/OBP/DBRRII
Tertiary Reviewer for OBP	Howard Anderson	OPQ/OBP/DBRRII
RBPM	Keith Olin	OPQ/OPRO
TBBS	Michele Dougherty	Leah Christl
	Sue Lim	
OSE-RPM	Frances Fahnbulleh/ Alice Chi-Ming Tu	
OSE/DMEPA	Tingting Gao	
OSI Consult	Navid Homayouni/ Susan Thompson	
OPDP	Kevin Wright	
CDRH Consult	Jacob Richards/ Eunice Lee (TL)	

1. Introduction

On July 28, 2017, the applicant submitted a biologics license application (BLA) under the 351(k) pathway of the Public Health Service Act (PHS Act) for ABP-980, a proposed biosimilar to US-licensed Herceptin (trastuzumab), hereinafter US-Herceptin². The applicant is seeking licensure of ABP-980 (KANJINTI, Trastuzumab-anns) for the same indications as US-Herceptin:

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

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

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

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 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.

To support the demonstration that ABP-980 is highly similar to US- Herceptin, the applicant evaluated and compared ABP-980 to US- Herceptin using a battery of biochemical, biophysical, and functional assays, including assays that addressed each major potential mechanism of action. The sponsor also performed analytical comparisons of ABP-980, US-Herceptin and EU-approved Herceptin (hereinafter EU-Herceptin) to establish the analytical portion of the scientific bridge to justify the use of nonclinical and clinical data generated

² In this document, any reference to “Herceptin” should be considered a specific reference to US-licensed Herceptin. EU-approved trastuzumab will be referred to as EU-Herceptin. References to unknown sources of trastuzumab (e.g., based on historical studies) will use “trastuzumab”.

using EU-Herceptin as the comparator. The amino acid sequences of ABP-980 and US-Herceptin are identical and a comparison of the secondary and tertiary structures and the impurity profiles of ABP-980 and US-Herceptin support the conclusion that the two products are highly similar. The immunogenicity assays used to evaluate anti-drug antibodies in comparative immunogenicity study provided in support of this BLA are adequately validated.

The applicant conducted a comparison of the non-clinical pharmacokinetics (PK) and toxicity profiles of ABP-980 and EU-Herceptin in rats and cynomolgus monkeys. Overall, the animal studies provided in the BLA submission did not identify any safety concerns with ABP-980 or differences in the PK or toxicity profile of ABP-980 compared to EU-Herceptin in mice and monkeys. The analytical comparisons of ABP-980, US-Herceptin and EU-Herceptin established the analytical portion of the scientific bridge to support the justification for the use of nonclinical data generated using EU-Herceptin as the comparator.

Further, the applicant conducted a pharmacokinetic (PK) similarity study, 20130117, and a comparative clinical study, 20120283, to support the demonstration of no clinically meaningful differences between ABP-980 and US-Herceptin. Study 20130117 was a single-dose, randomized, single-blind, 3-arm, parallel group study in healthy male subjects designed to determine the PK similarity of ABP 980, US-licensed Herceptin, and EU-approved Herceptin. The results of the study established the PK similarity between ABP 980 and US-licensed Herceptin. The study results also provide the PK portion of the scientific bridge and supports the use of EU-approved Herceptin in the comparative clinical Study 20120283.

The results of the clinical development program indicate that the applicant's data support a determination of no clinically meaningful differences between ABP-980 and US-Herceptin in terms of safety and efficacy in the indication studied (early breast cancer). Specifically, the comparative clinical study, Study 20120283, was a two-part multicenter, double-blind, randomized, parallel-group. Study 20120283 had two parts:

- Neoadjuvant phase: All patient received run-in chemotherapy. Subjects were randomized to ABP 980 or EU-Herceptin plus paclitaxel.
- Adjuvant phase: Patients who initially received ABP 980 during the neoadjuvant phase continued on ABP 980 during the adjuvant phase to complete 1 year of a trastuzumab product. Patients initially randomized to EU-Herceptin during the neoadjuvant phase were re-randomized to either continue with EU-Herceptin or switch to ABP 980 during the adjuvant phase to complete 1 year of a trastuzumab product. This re-randomization was blinded.

The co-primary efficacy endpoints were risk difference and risk ratio of the incidence of pCR in breast tissue and axillary lymph nodes by local laboratory assessment. In general, majority of analyses of RR and RD of pCR conducted in the PP or ITT population based on local laboratory assessment resulted in 90% CIs with upper bounds that slightly exceed that of the pre-defined margin. However, this is unlikely to result in any clinically meaningful difference in other endpoints such as disease free survival (DFS) or overall survival. Analyses of RD and RR of pCR based on central laboratory assessment resulted in 90% CIs that were within the pre-defined margins. For this application, the FDA clinical review team considers central assessment for pCR to be acceptable because central assessment for pCR is generally a more reliable method and the applicant was able to obtain sufficient samples for analysis to ensure

reliability of this analysis in this study. The results of the comparative clinical study support a demonstration of no meaningful differences between ABP980 and US-Herceptin.

The incidence of immunogenicity for ABP 980 and EU-approved Herceptin was also compared in Study 20120283. The results indicate similar incidence and titers of anti-drug antibodies (ADA) for both products. No apparent impact of ADA on safety, efficacy, or PK endpoints was noted.

The applicant is seeking indications that are the same as those for US-Herceptin and provided adequate scientific justification for extrapolation of data and information to support licensure of ABP-980 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 ABP-980 is highly similar to US-Herceptin, notwithstanding minor differences in clinically inactive components, and supports a demonstration that there are no clinically meaningful differences between ABP-980 and US-Herceptin in terms of safety, purity, and potency; however, due to DP manufacturing facility inspection 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(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.”

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. When an applicant’s proposed biosimilar development program includes data generated using a non-US-licensed comparator to support a demonstration of biosimilarity to the US-licensed reference product, the applicant must provide adequate data or information to scientifically justify the relevance of these comparative data to an assessment of biosimilarity and establish an acceptable bridge to the US-licensed reference product.

Regulatory History

The following summarizes the key milestones in the U.S. regulatory history:

Sept 21, 2012: Pre-IND meeting for IND 115424

Discussed biosimilar development plans for trastuzumab 150 mg powder for concentrate for solution for infusion, study treatment for MBC should not be limited to 15 months and should be continued for patients enrolled as long as patients are deriving clinical benefit, for MBC risk ratio should be primary endpoint, for MBC lower bound to rule out superiority should be specified, totality of evidence will be used to determine whether biosimilarity demonstrated for MBC, in a neoadjuvant trial adjuvant trastuzumab for 1 year is needed and patients would have to be followed for DFS and OS to support the primary endpoint of pCR, if the study will be conducted outside of the US the studied patient population should be representative of the US breast cancer patient population, guidance on extrapolation, analytical similarity and PK must be performed that compares the biosimilar product directly with the US reference product

March 15, 2013: Biologics Product Development, Type 2 Meeting – Clinical

Discussed revised protocol and SAP, equivalence margins for risk ratio of 0.79 to 1.27 using 80% upper bound for the trastuzumab effect and retaining 49% of that effect with sample size 818 patients, agreement on risk ratio of pCR as primary endpoint, applicant to provide 12 months of safety and immunogenicity data from the neoadjuvant and adjuvant phases, agreement to transition from EU-Herceptin to ABP 980 in the adjuvant phase for half of the patients to provide additional safety data and not for supporting interchangeability, discussed why local assessment of pCR was justified and why central assessment would be impractical, a central read of the pCR report would be conducted

January 26, 2016: Biologics Product Development, Type 2 Meeting – Clinical

Discussion on the PK study 20130119, risk ratio should be used as the primary endpoint for evaluating pCR, all EOI events should be documented in narratives and hyperlinked eCRFs,

FDA agreed with axillary lymph node assessment, long term safety and immunogenicity data to be submitted in day 120 safety update

May 16, 2016: Biosimilar Biological Product Development (BPD), Type 2 Meeting – CMC Only

March 17, 2017: BPD, Type 4 Meeting
Discussion about presentation and organization of electronic submission of data for BLA

June 29, 2017: BPD, Type 1 Meeting – CMC Only

July 28, 2017: BLA 761073 submitted to FDA.

3. CMC/Device

Source: CMC/Quality/Micro/Facilities Review Team

Discipline	Reviewer	Branch/Division
Drug Substance	Chen Sun	OPQ/OBP/DBRRII
Analytical Similarity	Chen Sun	OPQ/OBP/DBRRII
Drug Product	Chih-Jung Hsu	OPQ/OBP/DBRRII
Immunogenicity Assays	Chih-Jung Hsu	OPQ/OBP/DBRRII
Labeling	Vicky Borders-Hemphill	OPQ/OBP
Facilities	Wayne Seifert	OPQ/OPF/DIA
Facilities Team Lead	Zhihao Peter Qui	OPQ/OPF/DIA
Microbiology Drug Substance	Kathleen Jones	OPQ/OPF/DMA
Microbiology Drug Product	Jessica Hankins	OPQ/OPF/DMA
Microbiology QAL	Reyes Candau-Chacon	OPQ/OPF/DMA
Application Technical Lead	Patrick Lynch	OPQ/OBP/DBRRII
Tertiary Reviewer for OBP	Howard Anderson	OPQ/OBP/DBRRII
RBPM	Keith Olin	OPQ/OPRO

Final Product Quality Team Recommendation: Complete Response

General Product Quality Considerations

ABP-980 is a humanized IgG1κ monoclonal antibody that binds human epidermal growth factor receptor 2 (HER2). A proposed mechanism of action is inhibition of ligand-independent HER2 signaling, which in turn inhibits the proliferation of tumor cells that overexpress HER2. A second proposed mechanism of action is antibody-dependent cellular cytotoxicity (ADCC) mediated through concomitant binding to HER2 and Fcγ receptors on the surface of immune system effector cells, which leads to anti-tumor immune responses.

The drug substance is produced by recombinant DNA technology in cultures of Chinese Hamster Ovary cells. The final drug product is supplied in vials as a white to pale yellow lyophilized powder for reconstitution with bacteriostatic water for injection (bWFI) or sterile water for injection (sWFI). ABP-980 drug product is formulated in 4.2 mM L-histidine, 51 mM α,α -trehalose, 0.008% (w/v) polysorbate 20 at pH 6. The formulation are the same as US-licensed Herceptin. (b) (4)

Analytical data submitted in the BLA support the conclusion that ABP-980 is highly similar to US-Herceptin. The applicant included a comprehensive analytical similarity assessment comparing ABP-980 to US-Herceptin. The applicant provided data from three-way analytical and 3-way PK comparisons amongst EU-Herceptin, US-Herceptin, and ABP-980 to establish a scientific bridge to support a justification for reliance on data derived from the use of EU-Herceptin. The analytical data supports similar biological activities pertaining to both Fab and Fc portions of the molecule, primary structures including post-translational modifications, higher order structures, product-related species, degradation pathways, thermal stability, and drug product attributes. The extent of analytical characterization data provided is robust. Known and potential mechanisms of action of trastuzumab were evaluated by multiple orthogonal methods sensitive to detect potential differences in the molecules. The numbers of product lots used in the analytical assessments were adequate to capture lot-to-lot variability. The analytical data supported the establishment of the analytical portion of the scientific bridge.

The manufacturing processes for ABP-980 drug substance and drug product are well controlled and consistently produce product that is safe, pure and potent. The drug substance process is qualified for removal of impurities and inactivation or removal of adventitious agents. The overall control strategy for drug substance and drug product is comprehensive for control of raw materials, process performance, and product quality attributes. ADCC activity of ABP-980 is controlled (b) (4)

During the review cycle, the applicant agreed to implement an Fc γ RIIIa binding test to the drug substance release specification. This test provides additional assurance that ADCC activity is fully controlled in commercial ABP-980 lots. The current proposed manufacturing control strategy is sufficient to ensure process consistency and product quality.

Please refer to the complete response letter for the list of deficiencies and comments.

Facilities Review/Inspection

In this BLA, the manufacturing site of ABP-980 DS is at (b) (4) and the manufacturing site of ABP-980 DP is at (b) (4)

Per Wayne Seifert and Zhihao (Peter) Qiu from the Division of Inspectional Assessment, OPF, OPQ, the proposed facilities for manufacture and testing of ABP 980 DS are currently in a state of compliance and are acceptable from a facilities assessment standpoint.

However, they recommended that the application not be approved due to multiple deficiencies related to CGMP that were observed at the FDA pre-license inspection (PLI) conducted (b) (4) to (b) (4) of the (b) (4) drug product manufacturing facility. During the inspection, the investigator noted deficiencies, including the following:

(b) (4)

The (b) (4) facility's response to observations was inadequate for (b) (4)

(b) (4)

During the inspection, the investigator noted the following deficiencies:

(b) (4)

The facility's response to the observation for (b) (4) manufacturing area that included the (b) (4) was inadequate.

Please refer to the review from Wayne Seifert and endorsed by Zhihao (Peter) Qiu for more information on the deficiencies and their comments.

Reviewer Comment: *I concur with Division of Inspectional Assessment, OPF, OPQ review team's conclusion that the application not be approved due to multiple deficiencies related to CGMP that were observed at the FDA pre-license inspection of the (b) (4) drug product manufacturing facility.*

Analytical Data Assessment

The analytical similarity assessment was performed to establish that ABP-980 and US-Herceptin are highly similar, notwithstanding minor differences in clinically inactive components. In addition, the assessment of analytical data from ABP-980, US-Herceptin, and EU-Herceptin confirmed the analytical portion of the scientific bridge among ABP-980, US-Herceptin, and EU-Herceptin to justify the relevance of the nonclinical and comparative clinical data generated using EU-Herceptin. The applicant performed pair-wise analytical comparisons of all 3 products.

For attributes primarily influenced by the drug substance manufacturing process, statistical analyses included only independent lots of ABP-980 drug product or drug substance. The applicant applied a tier-based system for evaluating similarity based on each attribute's potential to impact clinical outcomes. Potency and ADCC attributes reflect mechanisms of action and were therefore evaluated with the highest statistical rigor. The selection of methods and assignment of attributes to different tiers are justified. Data provided in the analytical assessment were collected using methods appropriately validated or qualified for intended use.

In summary, the data demonstrate that ABP-980, US-Herceptin, and EU-Herceptin have the same amino acid sequences apart from differences at the heavy chain C-terminal lysine residue. Differences in the levels of C-terminal lysine residue are justified based on current understanding that C-terminal lysine residues of monoclonal antibodies are cleaved in the bloodstream shortly after intravenous administration. The data also demonstrate similar higher order structures, which is supported by both biochemical and functional testing results.

Similar potency between ABP-980, US-Herceptin, and EU-Herceptin was demonstrated in a bioassay that measures dose-dependent inhibition of proliferation in BT-474 cells derived from breast cancer. Comparisons for all three products met pre-defined statistical equivalence criteria. Similar bioactivity between the 3 products was confirmed in an orthogonal assay that measures anti-proliferation activity against NCI-N87 cells derived from gastric cancer. Results from multiple orthogonal HER2 binding assays support ABP-980, US-Herceptin, and EU-Herceptin have similar affinities for the targeted HER2.

Similar ADCC activity between ABP-980, US-Herceptin, and EU-Herceptin was demonstrated when using peripheral blood mononuclear cells (PBMC) as immune system effector cells. The PBMCs were isolated from healthy donors heterozygous for FcγRIIIa (158V/F) alleles. Comparisons for all three products met pre-defined statistical equivalence criteria.

Majority of the tests met pre-defined statistical or qualitative criteria for assessing similarity of ABP-980 to US-Herceptin and establishing the analytical component of the three-way scientific bridge between ABP-980, US-Herceptin, and EU-Herceptin. In instances where differences were observed, residual uncertainty was mitigated by additional information or data to support no meaningful impact on biological behavior of the molecule. The differences do not preclude a determination that ABP-980 is highly similar to US-Herceptin or the establishment of the analytical component of the three-way scientific bridge.

In summary, the analytical data support the conclusion that ABP-980 is highly similar to US-Herceptin, notwithstanding minor difference in clinically inactive components. EU-approved Herceptin was used as a comparator in clinical studies provided in support of this BLA. Analytical comparisons of ABP-980, US-Herceptin, and EU-Herceptin provided in the BLA support establishment of the analytical component of the three-way scientific bridge. The immunogenicity assays used to evaluate anti-drug antibodies in comparative immunogenicity studies provided in support of this BLA are adequately validated.

Reviewer Comment: I concur with CMC/OBP review team's conclusion that data support a demonstration that ABP-980 is highly similar to US-Herceptin. The data also establish the analytical component of the three-way scientific bridge. However, the application cannot be approved due to multiple deficiencies related to CGMP that were observed at the FDA pre-license inspection of the drug product manufacturing facility.

CDRH

A CDRH consult was obtained to comment on the product label for BLA 761073, 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 diagnostic for trastuzumab could serve as companion diagnostics for ABP 980. The applicant provided a response on January 18, 2018. In Amgen's comparative clinical study, an FDA-approved companion diagnostic for trastuzumab was utilized at the central laboratory to confirm HER2-positivity. CDRH reviewers concluded that applicant's response explaining why it believes the approved companion diagnostics for trastuzumab could serve as companion diagnostics for ABP 980 is adequate. 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. Based on the applicant's justification and the proposed therapeutic labeling in section 14 referencing the original trastuzumab clinical studies, CDRH agreed that the language regarding "an FDA-approved companion diagnostic for a trastuzumab product" would be acceptable for the ABP 980 label.

4. Nonclinical Pharmacology/Toxicology

Source: Pharmacology and Toxicology Review (Drs. Kimberly Ringgold and Tiffany Ricks)

Final Pharmacology/Toxicology Team Recommendations: Approval.

The anti-tumor activity of ABP 980 and EU-Herceptin was compared in two xenograft tumor models overexpressing HER2. ABP 980 inhibited tumor growth in both breast and gastric cancer cells in a similar manner to EU-Herceptin.

The pharmacokinetics of ABP 980 and EU-Herceptin were assessed in cynomolgus monkeys toxicity study. Plasma exposures in monkeys were similar. Therefore, the PK of ABP 980 was concluded to be similar to EU-Herceptin. A comparative toxicology study was performed in monkeys with ABP 980 and EU-Herceptin. Toxicity findings were similar. No toxicological findings were observed in a toxicity study conducted in rats after ABP 980 or

EU-Herceptin administration. These results were expected since trastuzumab is not pharmacologically active in rats.

Tissue cross-reactivity studies were performed in human mammary neoplastic tissues overexpressing HER2 and normal human tissues and blood smears. ABP 980 staining was consistent with that of EU-Herceptin stained tissues.

Applicant provided the results from comparative analytic data to support the establishment of a scientific bridge between ABP 980, EU-Herceptin, and US-Herceptin to justify the relevance of data derived from studies conducted using EU-Herceptin to the demonstration of biosimilarity of ABP 980 to US-Herceptin.

In conclusion, from the nonclinical perspective, the data from animal studies were adequate to demonstrate similarity in the safety and PK profiles of ABP-980 and EU-Herceptin in rats and cynomolgus monkeys. No residual uncertainties were identified by the pharmacology and toxicology discipline.

Reviewer Comment: *I concur with nonclinical team's conclusion that the submitted pharmacology and toxicology data were adequate to demonstrate similarity in the safety and PK profiles of ABP 980 and US-licensed Herceptin in rats and cynomolgus monkeys.*

5. Clinical Pharmacology

Source: Clinical Pharmacology Review (Drs. Olanrewaju Okusanya, Sarah J. Schrieber and Nam Atiqur Rahman)

Final Clinical Pharmacology Team Recommendations: Approval

The applicant submitted a pharmacokinetic (PK) similarity study and a comparative clinical study to support a demonstration of no clinically meaningful differences between ABP 980 and US-licensed Herceptin. Study 20130117 was a single-dose, randomized, single-blind, 3-arm, parallel group study in 157 healthy male subjects designed to determine the PK similarity of ABP 980, US-licensed Herceptin, and EU-approved Herceptin following a single 6 mg/kg intravenous dose. The 90% confidence intervals for all three pairwise comparisons of the PK endpoints were within the pre-specified limits of 80 to 125%. The results of the study established the PK similarity between ABP 980 and US-licensed Herceptin. The study results also provide the PK portion of the scientific bridge and supports a justification for reliance on data derived from the use of EU-approved Herceptin.

Immunogenicity

The incidence of immunogenicity for ABP 980 and EU-approved Herceptin was compared in a multiple-dose, parallel-arm Study 20120283 in 725 patients with HER2-positive early breast

cancer. The results indicate similar incidence and titers of anti-drug antibodies (ADA) for both products. No apparent impact of ADA on safety, efficacy, or PK endpoints was observed.

In conclusion, from the clinical pharmacology perspective, the PK and immunogenicity results supports a demonstration of no clinically meaningful differences between ABP 980 and US-licensed Herceptin and add to the totality of the evidence to support a demonstration of biosimilarity between ABP 980 and US-licensed Herceptin.

Reviewer Comment: *I concur with clinical pharmacology team's conclusion that the submitted clinical pharmacology studies adequately demonstrated similarity of PK among ABP 980, US-Herceptin and EU-Herceptin and further supports a demonstration of no clinically meaningful differences between ABP 980 and US-licensed Herceptin.*

6. Clinical Microbiology

Not applicable.

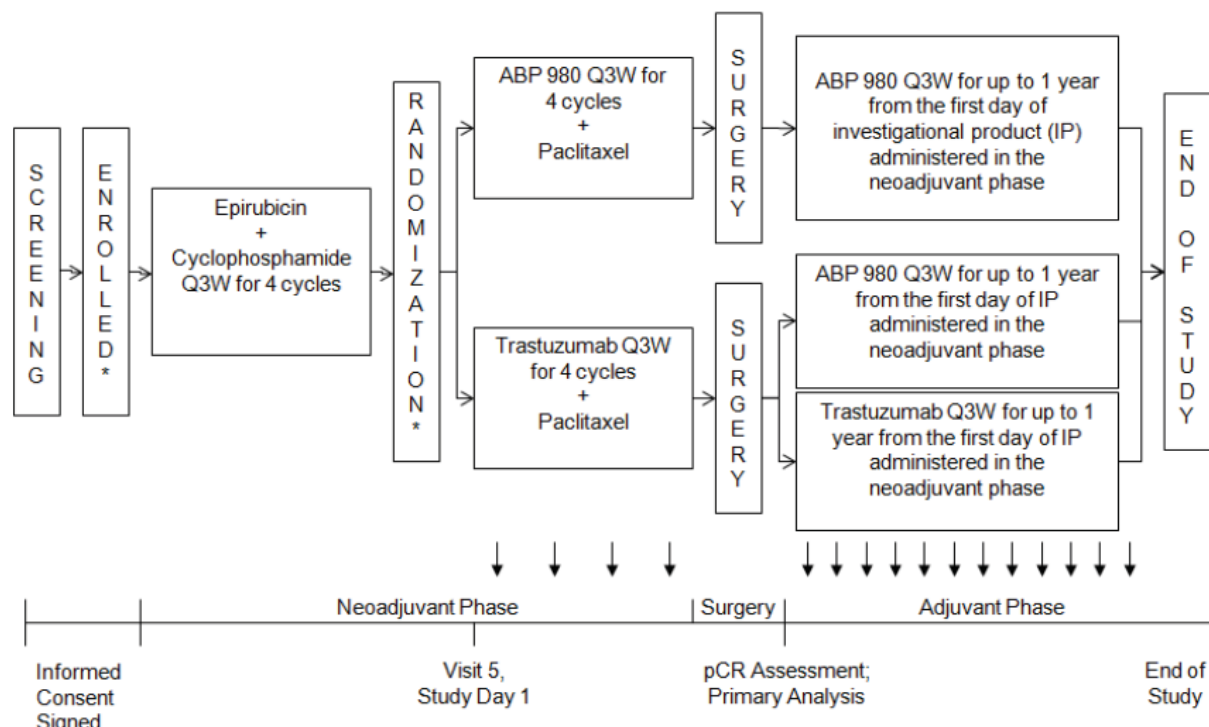
7. Clinical/Statistical- Efficacy

Source: Combined Clinical/Stat Review (Drs. Lynn Howie, Jennifer Gao, Joyce Cheng, Shenghui Tang and Jason Schroeder)

Final Clinical/Statistical Team Recommendations: Approval

The applicant submitted comparative clinical study 20120283 to support a demonstration of no clinically meaningful differences between ABP 980 and US-Herceptin.

Comparative Clinical Study 20120283 Schema



* Approximately 808 subjects enrolled, approximately 768 randomized

Study 20120283 is a two-part multicenter, double-blind, randomized, parallel-group, comparative clinical study. Patients were randomized 1:1 and stratified by tumor T stage, nodal status, hormone receptor status, planned paclitaxel dosing schedule, and geographic region.

- **Neoadjuvant phase:** All patients received run-in chemotherapy with epirubicin and cyclophosphamide. Subjects were randomized to ABP 980 or EU-Herceptin plus paclitaxel. Surgery was completed 3-7 weeks after the last dose of the trastuzumab product in the neoadjuvant phase.
- **Adjuvant phase:** Patients who initially received ABP 980 continued on ABP 980 during the adjuvant phase to complete 1 year of a trastuzumab product. Patients initially randomized to EU-Herceptin during the neoadjuvant phase were re-randomized to either continue with EU-Herceptin or switch to ABP 980 during the adjuvant phase to complete 1 year of a trastuzumab product. This re-randomization was blinded.

The co-primary efficacy endpoints were risk difference and risk ratio of the incidence of pCR in breast tissue and axillary lymph nodes by local laboratory assessment.

The primary endpoint of pCR (absence of invasive tumor cells in the breast tissue and axillary lymph nodes, regardless of residual ductal carcinoma in situ) was assessed based on local laboratory evaluation of the tumor sample.

Reviewers Comments: The neoadjuvant setting for breast cancer used in study 20120283 is an acceptable, homogenous, and sensitive patient population to evaluate for no meaningful differences between ABP 980 and EU-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 definition of pCR used (in breast and lymph nodes), is generally the preferred definition by the Agency for regulatory decision-making. Central Pathology Review is also generally preferred by the Agency for standardization. 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 20120283 is acceptable to support approval of ABP 980 for the indications for which US-Herceptin has been previously approved.

Sample size Calculations

The applicant planned to enroll approximately 808 subjects so that approximately 768 subjects would be randomized. This sample size would provide at least 90% power to demonstrate equivalence between ABP 980 and EU-Herceptin on the RR of pCR with a pre-defined equivalence margin of (0.7586, 1.3182) at a two-sided significance level of 0.05, accounting for a 5% dropout rate during run-in chemotherapy. This sample size would also provide at least 90% power to demonstrate equivalence based on the RD of pCR with a pre-defined margin of (-13%, 13%) at a 2-sided significance level of 0.05. These calculations all assumed a pCR rate of approximately 42.5% on both treatment arms and the RR and RD of pCR for ABP 980 to EU-Herceptin were to be analyzed with a two-sided 90% CI (i.e., alpha controlled $\leq$ 0.05). If the 90% CI completely falls in each respective pre-defined equivalence region, then equivalence would be declared. The equivalence region for RR of pCR was derived using a fixed-effect meta-analysis of historical trastuzumab trials that included both EU-Herceptin and US-Herceptin to estimate the treatment effect of trastuzumab with chemotherapy versus chemotherapy alone.

The applicant followed FDA draft guidance on non-inferiority clinical trials (2010) to derive the non-inferiority side of the margin for RR of pCR. The applicant chose to use a meta-analysis of two randomized controlled studies, Buzdar et al. 2007 and Gianni et al. 2010, to estimate the treatment effect. The resulting point estimate for RR of pCR between trastuzumab in combination with standard chemotherapy vs. chemotherapy alone was 0.4889 with a 60% confidence interval of (0.4154, 0.5754). To preserve 50% of the upper bound of the 60% confidence interval, the non-inferiority side of the equivalence margin was calculated as $\exp(\log(0.5754)*0.5) = 0.7586$ and consequently the superiority margin was $1/0.7586=1.3182$.

Results

This was an international study with patients enrolled from 20 countries in the ITT population. Patients' demographic characteristics and baseline disease characteristics were well balanced in both arms. (For more details, please see Clinical /Stat review)

The efficacy results for both primary endpoints and Sensitivity Analyses of pCR are summarized in tables below.

Study 20120283 Primary Efficacy Results

	ABP 980 N=358 n (%)	EU-Herceptin N=338 n (%)
Pathologic complete response (pCR), n (%)		
Yes	172 (48.0)	137 (40.5)
No	186 (52.0)	201 (59.5)
Risk Difference (ABP 980 – EU-Herceptin) ^a , %	7.3	
90% CI for RD ^a	(1.2, 13.4)	
Risk Ratio (ABP 980/EU-Herceptin) ^a	1.1877	
90% CI for RR ^a	(1.0327, 1.3660)	

^a Estimated using a generalized linear model adjusted for randomization stratification factors: T-stage, nodal status, hormone receptor status, planned paclitaxel dosing schedule, and geographic region
Source: CSR Table 14 and Study 20120283 dataset adpcr.xpt

Study 20120283 Sensitivity Analyses of pCR

	ABP 980 # responders/ # pts (pCR%)	EU-Herceptin # responders/ # pts (pCR%)	pCR RD (90% CI)	pCR RR (90% CI)
Assessed by Local Lab				
pCR evaluable with corrected stratification factors	172/358 (48.0)	137/338 (40.5)	7.4 (1.3, 13.6)	1.1939 (1.0383, 1.3727)
ITT using NRI ^a	172/364 (47.3)	137/352 (38.9)	8.1 (2.0, 14.1)	1.2096 (1.0501, 1.3933)
ITT using NRI with corrected stratification factors ^a	172/364 (47.3)	137/352 (38.9)	8.2 (2.2, 14.2)	1.2171 (1.0569, 1.4016)
PP population	166/351 (47.3)	134/328 (40.9)	6.4 (0.2, 12.6)	1.1623 (1.0084, 1.3396)
pCR evaluable pop. with additional model covariates	172/358 (48.0)	137/338 (40.5)	7.3 (1.1, 13.4)	1.1935 (1.0383, 1.3718)
Assessed by Central Lab				
pCR evaluable pop.	162/339 (47.8)	138/330 (41.8)	5.8 (-0.5, 12.0)	1.1419 (0.9934, 1.3124)
ITT using NRI ^a	162/364 (44.5)	138/352 (39.2)	5.1 (-0.9, 11.1)	1.1370 (0.9854, 1.3118)
PP population	156/333 (46.8)	137/321 (42.7)	4.1 (-2.3, 10.4)	1.0986 (0.9545, 1.2644)

^a Data from nine subjects

(b) (6)

manually assigned to EU-Herceptin were not included in this analysis.

Source: CSR Table 15 and Study 20120283 dataset adpcr.xpt

In general, all analyses of RR of pCR based on local laboratory assessment resulted in 90% CIs with upper bounds that slightly exceed that of the pre-defined margin (i.e. >1.3182). Analyses of RD of pCR based on local laboratory assessment also resulted in 90% CIs with upper bounds that slightly exceed that of the pre-defined margin (i.e. >13%), except for the analysis conducted in the PP population. Though the upper limits of the CIs for RR slightly exceed the prespecified margins, this is unlikely to result in any meaningful difference in other endpoints such as disease free survival (DFS).

Analyses of RD and RR of pCR based on central laboratory assessment resulted in 90% CIs that were within the pre-defined margins. Note that in these analyses pCR evaluation was based on central laboratory evaluation of tumor samples so the sample sizes of both the pCR evaluable and PP populations have changed to correspond with that data. The FDA clinical review team considers central assessment for pCR to be acceptable to support the conclusion of no meaningful differences between ABP 980 and EU-Herceptin because in general central assessment for pCR is a more reliable method and the applicant was able to obtain sufficient samples for analysis to ensure reliability of this analysis in this study.

For on-study EFS, a total of 34 subjects (by neoadjuvant treatment: 19 on the ABP 980 arm and 15 on the EU-Herceptin arm) had disease progression, recurrence, or died as of the initial data cut-off date of May 5, 2016. The estimated hazard ratio of ABP 980 relative to EU-Herceptin was 1.3155 (95% CI: 0.7342, 2.3572) and median EFS had not been reached.

For OS, a total of 5 subjects died on study (by neoadjuvant treatment: one on the ABP 980 arm and four on the EU-Herceptin arm).

In conclusion, the efficacy results of the clinical development program indicate that the applicant's data support a determination of no clinically meaningful differences between ABP 980 and US-Herceptin.

Reviewer Comment: *I concur with clinical and statistical team's conclusion that the submitted clinical data demonstrated no differences in terms of efficacy between ABP 980 and EU-Herceptin. As the applicant established an appropriate scientific bridge comprised of comparative PK and analytical data for ABP 980, EU-Herceptin and US-Herceptin (please see sections 3 and 5), the efficacy results support a demonstration of no clinically meaningful differences between ABP 980 and US-Herceptin.*

8. Safety

Source: Combined Clinical/Stat Review (Drs. Lynn Howie, Jennifer Gao, Joyce Cheng, Shenghui Tang and Jason Schroeder)

The safety evaluation for this application was based on comparative study 20120283. A total of 725 patients were in the safety population. The safety population consisted of all patients

who received at least one dose of study drug. There was no pooling of safety data as only one comparative study was conducted.

The frequency of TEAEs, serious events, and events leading to discontinuation of study drug had no meaningful differences between the treatment arms. The treatment-related TEAEs in the neoadjuvant and adjuvant phase were well balanced between the two study drugs without safety concerns and the majority were grade 1-2 in severity. Six patients died in the safety population over the entire study and very few patients experienced serious TEAEs during the neoadjuvant and adjuvant phases of study. Narratives were reviewed by FDA review team and no safety concerns were noted. Events of interest, based on the known safety profile of trastuzumab, were cardiac failure, neutropenia, infusion reactions, pulmonary toxicity, hypersensitivity, and infections and infestations. These were also balanced between the two study drugs. Immunogenicity was assessed on this study and no patient had neutralizing antibodies.

Reviewer Comment: *The safety results of the clinical development program indicate that the applicant's data support a determination of no meaningful differences between ABP 980 and EU-Herceptin. The safety analyses in study 20120283, which compared ABP 980 and EU-Herceptin in HER2-positive early breast cancer patients in the neoadjuvant and adjuvant settings, did not show any meaningful differences in safety between arms.*

9. Considerations for Extrapolation of Biosimilarity

Source: Combined Clinical/Stat Review (Drs. Lynn Howie, Jennifer Gao, Joyce Cheng, Shenghui Tang and Jason Schroeder)

The applicant seeks licensure for all indications for which US-Herceptin is licensed. However, the ABP 980 clinical program provides clinical efficacy and safety data largely from a clinical program in patients with early BC. The neoadjuvant setting is an acceptable, homogenous, and sensitive patient population to evaluate for no meaningful differences between ABP 980 and EU-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 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 used in study 20120283 is acceptable to support approval of ABP 980 for the indications for which US-Herceptin has been previously approved.

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

- ABP 980 is structurally and functionally similar to US-Herceptin and shares the same mechanism of action (MoA) across all indications.
- The data support a similar PK profile between ABP 980 and US-Herceptin.
- The biodistribution/disposition mechanisms for ABP 980 are expected to be similar to those of US-Herceptin.
- ABP 980 has demonstrated clinical efficacy similar to Herceptin in early breast cancer with no clinically meaningful differences in safety and immunogenicity. Efficacy in metastatic breast cancer, early breast cancer, and metastatic gastric cancer is related to the shared MoA. The statutory requirements for biosimilarity have been met and ABP 980 is expected to have a similar efficacy, safety, and immunogenicity profile as US-Herceptin in early breast cancer.

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 and information 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 ABP 980 is highly similar to US-Herceptin based on extensive analytical data and that there are no clinically meaningful differences in safety and efficacy between ABP 980 and US-Herceptin, which supports extrapolating the data to other indications. The reviewers consider extrapolation to be scientifically justified.

Reviewer Comment: *I concur with clinical team’s conclusion that the evidence indicates that the extrapolation of data, including clinical data, to support licensure as a biosimilar for the conditions of use for which US-licensed Herceptin has been previously approved is scientifically justified.*

10. Advisory Committee Meeting

An advisory committee meeting was not held for this application.

11. Pediatrics

Amgen requested a full waiver of pediatric studies for the requested indications and submitted an agreed iPSP in 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 Pediatric Review Committee met on April 4, 2018 and concurred with the plan for a full waiver. The minutes were entered to DARRTS on April 20, 2018.

12. Other Relevant Regulatory Issues

Application Integrity Policy (AIP)

The application contained statements from Amgen 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

The studies 20130119 and 20120283 were conducted through the CROs named (b) (4). In compliance with 21 CFR Part 54 Amgen, (b) (4) forwarded a certification/Disclosure Form to all clinical investigators. All investigators were assessed for equity interest, significant payments of other sorts, and other compensation by the Applicant and propriety interest. Financial disclosure information is provided for studies 20130119 and 20120283 in the BLA.

Bioequivalence Inspections

Hasan A. Irier, Ph.D., from the Division of Generic Drug Bioequivalence Evaluation (DGDBE) within the Office of Study Integrity and Surveillance (OSIS) completed a review dated December 19, 2017. He conducted an inspection of the bioanalytical portion of studies 20130119 and 20120283 submitted to BLA 761073. Form FDA 483 was issued at the inspection close-out. Significant objectionable conditions were observed during this inspection that impacted the reliability of the audited studies. The firm provided a response to the form 483 observations on November 21, 2017. The final inspection classification is Voluntary Action Indicated (VAI). In the form 483 response, Amgen stated that additional method validation data (freeze-thaw stability of anti-drug antibodies used in method validation) will be provided by January 2018. Additionally, the firm's response did not address deficiencies in the overall inter-assay precision of the NAb assay. Thus, pending the receipt and evaluation of additional method validation data, Hasan A. Irier recommended that the data from studies 20130119 and 2012083 not be accepted for further Agency review. Upon receipt, OSIS intended to evaluate the additional method validation data, and amend this EIR Review.

Hasan A. Irier entered into DARRT on February 8, 2018 an amendment to his previous review stating that on January 31, 2018, Amgen provided new stability data for additional freeze-thaw cycles in response to the FDA Form 483, Observation 4. The OSIS scientist reviewed the new data and found that it addressed the stability issue. However, Amgen did not provide additional data demonstrating overall inter-assay precision of the NAb assay. Therefore, the reviewer did not recommend accepting the NAb validation data for further Agency review at that time.

Hasan A. Irier entered into DARRT on March 7, 2018 an amendment to his previous reviews stating that Amgen provided an additional response to the issues identified during the inspection. After evaluation of the firm's additional response, the OSIS scientist, Hasan A. Irier Ph.D., recommends to accept the data for Agency review.

Angel S Johnson from the Division of Generic Drug Bioequivalence Evaluation (DGDBE) within the Office of Study Integrity and Surveillance (OSIS) completed a review dated January 3, 2018 and recommended to accept data without a clinical on-site inspection of Analytical facility (b) (4) as this site was recently inspected with the final classification VAI.

Xingfang Li, MD from the Division of Generic Drug Bioequivalence Evaluation (DGDBE) within the Office of Study Integrity and Surveillance (OSIS) completed a review dated March 5, 2018. Inspections of study 20130119 (BLA 761073) at Nucleus Network Limited, Melbourne, Victoria, Australia were conducted. No objectionable conditions were observed and Form FDA 483 was not issued at the inspection close-out. The final inspection classification is No Action Indicated (NAI). After reviewing the inspectional findings, reviewer found the data from the audited study 20130119 reliable. Thus, he recommended that the data from study 20130119 and other studies of similar design be accepted for further Agency review.

Clinical Inspections

Drs. Navid Homayouni, Susan Thompson (Team Leader) and Kassa Ayalew (Branch Chief) from OSI completed the clinical inspection summary (CIS) on February 15, 2018. FDA selected four clinical sites, and a CRO for audit. However, one inspection in Belarus was eventually cancelled due to visa issues just prior to start of the inspection. Additionally, inspection of the Sponsor, Amgen, was conducted by European Medicines Agency. There were no significant inspectional findings for these 3 clinical investigators. Although there were minor GCP violation by the CRO, they were unlikely to substantially impact the determination of efficacy and safety of the clinical trial and the final classification for the inspection was Voluntary Action Indicated by OSI. The OSI review concluded that the data from Study 20120283 submitted to the Agency in support of BLA 761073, appear reliable based on available information.

Reviewer Comment: *I concur with the OSI reviewers that the data from Study 20120283 submitted to the Agency appear reliable.*

Other discipline consults

Tingting Gao and Chi-Ming (Alice) Tu from the Office of Medication Error Prevention and Risk Management (OMEPRM) completed a review dated September 29, 2017, that concluded

that the proposed proprietary name, Kanjinti, was acceptable conditionally until the application is approved.

Tingting Gao and Chi-Ming (Alice) Tu from OMEPRM completed a review (dated January 30, 2018) that determined that the suffix anns for the non-proprietary name is acceptable (trastuzumab-anns) conditionally until the application is approved.

Tingting Gao and Chi-Ming (Alice) Tu completed a review dated March 29, 2018, that defined recommendations relating to carton and container and 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. Please refer to the primary clinical/statistical review.

13. Labeling

Proposed labeling submitted by Amgen 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 of the labeling were revised to reflect ABP 980 -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 and Risk Benefit Assessment

The Applicant is seeking licensure for indications that are the same as those licensed for US-Herceptin. The Applicant is seeking licensure for adjuvant breast cancer (which was studied in the ABP 980 clinical program), as well as the metastatic breast cancer and gastric cancer indications, which have not been directly studied in the ABP 980 clinical program. As explained above, extrapolation is scientifically justified.

The data submitted to the 351(k) BLA support a demonstration of biosimilarity for ABP 980. A demonstration that ABP 980 is highly similar to US-Herceptin, notwithstanding minor differences in clinically inactive components together with the clinical data discussed in this review, demonstrating no clinically meaningful differences between the products, support licensure of ABP 980 as a biosimilar to US-Herceptin under section 351(k) of the PHS Act. Because ABP 980 is biosimilar to US-Herceptin, ABP 980 is considered to have a favorable risk-benefit profile for all requested conditions of use.

However, because there were several issues with the Drug Product facility inspection deficiencies, 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 the complete response letter for 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/

LALEH AMIRI KORDESTANI
05/25/2018

CLINICAL REVIEW

Application Type	BLA, Original 351(k)
Application Number(s)	761073
Priority or Standard	Standard
Submit Date(s)	July 28, 2017
Received Date(s)	July 28, 2017
PsUFA Goal Date	May 28, 2018
Division / Office	DOP1/OHOP
Reviewer Name(s)	Jennifer Gao, MD Lynn Howie, MD Joyce Cheng, PhD
Review Completion Date	May 21, 2018
Established Name	Trastuzumab-anns
(Proposed) Trade Name	KANJINTI*
Therapeutic Class	HER2-binding humanized monoclonal antibody
Applicant	Amgen
Formulation(s)	IV
Dosing Regimen	8 mg/kg IV loading dose, then 6 mg/kg IV q3 wks
Proposed Indication(s)	KANJINTI 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	KANJINTI 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 "ABP-980".

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1. Recommendations/Risk Benefit Assessment

1.1. Recommendation on Regulatory Action

This biologics license application (BLA 761073) seeks approval of the product ABP-980 (proposed proprietary name Kanjinti), 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 ABP 980 support a demonstration of no clinically meaningful differences between ABP 980 and US-Herceptin. A demonstration that ABP 980 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 ABP 980 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) Human epidermal growth factor receptor 2 (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, approximately 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. 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 overall survival compared to chemotherapy alone. It is one of the key agents used to target these tumor subtypes and thus plays a central role in treatment of patients with breast and gastric cancer.

Trastuzumab is FDA approved for the treatment of HER2-overexpressing breast cancer in both the adjuvant and metastatic settings. 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 and as single agent for treatment in patients who have received prior chemotherapy for metastatic disease. Pertuzumab (Perjeta) is FDA approved as a first-line treatment of HER2-positive MBC in combination with trastuzumab and docetaxel, which was shown to have both a progression free survival (PFS) and overall survival (OS) benefit over trastuzumab and docetaxel alone. (11, 12) 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.

ABP 980 is a proposed biosimilar to US-Herceptin (trastuzumab). The applicant has submitted a BLA for ABP 980 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:

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 ABP 980 for the following indications:

Adjuvant Breast Cancer

For adjuvant treatment of HER2-overexpressing node positive or node negative (ER/PR negative or with one high risk feature) breast cancer

- as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
- as part of a treatment regimen with docetaxel and carboplatin

- as a single agent following multi-modality anthracycline based therapy.

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

Metastatic Breast Cancer

- 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.

Metastatic Gastric Cancer

- 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.

The results of the clinical development program support a demonstration of no clinically meaningful differences between ABP 980 and US-Herceptin. The applicant submitted data from study 20120283 assessing ABP 980 when used as treatment in patients with HER2-positive early breast cancer (EBC) in comparison to EU-licensed Herceptin (which will be referred to as EU-Herceptin for the remainder of this review) in the neoadjuvant setting. The study had co-primary efficacy endpoints of risk difference (RD) and risk ratio (RR) of the rate of pathologic complete response (pCR, defined as the absence of invasive tumor cells in the breast tissue and axillary lymph nodes regardless of DCIS) as assessed by local review for those treated with ABP-980 as compared to EU-Herceptin. However, the FDA considers RR to be the more appropriate metric for evaluating pCR. The RR of pCR in the ABP 980 arm as compared to the EU-Herceptin arm as assessed by local review was 1.1877 (90% CI: 1.0327, 1.3660), but the 90% CI was not contained within the pre-specified equivalence margin of (0.7586, 1.3182). Central blinded review of the RR of pCR was 1.1419 (90% CI: 0.9934, 1.3124), and this 90% CI was entirely within the pre-specified equivalence margin of (0.7586, 1.3182). The agency in general, considers the central blinded review of pCR a more reliable assessment of pCR and thinks that the data from the central blinded review is acceptable because the applicant was able to obtain sufficient samples for analysis to ensure reliability of this analysis. The clinical and statistical review team considers the analysis of the Central Review pathology results to support that there are no meaningful differences in efficacy between ABP 980 and EU-Herceptin, which supports a demonstration that ABP 980 has no clinically meaningful differences from US-Herceptin.

The safety findings of study 20120283 were reviewed, with special focus on cardiac, pulmonary, infusion reaction, and embryo-fetal toxicities. No meaningful differences between ABP 980 and EU Herceptin were found in the safety population.

The neoadjuvant setting for breast cancer used in study 20120283 is an acceptable, homogenous, and sensitive patient population to evaluate for no meaningful differences between ABP 980 and EU-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 20120283 is acceptable to support approval of ABP 980 for the indications for which US-Herceptin has been previously approved.

In addition, the applicant submitted data from study 20130119, a PK similarity study in healthy male volunteers, comparing the PK of ABP-980, EU-Herceptin, and US-Herceptin. A single IV dose of 6.0 mg/kg ABP-980, US-Herceptin or EU-Herceptin infused over 90 minutes was administered. The results demonstrated that the 90% confidence intervals for the ratios of the geometric means (GMs) were fully contained within the bioequivalence criteria of 0.80 to 1.25 for both the primary PK parameters (AUC_{inf} and C_{max}), and the secondary PK parameter (AUC_{last}) confirming the PK similarity between ABP 980 and US-Herceptin as well as between ABP 980 and EU-Herceptin. For the comparison of US-Herceptin to EU-Herceptin, the 90% CIs of the ratios of the geometric means were also fully contained within the bioequivalence criteria of 0.80 to 1.25 for both the primary PK parameters (AUC_{inf} and C_{max}), and the secondary PK parameter (AUC_{last}) confirming the PK similarity between US-Herceptin and EU-Herceptin. Based on the analytical and PK data, the applicant has established an adequate scientific bridge between EU-Herceptin, US-Herceptin, and ABP 980 to justify the relevance of clinical data generated using EU-Herceptin to support a demonstration of biosimilarity of ABP 980 to 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:

- ABP 980 is structurally and functionally similar to US-Herceptin and shares the same mechanism of action (MoA) across all indications.
- The data support a similar PK profile between ABP 980 and US-Herceptin.
- The biodistribution/disposition mechanisms for ABP 980 are expected to be similar to those of US-Herceptin.
- ABP 980 has demonstrated clinical efficacy similar to US-Herceptin in early breast cancer with no clinically meaningful differences in safety and immunogenicity. Efficacy in metastatic breast cancer, early breast cancer, and metastatic gastric

cancer is related to the shared MoA. The statutory requirements for biosimilarity have been met and ABP 980 is expected to have a similar efficacy, safety, and immunogenicity profile as US-Herceptin in early breast cancer.

The applicant has provided adequate justification for extrapolation. The applicant has demonstrated that ABP 980 is highly similar to US-Herceptin based on extensive analytical data and that ABP 980 has no clinically meaningful differences from US-Herceptin in efficacy and safety which supports approval for all indications for which US-Herceptin was previously approved (breast cancer treatment in the adjuvant and metastatic settings and metastatic gastric cancer). Therefore, the reviewers consider extrapolation to be scientifically justified.

A scientific bridge between EU-Herceptin, US-Herceptin, and ABP 980 has been established, based in part on the pharmacokinetic (PK) evaluation in study 20130119 which evaluated the pharmacokinetic (PK) similarities of ABP 980, EU-Herceptin and US-Herceptin. The analytical data supports a demonstration that ABP 980 and US-Herceptin are 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 ABP 980 and US-Herceptin. Extrapolation of data to support approval for all of the proposed indications is scientifically justified. Thus, the totality of the evidence supports biosimilarity of ABP 980 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.

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

ABP 980 (proposed trade name Kanjinti) 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 human epidermal growth factor receptor 2. 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 currently 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

ABP 980 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

Black box 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:

Sept 21, 2012: Pre-IND meeting for IND 115424

- Discussed biosimilar development plans for trastuzumab 150 mg powder for concentrate for solution for infusion, study treatment for MBC should not be limited to 15 months and should be continued for patients enrolled as long as patients are deriving clinical benefit, for MBC risk ratio should be primary endpoint, for MBC lower bound to rule out superiority should be specified, totality of evidence will be used to determine whether biosimilarity demonstrated for MBC, in a neoadjuvant trial adjuvant trastuzumab for 1 year is needed and patients would have to be followed for DFS and OS to support the primary endpoint of pCR, if the study will be conducted outside of the US the studied patient population should be representative of the US breast cancer patient population, guidance on extrapolation, analytical similarity and PK must be performed that compares the biosimilar product directly with the US reference product

March 15, 2013: Biologics Product Development, Type 2 Meeting – Clinical

- Discussed revised protocol and SAP, equivalence margins for risk ratio of 0.79 to 1.27 using 80% upper bound for the trastuzumab effect and retaining 49% of that effect with sample size 818 patients, agreement on risk ratio of pCR as primary endpoint, applicant to provide 12 months of safety and immunogenicity data from the neoadjuvant and adjuvant phases, agreement to transition from EU-Herceptin to ABP 980 in the adjuvant phase for half of the patients to provide additional safety data and not for supporting interchangeability, discussed why local assessment of pCR was justified and why central assessment would be impractical, a central read of the pCR report would be conducted

January 26, 2016: Biologics Product Development, Type 2 Meeting – Clinical

- Discussion on the PK study 20130119, risk ratio should be used as the primary endpoint for evaluating pCR, all EOI events should be documented in narratives and hyperlinked eCRFs, FDA agreed with axillary lymph node assessment, long term safety and immunogenicity data to be submitted in day 120 safety update

May 16, 2016: Biologics Product Development, Type 2 Meeting – CMC Only

March 17, 2017: Biologics Product Development, Type 4 Meeting

- Discussion about presentation and organization of electronic submission of data for BLA

June 29, 2017: Biologics Product Development, Type 1 Meeting – CMC Only

July 28, 2017: BLA 761073 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 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 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 study 20120283 was conducted in compliance with independent ethics committees (IECs), institutional review boards (IRBs), and the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines and in accordance with applicable regulations regarding clinical safety data management (E2A, E2B [R3]), European Community directives 2001/20, 2001/83, 2003/94, and 2005/28, and ICH guidelines regarding scientific integrity (E4, E8, E9, E10).

Study 20120283 was conducted in accordance with the Note for Guidance on gCP (ICH Harmonized Tripartite Guideline E6 (R1); US Code of Federal Regulations (21 CFR 50, 56, 312), the general guidelines indicated in the Declaration of Helsinki, and other applicable regulatory requirements.

3.3. Financial Disclosures

All investigators were assessed for equity interest, significant payments of other sorts, and other compensation by the applicant and propriety interest. Financial disclosure information is provided for covered studies 20130119 and 20120283. The applicant has stated that none of the clinical investigators involved with the ABP 980 studies have financial interests or arrangements to disclose as defined in 21 CFR 54.2(f).

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

4.1. Clinical Site Inspections

The following 3 clinical investigators and the CRO, (b) (4), was inspected and a summary of the findings are listed below in Table 2: Clinical Site Inspections

Table 2: Clinical Site Inspections

Name of CI, Site #, Address, Country if non-U.S. or City, State if U.S.	Protocol # # of Subjects	Inspection Dates	Classification
Olga Ponomarova, M.D. Site Number: 64007 69 Verkhovinnaya Strasse, Kyiv, Kiev, 03115, Ukraine	Protocol: 20120283 Number of Subjects Enrolled: 21	January 15-19, 2018	*NAI
Maria Turdean, M.D. Site Number: 50003 Strada Pasteur, Numarul 3-5, Cluj- Napoca, Cluj, 400006, Romania	Protocol: 20120283 Number of Subjects Enrolled: 16	December 4-8, 2017	NAI
Gabriel Ghizdavescu, M.D. Site Number: 50002 Strada Ana Ipatescu Nr 59, Ploiesti, Prahova, 100337, Romania	Protocol: 20120283 Number of Subjects Enrolled: 17	December 11-15, 2017	NAI
CRO: (b) (4)	Protocol: 20120283	(b) (4)	VAI (upgraded from NAI)

Reviewer Comments: European Medicines Agency, EMA, inspected Amgen in October, 2017 and Dr. Navid Homayouni was the FDA observer joining the inspection. Amgen was GCP compliant and EMA found their data acceptable.

4.2. Product Quality

Please refer to Dr. Chen Sun's and Dr. Chih-Jung Hsu's reviews for BLA 761073 for further details.

4.3. Clinical Microbiology

The manufacturing process of ABP 980 bulk drug substance and drug product aspects were assessed and recommended for approval from a microbial control and microbiology product quality perspective.

Please refer to Dr. Jessica Hankins's and Dr. Kathy Jones's reviews for BLA 761073 for further details.

4.4. Immunogenicity

The incidence of immunogenicity for ABP 980 and EU-Herceptin was compared in study 20120283. The results indicate similar incidence and titers of anti-drug antibodies (ADA) for both products. No apparent impact of ADA on safety, efficacy, or pharmacokinetic endpoints was observed. Therefore, the data indicates that there is no increase in immunogenicity risk for ABP 980 as compared to EU-Herceptin, which supports the demonstration of no clinically meaningful differences to US-Herceptin.

Please refer to Dr. Chih-Jung Hsu's review for BLA 761073 for further details.

4.5. Preclinical Pharmacology/Toxicology

Please refer to Dr. Kimberly Ringgold's review for BLA 761073 for further details.

4.6. Clinical Pharmacology

Please refer to Dr. Olanrewaju Okusanya's review for BLA 761073 for further details.

4.6.1. Mechanism of Action

Trastuzumab is a humanized IgG₁K monoclonal antibody directed against an epitope on the extracellular juxtamembrane domain of HER2. Multiple mechanisms of action have been proposed for trastuzumab, including inhibition of HER2 receptor dimerization, increased destruction of the endocytic portion of the HER2 receptor, inhibition of extracellular domain shedding, and activation of cell-mediated immune defenses such

as ADCC activity. Trastuzumab has not been shown to inhibit the dimerization of HER2 with the other isoforms; therefore, signaling through the other three receptor isoforms is maintained in the presence of the antibody. Studies have supported a mechanism by which trastuzumab is bound to the HER2 receptor and taken up by the target cell through endocytosis and subsequently degrades the receptor leading to a downregulation of downstream survival signaling, cell cycle arrest and apoptosis. Trastuzumab has also been shown to block the cleavage/shedding of the HER2 receptor extracellular domain thereby preventing the formation of the activated truncated p95, which has been correlated with a poor prognosis based on the detection of the released extracellular domain of HER2 in the serum of metastatic breast cancer patients. (4, 5, 6)

Please refer to Dr. Olanrewaju Okusanya's review for BLA 761073 for further details.

4.6.2. Pharmacodynamics

Please refer to Dr. Olanrewaju Okusanya's review for BLA 761073 for further details.

4.6.3. Pharmacokinetics

Please refer to Dr. Olanrewaju Okusanya's review for BLA 761073 for further details.

5. Sources of Clinical Data

5.1. Table of Studies

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

Figure 1: Table of Clinical Studies

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Subjects	Duration of Treatment	Study Status; Type of Report/ Location
Healthy Subject PK and Initial Tolerability Study Reports (Module 5.3.3.1)								
PK similarity	20130119	PK similarity of ABP 980 relative to trastuzumab (US) and to trastuzumab (EU); PK similarity of trastuzumab (US) relative to trastuzumab (EU); safety, tolerability, and immunogenicity	Randomized, single-blind, single-dose, 3-arm, parallel-group study	ABP 980 trastuzumab (US) trastuzumab (EU) 6 mg/kg IV infusion Single dose	157 (50 ABP 980, 52 trastuzumab [US], 55 trastuzumab [EU])	Healthy male subjects	Single dose	Complete; full CSR/ Module 5.3.3.1 20130119
Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication (Module 5.3.5.1)								
Clinical similarity	20120283	Efficacy, safety, and immunogenicity of ABP 980 vs trastuzumab (EU)	Randomized, multicenter, double-blind, active-controlled study	ABP 980 trastuzumab (EU) Initial dose 8 mg/kg IV followed by maintenance doses of 6 mg/kg IV every 3 weeks	725 (364 ABP 980, 361 trastuzumab)	HER2+ early breast cancer	15 months (including run-in ctx)	Concluded; Primary analysis CSR/ Module 5.3.5.1 20120283

CSR = clinical study report; ctx = chemotherapy; EU = European Union; HER2+ = human epidermal growth factor receptor 2-positive; IV = intravenous; PK = pharmacokinetic; US = United States.

Source: eCTD Module 5.2 – Tabular Listings of All Clinical Studies

5.2. Review Strategy

The efficacy review was conducted by Dr. Lynn Howie, the safety review was conducted by Dr. Jennifer Gao, and the statistical review was conducted by Dr. Joyce Cheng. The clinical review included the following:

1. Literature review of HER2-positive breast and gastric cancer
2. Research of the FDA database for regulatory history of ABP 980 and review of meeting minutes conducted during drug development
3. Review of applicant submitted CSR, protocol, protocol amendments, and selected datasets for Study 20120283
4. Review of selected case report forms (CRFs) for 20120283
5. Review of selected patient narratives for serious adverse events and deaths in 20120283
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 US-Herceptin label

5.3. Discussion of Individual Studies

5.3.1. Study Design

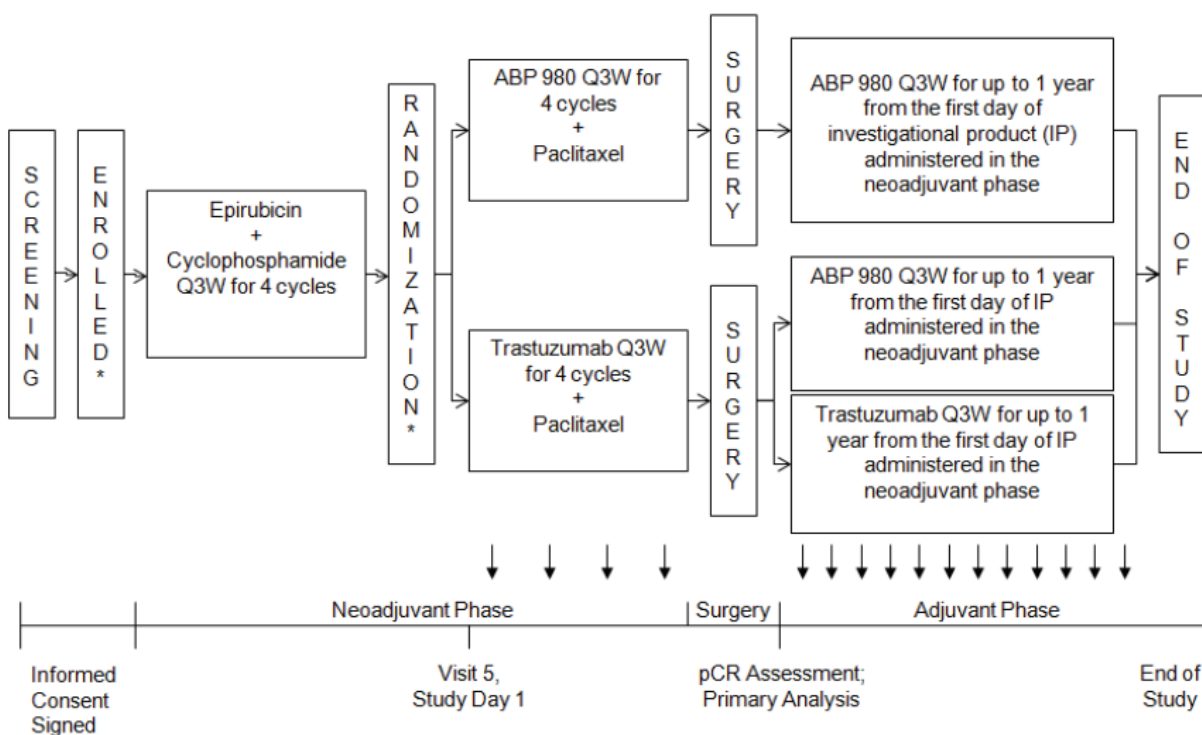
Study 20120283 is a two-part multicenter, double-blind, randomized, parallel-group, comparative clinical study. Patients were randomized 1:1 and stratified by tumor T stage, nodal status, hormone receptor status, planned paclitaxel dosing schedule, and geographic region.

- Neoadjuvant phase: All patient received run-in chemotherapy with epirubicin (90 mg/m²) and cyclophosphamide (600 mg/m²) every 3 weeks for 4 cycles. Subjects with adequate cardiac function at the completion of the chemotherapy run-in were randomized to ABP 980 or EU-Herceptin (9 mg/kg IV loading dose over 90 min followed by 6 mg/kg IV q3wk for 3 additional cycles) plus paclitaxel 175 mg/m² q3wk for 4 cycles (or paclitaxel 80 mg/m² q1wk for 12 weeks). Surgery (lumpectomy or mastectomy with sentinel lymph node dissection or axillary lymph node dissection) was completed 3-7 weeks after the last dose of the trastuzumab product in the neoadjuvant phase. The primary endpoint of pCR (absence of invasive tumor cells in the breast tissue and axillary lymph nodes, regardless of residual ductal carcinoma in situ) was assessed based on local laboratory evaluation of the tumor sample. Sensitivity analyses were conducted using central laboratory assessment to assess the robustness of the data.
- Adjuvant phase: Patients who initially received ABP 980 continued on ABP 980 q3wk during the adjuvant phase to complete 1 year of a trastuzumab product. Patients initially randomized to EU-Herceptin during the neoadjuvant phase were re-randomized to either continue with EU-Herceptin or switch to ABP 980 during the adjuvant phase, q3wk to complete 1 year of a trastuzumab product. This re-randomization was blinded.

The data cut-off for primary analysis was May 5, 2016, when the last subject had completed the first post-surgery clinical visit or withdrew. The co-primary efficacy endpoints were risk difference and risk ratio of the incidence of pCR in breast tissue and axillary lymph nodes by local laboratory assessment.

The study design is shown in Figure 2 below.

Figure 2: Study 30120283 Study Diagram



* Approximately 808 subjects enrolled, approximately 768 randomized

Source: Study 20120283 Protocol Version 3.0

Reviewer's Comment: The design of the comparative clinical study is acceptable. The early breast cancer population studied and the efficacy endpoint of pCR are acceptable. The applicant's primary analysis was based on the co-primary endpoints of RD and RR of pCR in the ABP980 arm to the EU-Herceptin arm. The FDA considers RR of pCR to be the more appropriate endpoint.

The schedule of assessments is shown in Figure 3 below.

Figure 3: Schedule of Assessments

Study Phase	SCR	Neoadjuvant Phase (1)									Adjuvant Phase (2)													EOT (3)	EOS (4)	
Study Visit	SCR (5)	1	2	3	4	5 Day 1	6	7	8	9	10 (6)	11	12	13	14	15	16	17	18	19	20 (7)	21 (7)	22 (7)	(7)	23	
Visit Window	≤ 28 days	Scheduled for Q3W ± 7 days									Scheduled for Q3W ± 7 days													± 7 days	± 7 days	
Study Assessments																										
Informed Consent	X																									
Enrollment (8)		X																								
Randomization (9)						X																				
Medical History	X																									
Physical Examination	X					X				X	X				X				X						X	X
Vital Signs and Weight	X					X				X	X				X				X						X	X
Electrocardiogram (ECG)	X																									
2D Echocardiogram (10)	X					X				X					X				X						X	X
ECOG Performance Status	X																									
Adverse Events Assessments																										
Serious Adverse Event (SAE) Assessments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications						X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Disease Progression or Recurrence	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments																										
Serum or Urine Pregnancy Test (11)	X																									
Serum Chemistry (11)	X		X	X	X	X	X	X	X	X	X				X				X						X	X
Hematology (11)	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-drug Antibody Sampling (12)						X				X	X				X				X						X	X
Pharmacokinetics Sampling (12)(13)						X	X	X	X(X)	X	X				X				X						X	X
Tumor Assessments																										
HER-2 Assessment (11)(12)(14)	X																									
Hormone Receptor Status (11)(12)(15)	X																									
Pathology (11)(12)											X															
Chemotherapy and Investigational Product																										
Epirubicin + Cyclophosphamide (EC)		X	X	X	X																					
Paclitaxel						X	X	X	X																	
IP (ABP 980 or trastuzumab) Administration						X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		

Footnotes:

(1)	Neoadjuvant Phase - Enrolled subjects will receive run-in chemotherapy consisting of epirubicin and cyclophosphamide (EC) every 3 weeks (Q3W) for 4 cycles. Once run-in chemotherapy is completed subjects will be randomized to receive investigational product (ABP 980 or trastuzumab), and paclitaxel, Q3W for 4 cycles (paclitaxel QW is also allowed, if local standard of care).
(2)	Adjuvant Phase - Following surgery, subjects will receive investigational product (ABP 980 or trastuzumab) Q3W for up to 1 year from the first day of investigational product administered in the neoadjuvant phase.
(3)	End of Treatment (EOT) visit - Subjects discontinuing investigational product before the planned end of study visit will have an end of treatment visit 30 days after the last dose of investigational product. These subjects should remain on the schedule of assessment until planned EOS visit at visit 23.
(4)	End of Study (EOS) visit - For subjects completing all doses of investigational product, the End of Treatment (EOT) visit and End of Study (EOS) visit is scheduled for 30 days after the last dose of investigational product. If the subject discontinues study before randomization, echocardiogram and pharmacokinetic and anti-drug antibody samples are not required.
(5)	Screening (SCR) - Will occur within 28 days before enrollment.
(6)	Surgery and the Adjuvant Phase - Subjects will undergo a lumpectomy or mastectomy with sentinel node or axillary node dissection. Surgery is expected to be scheduled within 3 to 7 weeks after the last dose of investigational product in the neoadjuvant phase. Following surgery, adjuvant therapy can be initiated up to 6 weeks after surgery. Subjects scheduled to receive chemotherapy in the adjuvant phase are not eligible to receive investigational product.
(7)	Study visits - Study visits may be removed if a subject has received investigation product for up to 1 year from the first day of investigational product administered in the neoadjuvant phase.
(8)	Enrollment - Will occur within 8 days before the first dose of run-in chemotherapy.
(9)	Randomization - Will occur within 8 days before the first dose of Investigational Product (ABP 980 or trastuzumab) and Paclitaxel. Subjects must complete all 4 cycles of run-in chemotherapy to be eligible for randomization and further participation in the study. If a subject does not complete the 4 cycles of run-in chemotherapy, the subject will be removed from study. Additionally, if the local determination HER-2 overexpression is not confirmed by the central laboratory, the subject will not be eligible for randomization and will be removed from the study. Echocardiogram is required and results must be obtained prior to randomization (see (10)).
(10)	At all indicated visits, echocardiogram must be performed and results obtained prior to IP administration. Visit 5 echocardiogram can be done at any time point after the final dose of EC and prior to randomization. Post-anthracycline EF must be ≥ 55% in order for subjects to be randomized.
(11)	Local Laboratory - Performed at a local laboratory.
(12)	Central Laboratory - Sample sent to a central laboratory.
(13)	Pharmacokinetics Sampling - Trough serum samples for pharmacokinetic analysis will be collected on all randomized subjects. At visit 8 a subset of approximately 150 subjects will also have an additional post-infusion serum sample collected, indicated by the (X).
(14)	HER-2 Assessment - Subjects will be enrolled based on local HER-2 assessment. Tumor sample must be sent to the central laboratory as soon as possible after a locally obtained HER-2 positive results for HER-2 confirmation.
(15)	Hormone Receptor Status - Stratification will be performed on hormone receptor status. Subjects will be enrolled based on locally determined hormone receptor status. Additionally, tumor sample must be sent to the central laboratory as soon as possible after a locally obtained result for confirmation of hormone receptor status.
(16)	Pathology - A sample of the tumor material will be sent to the central laboratory for central laboratory evaluation of pCR. Details of the procedures to be followed for sample collection, storage, and shipment will be documented in a separate Laboratory Manual.

Source: 20120283 Protocol Version 3.0

Reviewer's Comment: The schedule of activities is acceptable. Cardiac assessments were performed at screening, neoadjuvant phase study visit 5 day 1 (trastuzumab product cycle 1) and study visit 9 (3 weeks post trastuzumab

product cycle 4 completion), adjuvant phase study visit 14 and 18 (cycles 5 and 9), and at end of treatment and end of study. Laboratory, EKG, AE, and PK assessments are also clinically appropriate and acceptable.

5.3.2. Protocol Amendments

The following were available for review:

- o Original protocol, version 1.0, September 28, 2012
- o Protocol version 1.1, October 8, 2012
 - Updated study name to remove “The Magnolia Study”
- o Amendment 1.2, Hungary and Greece
- o Protocol version 2.0, May 21, 2013
 - Updated power calculations, add risk difference of pCR as co-primary endpoint and updated statistical methods, defined pCR evaluable population, added paclitaxel dosing as stratification factor, updated pregnancy inclusion criteria, specified cardiac function must be adequate after chemotherapy, removed Australia as site, specified interim analysis when 1/3 subjects assessed for pCR
- o Protocol version 3.0, August 6, 2015
 - Revised period required contraception, dose recalculation for patients with >10% weight change, updated definition analysis populations, allow flexibility in use of GCSF, updated expected study duration

Reviewer’s Comment: Protocol version 2 was adopted prior to the first patient being treated which occurred in July 2013. The dosing advice for patients with a >10% weight change that was incorporated had been specified in a previous protocol clarification. The protocol amendments and changes appear reasonable with no concerning changes.

5.3.3. Study Objectives/Endpoints

Primary Objective

- To compare the treatment effect of ABP 980 with EU-Herceptin on pCR in women with HER2 positive early breast cancer

Primary Endpoint

- The co-primary endpoints are risk ratio and risk difference of pCR, defined as the absence of invasive tumor cells in the breast tissue and in axillary lymph nodes, regardless of DCIS

Secondary Objectives

- To assess the safety, tolerability, and immunogenicity of ABP 980 compared with EU-Herceptin

Reviewer’s Comment: The objectives are acceptable. The risk ratio of pCR is the FDA preferred primary endpoint. The co-primary endpoints of risk ratio and risk

difference of pCR were agreed upon by the FDA with margins determined by a meta-analysis of two studies using trastuzumab, including both EU-Herceptin and US-Herceptin, in the neoadjuvant setting. (13, 14)

5.3.4. Eligibility Criteria

Inclusion Criteria

1. Females ≥ 18 years of age
2. Histologically confirmed invasive breast cancer
3. Planning for surgical resection of breast tumor and SN or axillary lymph node resection
4. Planning neoadjuvant chemotherapy
5. HER2 positive disease defined as:
 - 3+ overexpression by immunohistochemistry (IHC) or
 - HER2 amplification by fluorescence in situ hybridization (FISH)
6. Measurable disease (assessment method used in order of priority: ultrasound, mammography, MRI, or physical examination) in the breast after diagnostic biopsy, defined as longest diameter ≥ 2.0 cm
7. Known ER and PR hormone receptor status at study entry
8. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
9. Left ventricular ejection fraction (LVEF) of $\geq 55\%$ by 2D echocardiogram
10. Normal bone marrow function as defined by:
 - absolute neutrophil count (ANC) $> 1.5 \times 10^9$ g/dL (1,500/ μ L);
 - platelets $> 100 \times 10^9$ g/dL (100,000/ μ L);
 - hemoglobin > 10.0 g/dL.
11. Normal hepatic function as defined by:
 - total bilirubin within normal institutional limits;
 - aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $< 2.5 \times$ the upper limit of normal (ULN);
 - subjects with an elevated unconjugated bilirubin (Gilbert's syndrome) will be eligible if hepatic enzymes and function are otherwise within normal limits (ie, AST, ALT, and Alkaline Phosphatase are within normal limits), and there is no evidence of hemolysis.
12. Normal renal function as defined by creatinine $< 1.5 \times$ ULN or estimated creatinine clearance (CrCl) ≥ 50 mL/min calculated by the Cockcroft-Gault method
13. Subjects must sign an IRB/EC-approved informed consent form before any study specific procedures

Inclusion Criteria for Randomization

1. Left ventricular ejection fraction (LVEF) of $\geq 55\%$ by 2D echocardiogram
2. Complete all 4 cycles of run-in chemotherapy

Exclusion Criteria

1. Bilateral breast cancer

2. Presence of known metastases
3. Received prior treatment, including chemotherapy, biologic therapy, radiation or surgery with the exception of diagnostic biopsy for primary breast cancer
4. 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
5. Pre-existing clinically significant ($\geq$ grade 2) peripheral neuropathy
6. Any history of documented or current congestive heart failure, current high-risk uncontrolled arrhythmias, current angina pectoris requiring a medicinal product, current clinically significant valvular disease, current evidence of transmural infarction on electrocardiogram (ECG), or current poorly controlled hypertension
7. Severe dyspnea at rest requiring supplementary oxygen therapy
8. History of positivity for hepatitis B surface antigen, hepatitis C virus, or HIV
9. Recent infection requiring a course of systemic anti-infectives that were completed $\leq$ 14 days before enrollment (with the exception of uncomplicated urinary tract infection)
10. Woman of childbearing potential who is pregnant or is breast feeding
11. Woman of childbearing potential who is not consenting to use highly effective methods of birth control (eg, true abstinence [periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception], sterilization, or other non-hormonal forms of contraception) during treatment and for at least 7 months after the last administration of the protocol specified treatment
12. Currently receiving treatment in another investigational device or drug study, or less than 30 days since ending treatment on another investigational device or drug study
13. Other investigational procedures while participating in this study are excluded
14. Subject has known sensitivity to any of the products to be administered during the study, including mammalian cell derived drug products, trastuzumab, murine proteins, or to any of the excipients
15. Subject previously has enrolled and/or has been randomized in this study
16. Subject likely to not be available to complete all protocol-required study visits or procedures
17. 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 or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion

Reviewer's Comment: *The inclusion and exclusion criteria are appropriate.*

Drug Administration

Run-in chemotherapy: epirubicin 90 mg/m² and cyclophosphamide 600 mg/m² q3wk for 4 cycles. Cardiac function was assessed at the end of the run-in period.

Neoadjuvant period: ABP 980 or EU-Herceptin loading dose 8 mg/kg IV over 90 min, then 6 mg/kg IV q3wk for 3 additional cycles (total 4 cycles). Paclitaxel 175 mg/m² q3wk

for 4 cycles or 80 mg/m² q1wk for 12 cycles was given concomitantly. Surgery (lumpectomy or mastectomy with sentinel lymph node dissection or axillary lymph node dissection) completed 3-7 weeks after the last dose of the trastuzumab product in the neoadjuvant phase.

Adjuvant period: ABP 980 or EU-Herceptin q3wk for up to 1 year from the first day of investigational product administration in the neoadjuvant phase. Patients who received ABP 980 in the neoadjuvant period continued on ABP 980 (ABP 980/ABP 980). Patients who received EU-Herceptin in the neoadjuvant period were re-randomized to continue EU-Herceptin q3wk (EU-Herceptin/EU-Herceptin) or switch to ABP 980 q3wk (EU-Herceptin/ABP 980).

Reviewer Comment: The dosing of therapies is appropriate and is consistent with chemotherapy use in the US, though doxorubicin is typically used in the US rather than epirubicin. Despite this, there is no substantial difference in regimens and the chemotherapy backbone is the same between the two arms.

5.3.5. Dose Modifications

Trastuzumab product: no recommended or planned dose reductions for ABP 980 or EU-Herceptin. If chemotherapy was delayed due to toxicity, the trastuzumab product was given according to the original schedule of q3wk. Dose adjustment was allowed if the patient's body weight changed by >10% from screening weight. Patient with clinically significant heart failure were discontinued from the study. Study drug was held for patients who experienced a grade 3 or 4 adverse event with re-exposure permitted when the event resolved to grade 1 or lower or the subject's baseline.

Paclitaxel q3wk: two dose reductions to 130 mg/m² and 100 mg/m² were permitted before patients were discontinued.

Paclitaxel q1wk: two dose reductions to 60 mg/m² and 45 mg/m² were permitted before patients were discontinued.

Reviewer Comments: The dose modification schedule was appropriate.

5.3.6. Statistical Analysis Plan

Sample Size: The study was sized to evaluate the Risk Difference (RD) and Risk Ratio (RR) of the primary endpoint of pCR in breast tissue and axillary lymph nodes of the tumor samples.

Reviewer's Comment: While other global regulatory agencies may be interested in the RD of pCR, FDA considers RR to be the more appropriate metric for evaluating pCR.

The applicant planned to enroll approximately 808 subjects so that approximately 768 subjects (384 per arm) would be randomized. This sample size would provide at least 90% power to demonstrate equivalence between ABP 980 and EU-Herceptin on the RR of pCR with a pre-defined equivalence margin of (0.7586, 1.3182) at a two-sided significance level of 0.05, accounting for a 5% dropout rate during run-in chemotherapy. This sample size would also provide at least 90% power to demonstrate equivalence based on the RD of pCR with a pre-defined margin of (-13%, 13%) at a 2-sided significance level of 0.05. These calculations all assumed a pCR rate of approximately 42.5% on both treatment arms and the RR and RD of pCR for ABP 980 to EU-Herceptin were to be analyzed with a two-sided 90% CI (i.e., alpha controlled ≤ 0.05). If the 90% CI completely falls in each respective pre-defined equivalence region, then equivalence would be declared. The equivalence region for RR of pCR was derived using a fixed-effect meta-analysis of historical trastuzumab trials that included both EU-Herceptin and US-Herceptin to estimate the treatment effect of trastuzumab with chemotherapy versus chemotherapy alone.

Equivalence Margin: The applicant followed FDA draft guidance on non-inferiority clinical trials (2010) to derive the non-inferiority side of the margin for RR of pCR. The applicant chose to use a meta-analysis of two randomized controlled studies, Buzdar et al. 2007 and Gianni et al. 2010, to estimate the treatment effect. The resulting point estimate for RR of pCR between trastuzumab in combination with standard chemotherapy vs. chemotherapy alone was 0.4889 with a 60% confidence interval of (0.4154, 0.5754). To preserve 50% of the upper bound of the 60% confidence interval, the non-inferiority side of the equivalence margin was calculated as $\exp(\log(0.5754) \times 0.5) = 0.7586$ and consequently the superiority margin was $1/0.7586 = 1.3182$.

Reviewer's Comment: *In deriving the margin for an equivalence trial, several general points need to be considered. First, as per the FDA guidance for industry titled Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, a comparative clinical trial would be needed to resolve any residual uncertainties rather than demonstrating efficacy. Second, the equivalence margin is to assess whether there are meaningful differences between the two products. Third, the equivalence trial needs to be feasible and the sample size is not based on establishing efficacy. The equivalence margin of (0.7586, 1.3182) has been agreed upon by the FDA.*

Analysis Populations: The pCR evaluable population included all subjects randomized by IXRS who received any amount of investigational product, underwent surgery, and had a non-missing evaluable pCR assessment from the local laboratory evaluation. The intent-to-treat (ITT) population included all subjects randomized. The per-protocol (PP) population included all subjects who were randomized, had an evaluable local laboratory pCR assessment, and did not experience a PD that affected their evaluation for the primary objective of the study.

The primary efficacy analysis was conducted on the pCR evaluable population and

sensitivity analyses were conducted on the ITT and PP populations. Subjects were analyzed according to actual treatment received in the pCR evaluable and PP populations. Subjects were analyzed according to treatment group as randomized (regardless of treatment received) in the ITT population.

The safety analysis was conducted on the safety analysis population, which included all subjects who were randomized and received any amount of investigational product, according to the actual treatment received.

The pharmacokinetic (PK) analysis population was the subset of the safety analysis population with at least 1 evaluable serum concentration of ABP 980 or EU-Herceptin. Subjects were analyzed by actual treatment received.

Reviewer's Comment: *The applicant notes that due to a delay in manufacturing of ABP 980, the first 9 subjects on study who had already completed screening and run-in periods were manually assigned to EU-Herceptin to ensure uninterrupted supply and continuous treatment. The 9 subjects were:* (b) (6)

Data from these subjects were not included in the efficacy analyses using the pCR evaluable, ITT, or PP populations but were included in the safety analyses.

Primary efficacy analysis: The co-primary efficacy endpoints were the RD and RR of pCR as assessed by local laboratory. The pCR difference between the two arms with respect to RD and RR will be tested in sequence. Equivalence will first be tested on RD for pCR at a two-sided significance level at a fixed margin of (-13%, 13%). If the two-sided 90% CI of RD for pCR is contained within the margin, then the test of equivalence on RD is successful and equivalence will be tested on the RR of pCR at a two-sided significance level with a fixed margin of (0.7586, 1.3182). The test of equivalence on RR will be successful if the two-sided 90% CI of RR for pCR is contained within its margin. In both cases, the confidence interval will be estimated using a generalized linear model adjusted for stratification factors.

Secondary efficacy analyses: Secondary efficacy endpoints were RD and RR of pCR in breast tissue only and in breast tissue and axillary lymph nodes and absence of DCIS. These endpoints were analyzed based on local laboratory evaluation and central independent evaluation of the tumor samples in all three analysis populations (pCR evaluable, ITT, and PP). Note that, for analyses based on central independent evaluation, the pCR evaluable and PP populations were defined using observed central laboratory data. These secondary endpoints were analyzed with the same methods as the primary endpoints but are to be interpreted as descriptive only.

Sensitivity analyses: A number of sensitivity analyses were performed to assess the robustness of the primary pCR analysis (both RD and RR of pCR). The following were based on local pathology evaluation of the tumor samples:

1. Using the pCR evaluable population adjusted for corrected stratification factors (eCRF values)
2. Using the ITT population with nonresponder imputation (NRI). Subjects who had not undergone surgery or did not have an evaluable pCR assessment were counted as nonresponders.
3. Using the ITT population with NRI adjusted for corrected stratification factors
4. Using the PP population
5. Using the pCR evaluable population exploring the following baseline covariates (in addition to the randomization stratification factors) in the model using backward model selection: age group, race, baseline ECOG performance status

Analyses of the primary endpoints were also repeated using central independent evaluation pathology of the tumor samples in the pCR evaluable, ITT, and PP populations. RD and RR of pCR were also examined in a number of subgroups using the pCR evaluable population and results were summarized using forest plots.

Other Endpoints: On-study EFS and OS were analyzed in the safety analysis population in both the neoadjuvant plus adjuvant phases. The incidence of disease progression or recurrence or death during the study were summarized. EFS was further summarized by hazard ratios and two-sided 90 and 95% CIs from a stratified Cox proportional hazards model adjusted for randomization stratification factors, Kaplan-Meier curves, and median survival time estimates. These analyses were also performed in various subgroups and results were summarized in a forest plot.

Pharmacokinetic analysis: In the PK analysis population, pre-infusion serum ABP 980 and EU-Herceptin concentrations were summarized descriptively by treatment for each sampling visit, but trough PK samples (except those from baseline, visit 10 or the EOS visit) collected more than 4 weeks from the prior dose will be considered not evaluable and excluded. PK concentrations at day 1 (pre-infusion) and visit 8 (post-infusion) were summarized descriptively by treatment arm for subjects in the PK analysis population who had an additional serum sample collected after visit 8. At the discretion of the pharmacokineticist and following a blinded review and investigation of the available documentation, individual ABP 980 and EU-Herceptin serum concentrations were excluded from the PK summary if they were considered anomalous. It was planned that these exclusions would be documented and finalized before the interim database freeze/lock.

5.3.7. Charter Review

pCR

(b) (4) was contracted by the Applicant to perform a confirmation pCR analysis for Amgen study protocol 20120283 which was managed by (b) (4). The primary objective of the study is to compare the treatment effect of ABP 980 compared with EU-Herceptin on pCR. The primary analysis of pCR was based on local pathology evaluations of tumor samples and a sensitivity analysis was

based on the central evaluation of the samples by (b) (4).

The pCR analysis defines pCR based on the FDA draft guidance document as the “absence of any residual invasive cancer on hematoxylin and eosin evaluation of the resected breast specimen and all sampled lymph nodes following the completion of neoadjuvant systemic therapy (i.e. ypT0 ypN0 in the current AJCC staging system).” (15)

The pCR charter delineated sample preparation techniques for the local site to use with slide preparation instruction as well. Tissue blocks and slides were to be sent to (b) (4) for central review for analysis.

Each case was to be reviewed by two pathologists who were blinded to the other. Data regarding the specimens were collected on worksheets and captured adequacy of sample slides based on the presence/absence of tumor bed and the integrity/loss of nuclear detail, the presence/absence of invasion and the number of blocks with tumor found at examination, the presence/absence of ductal carcinoma in situ (DCIS), the presence/absence of lymph nodes, and the presence/absence of lymph node invasion.

A difference in reading by one of the two pathologists in the following items resulted in a 3rd pathologist review to adjudicate:

- Adequate or inadequate specimen quality
- Presence or absence of tumor bed
- Presence or absence of invasive breast cancer
- A differing result in the number of blocks with invasive breast cancer present
- Differing result of estimated viable residual tumor
- Presence or absence of DCIS
- Presence or absence of lymph nodes
- Presence or absence of lymph node invasive cancer

The investigative sites were assumed to have experience handling surgical specimens from neoadjuvant chemotherapy, the pretherapeutic size and localization of the tumor and orientation of the specimen was communicated to the pathologist to assist in the identification and processing of the tumor bed/tumor, the pathologist documented the size of the tumor bed/tumor at gross dissection, the tumor bed/tumor was serially sectioned into 0.4 cm blocks, and that the pathology gross description contained at least the description and size of the tumor bed/tumor, the localization, the margins, and the number of blocks obtained with sequential numbering of the blocks. Constraints were that investigative sites may not be using appropriate methods for tissue fixation, the tumor/tumor bed may not be adequately identified in the surgical specimen or adequately serially sampled. Risks of the central review included that all blocks and/or sample slides may not be sent to the central lab compromising the accuracy of pCR confirmation at the central laboratory and that lack of documentation of the original tumor size may limit complete evaluation of the specimens.

Actions to mitigate possible risks included detailed instructions to the sites on sample preparation in the pCR pathology manual, querying of sites for missing or discrepant information, and site retraining by the CRO if a site is not following instructions for sample preparation provided by the study.

In April 2016 samples at the central laboratory [REDACTED] (b) (4) were not properly adjudicated by a third pathologist when a discordance occurred. After realization of this fact, potentially impacted data were subsequently adjudicated by a third independent blinded pathologist.

Reviewer's Comment: The Pathological Complete Response Charter is acceptable. The definition of pCR used as the primary objective, pCR in breast and lymph nodes, is that preferred by the Agency for regulatory decision-making based on this endpoint. Central Pathology Review is preferred by the agency for standardization. The Applicant's methods for central review were acceptable and their mitigation of issues when it was noted that samples were not properly adjudicated in April 2016 was appropriate. This reviewer finds that these issues did not likely have an impact on the interpretation of study results.

6. Review of Efficacy

Efficacy Summary

The results of Study 20120283 support the determination of no clinically meaningful differences between ABP 980 and US-Herceptin. Specifically, the 90% confidence interval for RR of pCR by central review between ABP 980 and EU-Herceptin in Study 20120283 falls within the equivalence margins. A scientific bridge between EU-Herceptin, US-Herceptin, and ABP 980 has been established based in part on pharmacokinetic (PK) evaluation.

6.1. Indication

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

6.2. Methods

Similarity in clinical efficacy was assessed in Study 20120283 comparing ABP 980 with EU-Herceptin in adult women with HER2-positive early breast cancer. The applicant's primary analysis was based on the co-primary endpoints of RD and RR of pCR in the ABP980 arm to the EU-Herceptin arm. The FDA considers RR of pCR to be the more appropriate endpoint. The FDA's primary efficacy analysis was based on the primary endpoint of RR of pCR in the pCR evaluable 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 patients enrolled from 20 countries in the ITT population as seen in Table 3.

Table 3: Study 20120283 Enrollment by Country for ITT Population (by neoadjuvant treatment)

Country	ABP 980 N=364 n (%)	EU-Herceptin N=361 n (%)
Belarus	20 (5.5)	32 (8.9)
Brazil	12 (3.3)	9 (2.5)
Bulgaria	5 (1.4)	5 (1.4)
Canada	1 (0.3)	2 (0.6)
Chile	2 (0.5)	1 (0.3)
Czech Republic	6 (1.6)	2 (0.6)
Germany	9 (2.5)	9 (2.5)
Greece	1 (0.3)	3 (0.8)
Hungary	12 (3.3)	16 (4.4)
Italy	7 (1.9)	13 (3.6)
Mexico	18 (4.9)	19 (5.3)
Poland	32 (8.8)	25 (6.9)
Romania	24 (6.6)	20 (5.5)
Russian Federation	118 (32.4)	120 (33.2)
Serbia	14 (3.8)	13 (3.6)
Slovakia	6 (1.6)	8 (2.2)
South Africa	17 (4.7)	11 (3.0)
Spain	24 (6.6)	20 (5.5)
Ukraine	34 (9.3)	32 (8.9)
United Kingdom	2 (0.5)	1 (0.3)

Source: Study 20120283 adsl.xpt

Reviewer's Comment: The study was completed outside of the US for feasibility issues. This is appropriate given that trastuzumab is currently licensed globally.

Table 4: Demographic Characteristics for Study 20120283 in pCR Evaluable Population (by neoadjuvant treatment)

Demographic Parameters	ABP 980 N = 358 n (%)	EU-Herceptin N = 338 n (%)
Age		
Mean (SD)	52.75 (10.74)	52.51 (11.33)
Median	53	53
Age Group		
< 50 years	139 (38.8)	127 (37.6)
>= 50 years	219 (61.2)	211 (62.4)
Race		
White	325 (90.8)	313 (92.6)
Black or African American	10 (2.8)	2 (0.6)
Asian	2 (0.6)	2 (0.6)
American Indian or Alaska Native	1 (0.3)	0 (0.0)
Native Hawaiian or other Pacific Islander	0	0
Other	20 (5.6)	21 (6.2)
Ethnicity		
Hispanic or Latino	31 (8.7)	35 (10.4)
Not Hispanic or Latino	327 (91.3)	302 (89.3)
Not allowed to collect	0 (0.0)	1 (0.3)
Region		
Eastern Europe	267 (74.6)	259 (76.6)
Western Europe	42 (11.7)	40 (11.8)
Other	49 (13.7)	39 (11.5)

Source: Study 20120283 adsl.xpt; Study 20120283 CSR Table 13, page 84

Reviewer Comment: The demographic characteristics between the two arms in the pCR evaluable population are generally well-balanced.

Table 5: Baseline Disease Characteristics for Study 20120283 in pCR Evaluable Population (by neoadjuvant treatment)

	ABP 980 N = 358 n (%)	EU-Herceptin N = 338 n (%)	Total N=696 n (%)
Weight (kg)			
Mean (SD)	72.52 (14.90)	72.56 (13.88)	72.54 (14.40)
Median	70.55	70.50	70.55
Height (cm)			
Mean (SD)	162.32 (6.70)	162.24 (6.89)	162.28 (6.79)
Median	162.00	162.00	162.00
BMI (kg/m²)			
Mean (SD)	27.54 (5.54)	27.62 (5.29)	27.58 (5.42)
Median	26.90	27.02	26.98
LVEF			
Mean (SD)	64.57 (5.11)	64.56 (4.84)	64.56 (4.98)
Median	65.00	65.00	65.00
ECOG			
0	294 (82.1)	294 (87.0)	588 (84.5)
1	64 (17.9)	44 (13.0)	108 (15.5)
Tumor Stage Group (CRF)			
Less than T4	280 (78.2)	263 (77.8)	543 (78.0)
T4	78 (21.8)	75 (22.2)	153 (22.0)
Tumor Stage (CRF)			
T0	1 (0.3)	1 (0.3)	2 (0.3)
T1	7 (2.0)	5 (1.5)	12 (1.7)
T2	203 (56.7)	180 (53.3)	383 (55.0)
T3	69 (19.3)	77 (22.8)	146 (21.0)
T4	78 (21.8)	75 (22.2)	153 (22.0)
Axillary lymph node involvement			

Yes	272 (76.0)	250 (74.0)	522 (75.0)
No	86 (24.0)	88 (26.0)	174 (25.0)
Node Classification			
N0	86 (24.0)	88 (26.0)	174 (25.0)
N1	176 (49.2)	144 (42.6)	320 (46.0)
N2	64 (17.9)	68 (20.1)	132 (19.0)
N3	32 (8.9)	38 (11.2)	70 (10.1)
HR status			
ER+ and/or PR+	263 (73.5)	251 (74.3)	514 (73.9)
ER- and PR-	95 (26.5)	87 (25.7)	182 (26.1)
Histologic grading			
Grade 1	8 (2.2)	0 (0.0)	8 (1.1)
Grade 2	171 (47.8)	164 (48.5)	335 (48.1)
Grade 3	119 (33.2)	121 (35.8)	240 (34.5)
Unknown	60 (16.8)	53 (15.7)	113 (16.2)
Disease Duration (months)			
Mean (SD)	4.28 (2.47)	4.01 (0.87)	4.15 (1.88)
Median	3.85	3.80	3.80
Paclitaxel dosing schedule (corrected)			
Q3W	252 (70.4)	248 (73.4)	500 (71.8)
QW	106 (29.6)	90 (26.6)	196 (28.2)

Source: Study 20120283 adsl.xpt; Study 20120283 CSR Table 13, page 85

Reviewer Comment: The disease characteristics between the two arms were similar, though there was a slightly numerically greater number of patients in the ABP 980 arm with hormone receptor negative disease which may be associated with increased rates of pCR. Additionally, there were numerically greater N2 and N3 patients in the EU-Herceptin arm consistent with a greater disease burden.

6.4. Subject Disposition

The study screened 906 subjects, 827 were enrolled, and 725 were randomized. Table 6 details all analysis populations.

Table 6: Analysis Populations for Study 20120283 (by neoadjuvant treatment)

	ABP 980 n (%)	EU-Herceptin n (%)	Total n (%)
Subjects Randomized (ITT)	364	361	725
Subjects Treated (Safety Population)	364	361	725
pCR Evaluable Population	358	338	696
Subject received IP but did not undergo the surgery	6 (1.6)	14 (3.9)	20 (2.8)
Subjects manually randomized to trastuzumab	0	9 (2.5)	9 (1.2)
Subjects did not receive IP	0	0	0
Subjects with missing pCR assessment from local laboratory evaluation	0	0	0
Per Protocol Population	351	328	679
Subjects received IP but did not undergo the surgery	6 (1.6)	14 (3.9)	20 (2.8)
Subjects manually randomized to trastuzumab	0	9 (2.5)	9 (1.2)
> 50% of Paclitaxel missed in Neoadjuvant phase	2 (0.5)	4 (1.1)	6 (0.8)
Prohibited medications/procedures during neoadjuvant phase	4 (1.1)	2 (0.6)	6 (0.8)
IP kit administered not per IXRS assignment	1 (0.3)	2 (0.6)	3 (0.4)
EXC Concomitant malignancy past 5 years	0	1 (0.3)	1 (0.1)
Nodes resection not performed as per protocol	0	1 (0.3)	1 (0.1)
Subjects did not receive IP	0	0	0
Subjects with missing pCR assessment from the local laboratory evaluation	0	0	0
Pharmacokinetics analysis population	363	361	724

Source: Study 20120283 adsl.xpt; Study 20120283 CSR Table 12

Of the 725 subjects randomized, 715 patients (98.6%) completed investigational product in the neoadjuvant phase, 709 (97.8%) patients completed four cycles and 6 patients (0.8%) received <4 cycles of investigational product. Table 7 below captures the reason for treatment discontinuation of investigational product during the neoadjuvant phase.

Table 7. Treatment Disposition and Completion for ITT Population in the Neoadjuvant Period

	ABP 980 n (%)	EU-Herceptin n (%)	Total n (%)
Subjects Randomized (ITT)	364	361	725
Completed Neoadjuvant Phase	360 (98.9)	355 (98.3)	715 (98.6)
Received 4 cycles of IP during neoadjuvant period	357 (98.1)	352 (97.5)	709 (97.8)
Received less than 4 cycles of IP during neoadjuvant period and completed surgery	3 (0.8)	3 (0.8)	6 (0.8)
Discontinued IP in the neoadjuvant phase	4 (1.1)	6 (1.7)	10 (1.4)
Subject request	2 (0.5)	3 (0.8)	5 (0.7)
Adverse event	1 (0.3)	2 (0.6)	3 (0.4)
Death	1 (0.3)	0	1 (0.1)
Disease progression or recurrence	0	1 (0.3)	1 (0.1)
Discontinued IP after the neoadjuvant phase without entering the adjuvant phase	11 (3.0)	13 (3.6)	24 (3.3)
Adverse event	4 (0.3)	2 (0.6)	6 (0.8)
Disease progression or recurrence	3 (0.8)	2 (0.6)	5 (0.7)
Subject request	2 (0.5)	3 (0.8)	5 (0.7)
Alternative therapy requirement	1 (0.3)	1 (0.3)	2 (0.3)
Lost to follow up	1 (0.3)	0	1 (0.1)
Other	0	2 (0.6)	2 (0.3)
Death	0	1 (0.3)	1 (0.1)
Physician decision	0	1 (0.3)	1 (0.1)
Protocol violation	0	1 (0.3)	1 (0.1)
Treated with IP in the adjuvant phase	349 (95.9)	342 (94.7)	691 (95.3)

Source: CSR 20120283 addendum page 147, modified from Table 14-1.3.3

Table 8. Treatment Disposition for Adjuvant Period for ITT population

	ABP 980/ ABP 980 N=364 n (%)	EU- Herceptin/EU -Herceptin N=180 n (%)	EU- Herceptin/A BP 980 N=181 n (%)	Total (N=725) n (%)
Treated with IP during adjuvant phase	349 (95.9)	171 (95.0)	171 (94.5)	691 (95.3)
Completed adjuvant IP	323 (88.7)	164 (91.1)	158 (87.3)	645 (89.0)

Discontinued adjuvant IP	26 (7.1)	7 (3.9)	13 (7.2)	46 (6.3)
<i>Reasons for discontinuing IP in the adjuvant phase</i>				
Disease progression or recurrence	12 (3.3)	4 (2.2)	3 (1.7)	19 (2.6)
Adverse event	4 (1.1)	2 (1.1)	3 (1.7)	9 (1.2)
Subject request	3 (0.8)	1 (0.6)	4 (2.2)	8 (1.1)
Death	0	0	2 (1.1)	2 (0.3)
Physician Decision	1 (0.3)	0	0	1 (0.1)
Other	6 (1.6)	0	1 (0.6)	7 (1.0)
Discontinued IP at any time during the study	41 (11.3)	16 (8.9)	23 (12.7)	80 (11.0)
<i>Reasons for discontinuing IP at any time during the study</i>				
Disease progression or recurrence	15 (4.1)	5 (2.8)	5 (2.8)	25 (3.4)
Adverse event	9 (2.5)	5 (2.8)	4 (2.2)	18 (2.5)
Subject request	7 (1.9)	3 (1.7)	8 (4.4)	18 (2.5)
Death	1 (0.3)	1 (0.6)	2 (1.1)	4 (0.6)
Physician Decision	1 (0.3)	0	1 (0.6)	2 (0.3)
Other	6 (1.6)	0	3 (1.7)	9 (1.2)

Source: CSR 20120283 addendum page 29, modified from Table 3

Reviewer Comment: Reasons for treatment discontinuation were similar in each arm of treatment. The rates of completion of adjuvant treatment were similar in each arm and similar to other studies of anti-HER2 therapies. There were numerically greater patients who discontinued treatment on an ABP980 arm due to disease progression, though this may be due to small numbers. This difference does not impact our conclusion that there are no meaningful differences between ABP 980 and EU-Herceptin.

Protocol Violations/Deviations

In this clinical study, 108 subjects had a protocol violation (57 in the ABP 980 arm and 51 subjects in the EU-Herceptin arm) in the neoadjuvant phase. The most common major protocol violation and the only violation for >2% of subjects was misclassification in the IXRS system. Table 9 below is the Sponsor's assessment of the major protocol violations for this protocol.

Table 9. Sponsor Analysis of Protocol Deviations for the ITT population

Category Deviation	ABP 980 (N = 364) n (%)	Trastuzumab (N = 361) n (%)	Total (N = 725) n (%)
Number of subjects with at least one important protocol deviation	57 (15.7)	51 (14.1)	108 (14.9)
Stratification Errors	33 (9.1)	28 (7.8)	61 (8.4)
Misstratification in IXRS	33 (9.1)	28 (7.8)	61 (8.4)
Exclusion Criteria	7 (1.9)	7 (1.9)	14 (1.9)
EXC significant cardiovascular diseases present or not assessed	5 (1.4)	1 (0.3)	6 (0.8)
EXC Pregnant or breast feeding, or pregnancy test not done at screening	0 (0.0)	4 (1.1)	4 (0.6)
EXC Anti-infectives completed within 14 days before enrollment	1 (0.3)	0 (0.0)	1 (0.1)
EXC Concomitant malignancy past 5 years	0 (0.0)	1 (0.3)	1 (0.1)
EXC Hepatitis B, C or HIV	0 (0.0)	1 (0.3)	1 (0.1)
EXC Other investigational procedure planned	1 (0.3)	0 (0.0)	1 (0.1)
Inclusion Criteria	9 (2.5)	5 (1.4)	14 (1.9)
INC Hepatic function abnormal or not assessed	8 (2.2)	3 (0.8)	11 (1.5)
INC Randomization criteria not met or not assessed	1 (0.3)	2 (0.6)	3 (0.4)
INC Bone marrow function abnormal or not assessed	1 (0.3)	0 (0.0)	1 (0.1)
Investigational Product	4 (1.1)	6 (1.7)	10 (1.4)
Other IP issues	3 (0.8)	3 (0.8)	6 (0.8)
IP kit administered not per IXRS assignment	1 (0.3)	2 (0.6)	3 (0.4)
≥ 1 dose of IP administered out of window in neoadjuvant phase	0 (0.0)	1 (0.3)	1 (0.1)
Lab/Endpoint Data	3 (0.8)	5 (1.4)	8 (1.1)
Pharmacokinetic and/or anti-drug antibody sampling missed	3 (0.8)	4 (1.1)	7 (1.0)
Nodes resection not performed as per protocol	0 (0.0)	1 (0.3)	1 (0.1)
Prohibited Co-Medication	4 (1.1)	2 (0.6)	6 (0.8)
Prohibited medications/procedures during neoadjuvant phase	4 (1.1)	2 (0.6)	6 (0.8)
Other-Unblinding	0 (0.0)	1 (0.3)	1 (0.1)
Disclosing unblinded records to blinded personnel	0 (0.0)	1 (0.3)	1 (0.1)

EXC = exclusion criterion; HIV = human immunodeficiency virus; INC = inclusion criterion; IP = investigational product; IXRS = interactive voice and web response system

Note: For each category and deviation, subjects were included only once, even if they experienced multiple events in that category or deviation. Protocol deviations that occurred during screening and the run-in phase were included in this summary.

Source: 20120283 Clinical Study Report page 77

Reviewer Comment: Reasons for protocol deviations were similar across the two arms. Of note, there were numerically greater patients with cardiovascular issues included in the ABP980 arm than in the EU-Herceptin arm. There were no other clinically significant differences between the two arms. This is unlikely to have affected the primary outcome of the study.

6.5. Analysis of Primary Endpoint(s)

RD and RR of pCR in breast tissue and axillary lymph nodes were the co-primary efficacy endpoints in Study 20120283. The results for both endpoints are summarized in Table 10.

Table 10: Study 20120283 Pathologic Complete Response, pCR Evaluable Population

	ABP 980 N=358 n (%)	EU- HerceptinN=338 n (%)
Pathologic complete response (pCR), n (%)		
Yes	172 (48.0)	137 (40.5)
No	186 (52.0)	201 (59.5)
Risk Difference (ABP 980 – EU-Herceptin) ^a , %	7.3	
90% CI for RD ^a	(1.2, 13.4)	
Risk Ratio (ABP 980/EU-Herceptin) ^a	1.1877	
90% CI for RR ^a	(1.0327, 1.3660)	

^a Estimated using a generalized linear model adjusted for randomization stratification factors: T-stage, nodal status, hormone receptor status, planned paclitaxel dosing schedule, and geographic region

Source: CSR Table 14 and Study 20120283 dataset adpcr.xpt

Reviewer's Comment: The RD of pCR (adjusted for stratification factors) between ABP 980 and EU-Herceptin was 7.3% with a 90% CI of (1.2%, 13.4%). The upper bound of this interval slightly exceeds the pre-specified margin of (-13%, 13%). The RR of pCR (adjusted for stratification factors) between ABP 980 and EU-Herceptin was 1.1877 with a 90% CI of (1.0327, 1.3660). The upper bound of this interval also slightly exceeds the pre-specified margin of (0.7586, 1.3182). Note that since the test of equivalence for RD of pCR did not meet pre-specified criteria, results from the analysis of RR of pCR should be interpreted as descriptive only.

Sensitivity Analyses for RD and RR of pCR

Results of sensitivity analyses for RD and RR of pCR as conducted by the applicant are presented in Table 11.

Table 11: Study 20120283 Sensitivity Analyses of pCR

	ABP 980	EU-Herceptin	pCR RD (90% CI)	pCR RR (90% CI)
	# responders/ # pts (pCR%)	# responders/ # pts (pCR%)		
Assessed by Local Lab				
pCR evaluable with corrected stratification factors	172/358 (48.0)	137/338 (40.5)	7.4 (1.3, 13.6)	1.1939 (1.0383, 1.3727)
ITT using NRI ^a	172/364 (47.3)	137/352 (38.9)	8.1 (2.0, 14.1)	1.2096 (1.0501, 1.3933)
ITT using NRI with corrected stratification factors ^a	172/364 (47.3)	137/352 (38.9)	8.2 (2.2, 14.2)	1.2171 (1.0569, 1.4016)
PP population	166/351 (47.3)	134/328 (40.9)	6.4 (0.2, 12.6)	1.1623 (1.0084, 1.3396)
pCR evaluable pop. with additional model covariates	172/358 (48.0)	137/338 (40.5)	7.3 (1.1, 13.4)	1.1935 (1.0383, 1.3718)
Assessed by Central Lab				
pCR evaluable pop.	162/339 (47.8)	138/330 (41.8)	5.8 (-0.5, 12.0)	1.1419 (0.9934, 1.3124)
ITT using NRI ^a	162/364 (44.5)	138/352 (39.2)	5.1 (-0.9, 11.1)	1.1370 (0.9854, 1.3118)
PP population	156/333 (46.8)	137/321 (42.7)	4.1 (-2.3, 10.4)	1.0986 (0.9545, 1.2644)

^a Data from nine subjects (

(b) (6)

manually assigned to EU-Herceptin were not included in this analysis.

Source: CSR Table 15 and Study 20120283 dataset adpcr.xpt

Reviewer's Comment: In general, all analyses of RR of pCR based on local laboratory assessment resulted in 90% CIs with upper bounds that slightly exceed that of the pre-defined margin (i.e. >1.3182). Analyses of RD of pCR based on local laboratory assessment also resulted in 90% CIs with upper bounds that slightly exceed that of the pre-defined margin (i.e. >13%), except for the analysis conducted in the PP population. All analyses of RD and RR of pCR based on

central laboratory assessment resulted in 90% CIs that were within the pre-defined margins. Note that in these analyses pCR evaluation was based on central laboratory evaluation of tumor samples so the sample sizes of both the pCR evaluable and PP populations have changed to correspond with that data. The review team considers central assessment for pCR to be acceptable to support the conclusion of no meaningful differences between ABP 980 and EU-Herceptin because in general central assessment for pCR is a more reliable method and the applicant was able to obtain sufficient samples for analysis to ensure reliability of this analysis in this study.

6.6. Analysis of Secondary Endpoint(s)

Secondary efficacy endpoints were RD and RR of pCR in breast tissue only and in breast tissue and axillary lymph nodes and absence of DCIS. Results from both local and central lab assessment in the pCR Evaluable, ITT, and PP populations are all shown in Table 12. Note that these analyses were also repeated using corrected stratification values and results were consistent with the results from the primary analyses.

Table 12: Secondary Efficacy Endpoint Results

	Risk Difference (90% CI)		Risk Ratio (90% CI)	
	Local Lab	Central Lab	Local Lab	Central Lab
In Breast Tissue only				
pCR Evaluable	6.0 (-0.2, 12.2)	4.1 (-2.1, 10.4)	1.1463 (1.0080, 1.3035)	1.1019 (0.9723, 1.2488)
ITT using NRI ^a	6.9 (0.8, 13.0)	4.0 (-2.0, 10.1)	1.1667 (1.0241, 1.3291)	1.1083 (0.9739, 1.2612)
PP population	5.0 (-1.3, 11.2)	2.1 (-4.2, 8.5)	1.1194 (0.9827, 1.2751)	1.0571 (0.9314, 1.1996)
Breast Tissue and Axillary Lymph Nodes and Absence of DCIS				
pCR Evaluable	8.0 (2.1, 13.9)	3.6 (-2.2, 9.3)	1.2746 (1.0673, 1.5222)	1.1639 (0.9493, 1.4270)
ITT using NRI ^a	8.6 (2.8, 14.3)	3.2 (-2.2, 8.7)	1.3035 (1.0903, 1.5585)	1.1651 (0.9478, 1.4321)
PP population	7.3 (1.4, 13.3)	2.6 (-3.2, 8.3)	1.2478 (1.0425, 1.4934)	1.1158 (0.9077, 1.3717)

^a Data from nine subjects

(b) (6)

manually assigned to EU-Herceptin were not included in this analysis.

Source: CSR Tables 16 and 17 and Study 20120283 dataset adpcr.xpt

6.7. Other Endpoints

For on-study EFS in the safety analysis population, a total of 34 subjects (by neoadjuvant treatment: 19 on the ABP 980 arm and 15 on the EU-Herceptin arm) had disease progression, recurrence, or died as of the initial data cut-off date of May 5, 2016. The estimated hazard ratio of ABP 980 relative to EU-Herceptin was 1.3155 (95% CI: 0.6565, 2.6359) and median EFS had not been reached.

For OS, a total of 5 subjects died on study (by neoadjuvant treatment: one on the ABP 980 arm and four on the EU-Herceptin arm).

6.8. Subpopulations

Subgroup analyses of RR for pCR

Subgroup analyses of RR for pCR in the pCR evaluable population were performed by the stratification factors (T-stage, nodal status, hormone receptor status, planned paclitaxel dosing schedule, and geographic region), as well as age, ECOG status, and race. Results are shown in Table 13.

Table 13: FDA Subgroup Analyses of RR of pCR in the pCR Evaluable Population

	ABP980 # responders/ # pts (%pCR)	EU-Herceptin # responders/ # pts (%pCR)	RR (90% CI)
Overall	172/358 (48.0)	137/338 (40.5)	1.1877 (1.0327, 1.3660)
Age			
<50 years	55/139 (39.6)	49/127 (38.6)	1.0475 (0.8166, 1.3438)
>=50 years	117/219 (53.4)	88/211 (41.7)	1.2818 (1.0811, 1.5198)
Race			
White	154/325 (47.4)	128/313 (40.9)	1.1581 (1.0014, 1.3393)
Non-White	18/33 (54.5)	9/25 (36.0)	NE (NE, NE)
T-stage (per CRF)			
Less than T4	135/280 (48.2)	113/263 (43.0)	1.1285 (0.9686, 1.3149)
T4	37/78 (47.4)	24/75 (32.0)	1.5316 (1.0899, 2.1522)
Axillary lymph node Involvement (per CRF)			
Yes	126/272 (46.3)	99/250 (39.6)	1.1755 (0.9950, 1.3888)
No	46/86 (53.5)	38/88 (43.2)	1.2885 (0.9890, 1.6786)
Hormone receptor status (per CRF)			
ER+ and/or PR+	118/263 (44.9)	102/251 (40.6)	1.1036 (0.9343, 1.3036)
ER- and PR-	54/95 (56.8)	35/87 (40.2)	1.4265 (1.1013, 1.8479)
Paclitaxel dosing schedule (per CRF)			
QW	50/106 (47.2)	39/90 (43.3)	1.0982 (0.8476, 1.4229)
Q3W	122/252 (48.4)	98/248 (39.5)	1.2336 (1.0444, 1.4570)
Geographic Region (per CRF)			
Eastern Europe	121/267 (45.3)	101/259 (39.0)	1.1713 (0.9897, 1.3862)
Western Europe	24/42 (57.1)	21/40 (52.5)	1.0990 (0.7856, 1.5374)
Other	27/49 (55.1)	15/39 (38.5)	1.4944 (1.0124, 2.2058)
Baseline ECOG			
0	140/294 (47.6)	118/294 (40.1)	1.1984 (1.0287, 1.3962)
1	32/64 (50.0)	19/44 (43.2)	1.2650 (0.8585, 1.8641)
Binding ADA status			
Positive	1/2 (50.0)	2/5 (40.0)	NE (NE, NE)
Negative	171/356 (48.0)	135/333 (40.5)	1.1877 (1.0319, 1.3672)

Source: CSR Figure 2 and Study 20120283 adsl.xpt and adpccr.xpt

Reviewer's Comment: Stratification factor subgroups were defined by their actual values from CRF. Similar to the primary analysis, the RRs and corresponding CIs reported were estimated from generalized linear models adjusted for stratification factors using their values at randomization. When considering stratification factor subgroups, the generalized linear model was adjusted for all stratification factors except for the one being examined. As noted by the applicant, the following subgroups had model convergence problems: for the subgroup with axillary lymph node involvement=no, the model converged with relative Hessian convergence criterion greater than the default limit of 0.0001, and for the subgroups of Race=Non-White and Binding ADA status=Positive, the model did not converge so no estimates are given. Otherwise, results from subgroup analyses were consistent with the results of the primary analysis.

6.9. Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable to this application.

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

As of March 29, 2017, there have been 20 (5.5%) patients in the neoadjuvant ABP 980 arm/adjuvant ABP 980, 11 (5.8%) patients in the neoadjuvant EU-Herceptin/adjuvant EU-Herceptin arm and 6 (3.5%) patients in the neoadjuvant EU-Herceptin/adjuvant ABP 980 arm who had an EFS event. There does not appear to be a difference in disease progression between ABP 980 and EU-Herceptin.

6.11. Additional Efficacy Issues/Analyses

Treatment Compliance

Study treatment was delivered in the clinic by site personnel; therefore, no measurement of treatment compliance was required.

Concomitant Medications

Nearly all patients used concomitant medications (98.9% in the ABP 980 arm and 99.2% in the EU-Herceptin arm) during the neoadjuvant phase. The most commonly used concomitant medications in both treatment groups were part of pre- or post-chemotherapy treatment: corticosteroids for systemic use (ABP 980 89.3%, EU-Herceptin 90.3%), drugs for acid-related disorders (88.7% versus 90.9%) antiemetics (79.6% versus 77.2%), and antihistamines for systemic use (40.7% versus 45.2%).

ADCC in Relation to pCR

We sent information requests to the applicant asking them to conduct an analysis of pCR excluding any patients exposed to EU-Herceptin lots with lower ADCC.

The applicant conducted two analyses using two different assays to define low ADCC including:

1. NK92 ADCC Assay with a cut-off of ADCC Activity Levels $\leq 60\%$

2. PBMC ADCC Assay with a cut-off of ADCC Activity Levels $\leq 65\%$

Results of the pCR analysis excluding subjects exposed to lots with low ADCC based on the NK92 Assay are shown in Table 14.

Table 14: pCR Results Excluding Subjects Exposed to Lots with Low ADCC by NK92 Assay

	ABP 980	EU-Herceptin: Not Exposed to Lots w/ ADCC $\leq 60\%$	RD	90% CI for RD	RR	90% CI for RR
Assessed by local laboratory						
pCR evaluable pop	172/358 (48.0)	130/321 (40.5)	7.3	(1.0, 13.5)	1.1879	(1.0304, 1.3695)
PP population	166/351 (47.3)	127/311 (40.8)	6.3	(0.0, 12.6)	1.1610	(1.0050, 1.3412)
Assessed by central laboratory						
pCR evaluable pop	162/339 (47.8)	130/313 (41.5)	5.9	(-0.4, 12.3)	1.1465	(0.9945, 1.3218)
PP population	156/333 (46.8)	129/304 (42.4)	4.2	(-2.3, 10.6)	1.1010	(0.9539, 1.2708)

Source: Applicant's Clinical Amendment Post Application Orientation Meeting dated 9/26/17 Table 1

Results of the pCR analysis excluding subjects exposed to lots with low ADCC based on the PBMC Assay are shown in Table 15.

Table 15: pCR Results Excluding Subjects Exposed to Lots with Low ADCC by PBMC Assay

	ABP 980	EU-Herceptin: Not Exposed to Lots w/ ADCC $\leq 65\%$	EU-Herceptin: Exposed to Lots w/ ADCC $\leq 65\%$	R D	90% CI for RD	RR	90% CI for RR
Assessed by local laboratory							
pCR evaluable	172/358 (48.0)	116/267 (43.4)	21/71 (29.6)	4.4	(-2.1, 11.0)	1.1166	(0.9656, 1.2913)

PP population	166/35 1 (47.3)	113/258 (43.8)	21/70 (30.0)	3. 5	(-3.1, 10.2)	1.090 5	(0.9409, 1.2639)
Assessed by central laboratory							
pCR evaluable	162/33 9 (47.8)	114/259 (44.0)	24/71 (33.8)	3. 5	(-3.2, 10.2)	1.079 5	(0.9324, 1.2499)
PP population	156/33 3 (46.8)	113/251 (45.0)	24/70 (34.3)	1. 6	(-5.2, 8.4)	1.036 0	(0.8939, 1.2007)

Source: Applicant's Response to 26 January 2018 Statistical IR Table 1

Reviewer's Comment: The results from the pCR analysis excluding subjects exposed to lots with low ADCC by the NK92 assay (affecting 17 subjects) were consistent with what was seen in Study 20120283. The upper bound of the 90% CI for RR of pCR exceeds the pre-specified equivalence margin of (0.7586, 1.3182) in all cases except for the PP population as assessed by central laboratory. Based on this analysis, it does not appear that exposure to EU-Herceptin with low ADCC influenced the efficacy results observed in Study 20120283. However, we do note that only 17 subjects were excluded.

The results from the pCR analysis excluding subjects exposed to lots with low ADCC by the PBMC assay (affecting 71 subjects) show that the 90% CI for RR of pCR is within the pre-specified equivalence margin in all cases considered. These results appear to support the observation that exposure to EU-Herceptin with low ADCC influenced the efficacy results observed in Study 20120283. However, one of the lots excluded (Lot H4180B02) has an expiration date of August 2016, which was before the start of the trastuzumab ADCC trend based on published reports.

This information does not affect our conclusion that there are no clinically meaningful differences between ABP 980 and US-Herceptin.

Applicant's Sensitivity Analyses of the Clinical Data

The applicant compared ABP 980 to trastuzumab based on data from both the PK similarity study assessing EU-Herceptin and US-Herceptin and the comparative clinical study assessing EU-Herceptin. This section summarizes the two approaches taken and their results.

Reviewer's Comment: These analyses were proposed by the applicant in the IND stage, and FDA commented that they appeared generally acceptable but noted that they were to be considered sensitivity analyses only if results from the comparative clinical study were positive in terms of equivalence.

The applicant has manuscripts prepared detailing each of the approaches. According to the applicant, the manuscript detailing the statistical strategy for the Bayesian approach was submitted 29 August 2017 to Statistics in Medicine and the manuscript detailing the statistical strategy for the frequentist approach was accepted by the Journal of Biopharmaceutical Statistics with online publication in November 2017.

The first approach used a Bayesian model to estimate the risk ratio of pCR between ABP 980 and EU-Herceptin. The prior distributions for the Bayesian model were derived from a meta-analysis of 10 historical trastuzumab trials as well as results from the PK similarity study. Further, the amount of information borrowed from the PK similarity study was controlled by a variable M. It was planned that the stronger the evidence, the smaller the M. Based on the strong evidence observed in the PK similarity study, the applicant pre-specified M=0.05 with sensitivity analyses using M=0.1 and 0.2.

Results for the RD and RR of pCR for the pCR Evaluable population using M=0.5, 0.1, and 0.2 are shown in Table 16.

Reviewer's Comment: The Bayesian approach performed as expected, and when M=0.05, the 90% credible interval for RR of pCR appears to be within the pre-specified equivalence margin of (0.7586, 1.3182). However, we note that these results are exploratory only.

Table 16: Bayesian Assessment of the Clinical Data for pCR

	Amount of information borrowed (M)					
	M=0.05		M=0.1		M=0.2	
	ABP 980 N=358	EU- Herceptin N=338	ABP 980 N=358	EU- Herceptin N=338	ABP 980 N=358	EU- Herceptin N=338
pCR, n (%)	172 (48.0)	137 (40.5)	172 (48.0)	137 (40.5)	172 (48.0)	137 (40.5)
RD (ABP 980-EU-Herceptin) (%)						
Posterior Mean	4.5%		7.0%		8.1%	
90% CI for RD	(-0.24, 9.29)		(1.11, 12.91)		(1.69, 14.55)	
95% CI for RD	(-1.22, 10.22)		(0.03, 14.12)		(0.53, 15.71)	
RR (ABP 980/EU-Herceptin)						
Posterior Mean	1.1026		1.1614		1.1897	
90% CI for RR	(0.9949, 1.2182)		(1.0236, 1.3123)		(1.0369, 1.3559)	
95% CI for RR	(0.9748, 1.2421)		(1.0007, 1.3467)		(1.0113, 1.3909)	

Source: Totality of Clinical Evidence Report Table 1.1

The second approach used frequentist methods to refine the estimated confidence interval for the comparative clinical study by making use of results from the PK similarity study and the expected relationship between the PK and clinical studies. Derivation of the refined confidence interval required defining a structural relationship between

relative similarity measurements from the PK similarity study and the comparative clinical study. The structural relationship basically notes that if relative similarity in the PK similarity study is within the bound c_1 then the difference between the two products in the comparative clinical study should be within the margins. In other words, the constant c_1 corresponds to the ability of the PK data to predict clinical efficacy. A smaller c_1 corresponds to a weaker relationship.

Therefore, there are two scenarios for rejecting the null hypothesis that the two products are not equivalent for the comparative clinical study:

1. The empirical evidence in the PK similarity study concludes that the relative similarity measure is less than c_1 .
2. The empirical evidence in the comparative clinical study indicates the two products are similar.

To control the overall type 1 error at level α , the α is split so that the error for case (1) must be under α_1 and the error for case (2) must be under $(\alpha - \alpha_1)$. The applicant uses this construct, which combines the PK similarity and comparative clinical studies' data, to define the refined confidence interval for the comparative clinical study which is then compared to the pre-specified equivalence margin.

The applicant points out that α_1 is arbitrary and their proposed method searches for the optimal α_1 such that the power under the alternative hypothesis in the comparative clinical study is maximized. We note that their method of determining the optimal α_1 starts with point estimates obtained from the actual PK similarity data.

This frequentist analysis was performed with c_1 pre-specified as 0.4 due to the high degree of similarity in structure and function, the highly similar exposure (PK), and results from a simulation study. Analyses were also performed with c_1 set to 0.435 and 0.370 to ensure expected model performance.

Results for the RD and RR of pCR for the pCR Evaluable population using $c_1=0.4$ are shown in Table 17.

Table 17: Frequentist Assessment of the Clinical Data for pCR, $c_1=0.4$

	ABP 980 N=358	EU-Herceptin N=338
pCR, n (%)	172 (48.0)	137 (40.5)
RD (ABP 980-EU-Herceptin)	7.3%	
Refined 90% CI	(0.96, 13.00)	
Refined 95% CI	(-0.37, 13.00)	
RR (ABP 980/EU-Herceptin)	1.1877	
Refined 90% CI	(1.0283, 1.3182)	
Refined 95% CI	(0.9974, 1.3182)	

Source: Totality of Clinical Evidence Report Table 2.1

Reviewer's Comments: The frequentist approach performed as expected across all values of c1. The refined 90% confidence interval for RR of pCR was just within the pre-specified equivalence margin of (0.7586, 1.3182). Evidence from the PK similarity study is such that the results were the same when c1 was set as 0.435 and 0.370. We note that the upper bound of the refined 90% confidence interval is equivalent to the upper bound of the pre-specified equivalence margin due to how the refined confidence interval is set up/defined. Again, we also note that these results are exploratory only.

7. Review of Safety

Safety Summary

The results of the clinical development program indicate that the Applicant's data support a determination of no clinically meaningful differences between ABP 980 and US-Herceptin in terms of safety. The safety analyses in study 20120283, which compared ABP 980 and EU-Herceptin in HER2 positive early breast cancer patients 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 off study 20120283. Details of the design for 20120283 are presented in Section 5 above. Key features of the PK similarity study are summarized in Section 5.1. Efficacy results for 20120283 are presented in Section 6. The applicant proposed that ABP 980 have 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 20120283 is the primary study used for the overall safety assessment of ABP 980. There is no pooling of safety data as only one comparative study was conducted. The safety assessments for 20120283 are adequate. Events of interest, based on the known safety profile of trastuzumab, were cardiac failure, neutropenia, infusion reactions, pulmonary toxicity, hypersensitivity, and infections and infestations.

A total of 725 patients are in the safety population. Patients randomized to EU-Herceptin in the neoadjuvant phase were re-randomized at the start of the adjuvant phase to either continue on EU-Herceptin or switch to ABP 980. The total number of patients who receive each treatment sequence is:

- o ABP 980/ABP 980 = 349
- o EU-Herceptin/ABP 980 = 171
- o EU-Herceptin/EU-Herceptin = 171
- o ABP 980/Not treated = 15

- o EU-Herceptin/Not treated = 19

Of these 725 patients, 626 (86.3%) experienced TEAEs and 99 (13.7%) had no reported TEAEs:

- o ABP 980/ABP 980 = 303
- o EU-Herceptin/ABP 980 = 149
- o EU-Herceptin/EU-Herceptin = 145
- o ABP 980/Not Treated = 12
- o EU-Herceptin/Not treated = 17

An overview of TEAEs occurring during the neoadjuvant phase is provided below in Table 18.

Table 18: Overview of TEAEs, Neoadjuvant Phase

Neoadjuvant Phase	ABP 980 N=364	EU- Herceptin N=361
Total Safety Population (based on ADSL.xpt)	364 (100.0)	361 (100.0)
Safety Population that experienced any AE (based on ADAE.xpt)	316 (86.8)	312 (86.4)
TEAEs of any grade	314 (86.3)	309 (85.6)
Grade 3 and higher TEAEs	59 (16.2)	55 (15.2)
Discontinued from study due to TEAEs	4 (1.1)	2 (0.6)
Study drug stopped due to TEAEs	3 (0.8)	2 (0.6)
Serious TEAEs	18 (4.9)	5 (1.4)
Deaths	1 (0.3)	0*

Source dataset: ADAE.xpt

* 2 patients who received EU-Herceptin died of documented CNS metastases more than 30 days after the last dose of study drug treatment in the neoadjuvant phase. They did not start the adjuvant phase.

An overview of TEAEs occurring during the adjuvant phase is provided below in Table 19.

Table 19: Overview of TEAEs, Adjuvant Phase

Adjuvant Phase	ABP 980/ ABP 980 N=349 (%)	EU- Herceptin/ ABP 980 N=171(%)	EU-Herceptin/ EU-Herceptin N=171(%)
Total Safety Population (based on ADSL.xpt)	349 (100.0)	171 (100.0)	171 (100.0)
Safety Population that experienced any AE (based on ADAE.xpt)	303 (86.8)	149 (87.1)	145 (84.8)
Treatment emergent adverse events (TEAEs) of any grade	215 (61.6)	108 (63.2)	96 (56.1)
Grade 3 and higher TEAEs	32 (9.2)	14 (8.2)	11 (6.4)
Discontinued from study due to TEAEs	7 (2.0)	2 (1.2)	2 (1.2)
Study drug stopped due to TEAEs	7 (2.0)	4 (2.3)	3 (1.8)
Serious TEAEs	18 (5.2)	6 (3.5)	6 (3.5)
Deaths	0 (0.0)	3 (1.8)	0 (0.0)

Source: ADAE.xpt from Day 120 Safety Update

*1 patient died of respiratory failure and septic shock, 1 died of progressive disease (PD), 1 was HIV+ and died of PCP pneumonia

7.1.2. Categorization of Adverse Events

The Applicant defined an adverse event (AE) as any untoward medical occurrence in a clinical subject and did not necessarily have to have a causal relationship with the study treatment. This included worsening of a pre-existing medical condition. The term “disease progression of the primary tumor” was not captured as an AE, including fatal AE. Signs and/or symptoms of disease progression that were new or worsened from baseline were reported as AEs. New primary malignancies were considered AEs.

The applicant defined a serious adverse event (SAE) as any AE that met at least 1 of the following criteria:

- Fatal
- Life threatening
- Requires inpatient hospitalization or prolongs existing hospitalization
- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other medically important serious event

All AE summaries supplied by the applicant included only treatment-emergent adverse events (TEAE), which were defined as adverse events that occurred on or after the date of the subject’s first administration of investigational product and within 30 days of the

subject's last administration of investigational product. TEAEs were attributed to the adjuvant phase if the event start date was on or after the date of the first dose of investigational product after surgery; all other TEAEs were attributed to the neoadjuvant phase.

AEs and SAEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) v.19.0. AEs were graded for severity using National Cancer Institute Common Terminology criteria for Adverse Events (NCI CTCAE) version 4.0. AEs were summarized by MedDRA primary system organ class (SOC) and preferred term (PT).

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

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

7.2. Adequacy of Safety Assessments

A total of 725 patients were included in the subject listing dataset safety population. With the original BLA submission, there were 102 patients without documented TEAEs and 97 patients without any documented AEs (treatment-emergent and not treatment-emergent).

An IR was sent to the applicant on 9/6/17 requesting the TEAE information for the 102 patients:

The following safety population patients from the ADSL dataset have no treatment emergent data in the ADAE dataset. Provide the missing treatment emergent AE data for all these patients and send an updated ADAE dataset:

SUBJID	TRTSEQA	(b) (6)	(b) (6)
(b) (6)	ABP 980/ABP 980	trastuzumab/ABP 980	trastuzumab/ABP 980
(b) (6)	ABP 980/Not Treated	trastuzumab/trastuzumab	ABP 980/Not Treated
(b) (6)	trastuzumab/ABP 980	ABP 980/ABP 980	ABP 980/Not Treated
(b) (6)	ABP 980/ABP 980	ABP 980/ABP 980	trastuzumab/trastuzumab
(b) (6)	trastuzumab/trastuzumab	ABP 980/ABP 980	ABP 980/ABP 980
(b) (6)	trastuzumab/ABP 980	ABP 980/ABP 980	trastuzumab/trastuzumab
(b) (6)	trastuzumab/trastuzumab	ABP 980/ABP 980	ABP 980/ABP 980
(b) (6)	ABP 980/ABP 980	trastuzumab/trastuzumab	ABP 980/ABP 980
(b) (6)	trastuzumab/trastuzumab	ABP 980/ABP 980	trastuzumab/ABP 980
(b) (6)	trastuzumab/trastuzumab	ABP 980/ABP 980	ABP 980/ABP 980
(b) (6)	ABP 980/ABP 980	trastuzumab/trastuzumab	trastuzumab/Not Treated
(b) (6)	ABP 980/ABP 980	ABP 980/ABP 980	ABP 980/ABP 980
(b) (6)	ABP 980/ABP 980	ABP 980/ABP 980	trastuzumab/ABP 980
(b) (6)	trastuzumab/ABP 980	ABP 980/ABP 980	trastuzumab/ABP 980
(b) (6)	ABP 980/ABP 980	trastuzumab/ABP 980	trastuzumab/trastuzumab
(b) (6)	trastuzumab/ABP 980	ABP 980/ABP 980	ABP 980/ABP 980
(b) (6)	trastuzumab/trastuzumab	ABP 980/ABP 980	ABP 980/ABP 980
(b) (6)	trastuzumab/trastuzumab	ABP 980/ABP 980	trastuzumab/trastuzumab
(b) (6)	trastuzumab/trastuzumab	trastuzumab/trastuzumab	trastuzumab/Not Treated
(b) (6)	trastuzumab/ABP 980	trastuzumab/trastuzumab	trastuzumab/trastuzumab
(b) (6)	ABP 980/ABP 980	ABP 980/ABP 980	ABP 980/ABP 980
(b) (6)	trastuzumab/ABP 980	trastuzumab/ABP 980	trastuzumab/ABP 980
(b) (6)	ABP 980/ABP 980	trastuzumab/ABP 980	trastuzumab/trastuzumab
(b) (6)	ABP 980/ABP 980	trastuzumab/ABP 980	ABP 980/ABP 980
(b) (6)	ABP 980/ABP 980	ABP 980/ABP 980	trastuzumab/ABP 980
(b) (6)	trastuzumab/trastuzumab	trastuzumab/trastuzumab	trastuzumab/trastuzumab
(b) (6)	ABP 980/ABP 980	ABP 980/ABP 980	trastuzumab/ABP 980
(b) (6)	ABP 980/ABP 980	ABP 980/ABP 980	ABP 980/ABP 980
(b) (6)	trastuzumab/trastuzumab	ABP 980/ABP 980	trastuzumab/trastuzumab
(b) (6)	trastuzumab/trastuzumab	trastuzumab/ABP 980	trastuzumab/ABP 980
(b) (6)	ABP 980/ABP 980	ABP 980/ABP 980	ABP 980/ABP 980
(b) (6)	trastuzumab/trastuzumab	trastuzumab/ABP 980	trastuzumab/ABP 980
(b) (6)	trastuzumab/trastuzumab	ABP 980/ABP 980	
(b) (6)	ABP 980/ABP 980	ABP 980/ABP 980	

The applicant responded on 9/26/17 with the following:

According to the Statistical Analysis Plan for Study 20120283 (Section 16.1.9 in Study 20120283 clinical study report [CSR]), a treatment-emergent adverse event was defined as an adverse event occurring on or after the subject's first administration of investigational product and within 30 days after the subject's last administration of investigational product.

As displayed in Table 14-6.1.3 in Study 20120283 clinical study report (CSR), in the primary analysis, a total of 623 (85.9%) subjects experienced any treatment-emergent adverse event. For the remaining 102 (14.1%) subjects (those from the ADSL dataset that have no treatment-emergent data in the ADAE dataset included in the table above), no treatment-emergent adverse events were reported in the primary analysis.

Therefore, no treatment-emergent adverse event data are missing for these subjects and no updated ADAE dataset for the primary analysis is needed.

The 14.1% rate of patients with no TEAEs throughout the year-long neoadjuvant and adjuvant treatment period is higher than expected (on average, around 95-98% of patients experience TEAEs for treatment with a trastuzumab product in this treatment setting). The sites with the most number of missing TEAE data is shown in Table 20 below:

Table 20: Sites with Most Missing TEAE Data

Site ID	Number of Patients	Country
51009	14	Russia
51001	7	Russia
80001	7	Belarus
51010	6	Russia
51013	6	Russia
50003	5	Romania
50004	5	Romania
50002	4	Romania
80005	4	Belarus

Source: ADSL.xpt and ADAE.xpt

Dr. Jinzhong Liu examined the ADLB.xpt (lab test analysis dataset) of all 725 safety population patients reported in the subject listing (ADSL.xpt) dataset and all patients reported lab results, which matched the applicant's study report. Dr. Liu also examined the LVEF dataset (ADLVEF.xpt) and confirmed all the patients with missing TEAE data had at least 1 documented LVEF measurement. Of the patients with missing TEAE data, the following 12 patients also had missing LVEF measurements (Table 21).

Table 21: Patients with Missing TEAE and LVEF Data

Patient	# Missing LVEF	Treatment	Site	Site # Randomized	Site # Premature Discontinued
(b) (6)	2	ABP 980/ ABP 980	48005 (Poland)	5	0
	1	EU-Herceptin/ ABP 980	48006 (Poland)	15	6
	1	ABP 980/ ABP 980	48006 (Poland)	15	6
	1	EU-Herceptin/ EU-Herceptin	51001 (Russia)	18	3
	1	EU-Herceptin/ EU-Herceptin	51001 (Russia)	18	3
	2	ABP 980/ ABP 980	51001 (Russia)	18	3
	1	EU-Herceptin/ ABP 980	51001 (Russia)	18	3
	1	ABP 980/ ABP 980	51001 (Russia)	18	3
	1	ABP 980/ ABP 980	51013 (Russia)	8	1
	1	EU-Herceptin/ ABP 980	51013 (Russia)	8	1
	1	EU-Herceptin/ ABP 980	54004 (Slovakia)	9	0
	1	EU-Herceptin/ EU-Herceptin	64010 (Ukraine)	2	1

Source: ADAE.xpt and ADLVEF.xpt

With the Day 120 Safety Update, 3 additional patients from the safety population reported at least one TEAE through the final database lock date of 3/29/17:

- Patient (b) (6) treated with ABP 980/ABP 980
- Patient (b) (6) treated with EU-Herceptin/ABP 980
- Patient (b) (6) treated with EU-Herceptin/ABP 980

Reviewer's Comment: 99 patients had no reported TEAEs throughout the entire treatment, which is about 14% of the study population, compared with the ~5% expected based on clinical experience with US-Herceptin (Gianni et al., Lancet 2010, NOAH trial). This raises concerns about the adequacy of reporting. Of these patients, 12 also had at least 1 or more missing LVEF value. 5 received ABP 980/ABP 980, 3 received EU-Herceptin/EU-Herceptin, and 4 received EU-Herceptin/ABP 980. The available LVEF data of these 12 patients were reviewed and all had LVEF ranging from 55-78%. Therefore, it is less likely the 12 patients

with no TEAEs and missing LVEF values would have meaningful differences in cardiac safety. Therefore overall although 14% of the study population had no TEAEs, this is unlikely to have meaningful differences in safety.

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

The safety analysis population consisted of all patients who received any amount of investigational product. Table 22 below list the exposure to ABP 980 and/or EU-Herceptin for study 20120283.

Table 22: Safety Population Study Drug Exposure

**Table 14-5.1.3. Investigational Product Exposure Summary – Entire Study
(Safety Analysis Population)**

Variable	ABP 980/ABP 980 (N = 364)	Trastuzumab/ Trastuzumab (N = 190)	Trastuzumab/ABP 980 (N = 171)
Weight-based average dose administered (mg/kg) ^a			
n	364	190	171
Mean (std)	6.30 (0.163)	6.32 (0.223)	6.28 (0.110)
Median	6.25	6.25	6.25
Q1, Q3	6.25, 6.27	6.25, 6.27	6.24, 6.27
Min, Max	6.0, 8.0	6.0, 8.0	6.1, 7.0
Weight-based cumulative dose administered (mg/kg) ^a			
n	364	190	171
Mean (std)	94.3 (18.36)	91.4 (24.67)	98.0 (12.06)
Median	100.0	100.0	100.0
Q1, Q3	94.0, 100.0	94.0, 102.0	96.0, 106.0
Min, Max	8, 108	8, 108	34, 108
Total cumulative dose administered (mg) ^{a,b}			
n	364	190	171
Mean (std)	6824.92 (1945.895)	6582.23 (2197.186)	7189.56 (1634.862)
Median	6800.00	6825.00	7060.00
Q1, Q3	5815.00, 7950.00	5800.00, 7844.00	6200.00, 8268.00
Min, Max	536.0, 12190.0	681.8, 11400.0	2240.0, 12190.0

^a If a partial dose is given at a visit where loading/re-loading dose is indicated on the IP administration eCRF, it will be approximated to be 4 mg/kg. If a partial dose is given at a visit where a maintenance dose is indicated on the IP administration eCRF, it will be approximated to be 3 mg/kg.

^b Total cumulative dose administered is calculated using the screening weight.

^c Subjects can have more than 1 reason for dose delay.

Source Dataset: ADEX, Program: t_exfull.sas, Output: t-14-05-001-003-ex-full.rtf, Generated on: 19APR2017 08:58

Source: Study 20120283 CSR Table 14-5.1.3

For the neoadjuvant phase there were a total of 525 patients, 364 who received ABP 980 and 361 who received EU-Herceptin.

For the adjuvant phase, a total of 349 patients received ABP 980/ABP 980 (neoadjuvant/adjuvant phase treatment received), 171 received EU-Herceptin/EU-Herceptin, and 171 received EU-Herceptin/ABP 980. Patients who received treatment in the neoadjuvant phase but not in the adjuvant phase are counted in the neoadjuvant/adjuvant treatment arm under the treatment received in the neoadjuvant phase. Over the entire study, the safety population consisted of 34 patients who received treatment only in the neoadjuvant phase (15 received ABP 980 and 19 received EU-Herceptin in the neoadjuvant phase). Of the 19 who received neoadjuvant EU-Herceptin, 10 were initially randomized to ABP 980 for the adjuvant phase but did not receive adjuvant treatment.

Reviewer's Comment: The exposure was well balanced between the arms. The maximum weight-based dose administered was 8.0 mg/kg.

Study 20120283 was conducted at 123 sites in 20 countries (Belarus, Brazil, Bulgaria, Canada, Chile, Czech Republic, Germany, Greece, Hungary, Italy, Mexico, Poland, Romania, Russia, Serbia, Slovakia, South Africa, Spain, Ukraine, United Kingdom). Table 23 below provides an overview of the demographic characteristics of the safety population (n=628).

Table 23: Safety Population Demographics

	ABP 980/ ABP 980 n=349	ABP 980/ Not Treated n=15	EU- Herceptin/ EU- Herceptin n=171	EU- Herceptin/ ABP 980 n=171	EU- Herceptin/ Not Treated n=19
Age					
Mean	52.7	54.4	52	52.7	58.6
SD	10.7	12.4	10.8	11.7	10.4
Median	53	55	52	53	60
Range	28-85	30-72	26-79	28-79	36-75
< 50	123 (35.2)	4 (26.7)	65 (38.0)	66 (38.6)	3 (15.8)
>=50	213 (61.0)	11 (73.3)	106 (62.0)	105 (61.4)	16 (84.2)
ECOG					
0	286 (81.9)	8 (53.3)	148 (86.5)	149 (87.1)	15 (78.9)
1	63 (18.1)	3 (20.0)	23 (13.5)	22 (12.9)	4 (21.1)
Race					
American Indian Or Alaska Native	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Asian	2 (0.6)	0 (0.0)	2 (1.2)	1 (0.6)	0 (0.0)
Black or African American	10 (2.9)	0 (0.0)	0 (0.0)	2 (1.2)	2 (10.5)
Other	20 (5.7)	0 (0.0)	11 (6.4)	10 (5.8)	0 (0.0)
White	316 (90.5)	11 (73.3)	158 (92.4)	158 (92.4)	17 (89.5)
Region					
Eastern Europe	261 (74.8)	10 (66.7)	128 (74.9)	132 (77.2)	13 (68.4)
Western Europe	39 (11.2)	4 (26.7)	22 (12.9)	22 (12.9)	2 (10.5)
Other	49 (14.0)	1 (6.7)	21 (12.3)	17 (9.9)	4 (21.1)
Tumor Size					
T0	1 (0.3)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
T1	7 (2.0)	0 (0.0)	3 (1.8)	2 (1.2)	0 (0.0)
T2	198 (56.7)	7 (46.7)	85 (49.7)	95 (55.6)	11 (57.9)
T3	67 (19.2)	2 (13.3)	44 (25.7)	37 (21.6)	3 (15.8)
T4	76 (21.8)	6 (40.0)	38 (22.2)	37 (21.6)	5 (26.3)
Nodal Status					
N0	81 (23.2)	6 (40.0)	46 (26.9)	41 (24.0)	8 (42.1)
N1	172 (49.3)	8 (53.3)	76 (44.4)	73 (42.7)	6 (31.6)
N2	64 (18.3)	0 (0.0)	33 (19.3)	35 (20.5)	2 (10.5)
N3	32 (9.2)	1 (6.7)	16 (9.4)	22 (12.9)	3 (15.8)
Histological Grade					
1	7 (2.0)	1 (6.7)	0 (0.0)	0 (0.0)	1 (5.3)
2	167 (47.9)	7 (46.7)	86 (50.3)	80 (46.8)	7 (36.8)
3	115 (33.0)	5 (33.3)	58 (33.9)	65 (38.0)	9 (47.4)
Unknown	60 (17.2)	2 (13.3)	27 (15.8)	26 (15.2)	2 (10.5)
Hormone Receptor					
ER+/PR+	94 (26.9)	5 (33.3)	43 (25.1)	43 (25.1)	7 (36.8)
ER+ or PR+	255 (73.1)	10 (66.7)	128 (74.9)	128 (74.9)	12 (63.2)

Source: ADSL.xpt

Reviewer's Comment: Few patients completed the neoadjuvant phase and did not receive adjuvant treatment (ABP 980/not treated 15, EU-Herceptin/not treated 19). Of the patients who received treatment in the neoadjuvant and adjuvant settings, the demographics were well balanced. The majority were patients greater than or equal to 50 years old, ECOG 0, White, treated in Eastern Europe, T2 tumors, N1 nodal status, grade 2, and ER or PR positive.

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 20120283 was described in Protocol Version 3.0 Table 1 (refer to Figure 3 above). The frequency of monitoring was considered adequate within the context of the study. Cardiac monitoring was 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

7.3.1. Deaths

Six patients died in the safety population over the entire study (Table 24 below).

Table 24: Deaths

Patient	Age	Treatment (neoadjuvant/adjuvant)	Timing	Cause
(b) (6)	69	ABP 980/Not Treated	Neoadjuvant	Pneumonia
	72	EU-Herceptin/Not Treated	Neoadjuvant	PD
	55	EU-Herceptin/Not Treated	Neoadjuvant	PD
	52	EU-Herceptin/ABP 980	Adjuvant	Septic shock
	63	EU-Herceptin/ABP 980	Adjuvant	PD
	34	EU-Herceptin/ABP 980	Adjuvant	PCP Pneumonia (HIV+)

Source: ADSL.xpt

PD = progressive disease

- Patient (b) (6) 69F assigned to ABP 980. She experienced grade 1 pyrexia and grade 4 pneumonia during the **neoadjuvant phase**, 60 days after her first dose of study drug and 20 days after her most recent dose. She was hospitalized and received IV antibiotics and supplemental oxygen. She died 2 days later and cause of death was multiple organ failure and sepsis due to **pneumonia**.
- Patient (b) (6): 72F assigned to EU-Herceptin. Her first dose of study drug

was administered (b) (6). On (b) (6) she had grade 2 neutropenia resulting in delay in paclitaxel. On (b) (6) she had grade 2 neutropenia resulting in delay in paclitaxel. On (b) (6) she had grade 2 neutropenia resulting in paclitaxel delay. On (b) (6), **neoadjuvant phase** study day 154, she had documented lesions on MRI brain grade 5 metastases to nervous system, described as nervous system metastases NOS. Last study drug administered (b) (6). She died of CNS metastases on (b) (6). Study drug C1D1 (b) (6), C2D1 (b) (6), C3D1 (b) (6), C4D1 (b) (6). She completed 4 courses of neoadjuvant treatment and about 8 weeks after completing neoadjuvant treatment, had **documented CNS metastases**. Thus her death is counted as occurring during the neoadjuvant phase as she did not start the adjuvant phase. Her death is not counted as treatment emergent as it occurred more than 30 days after she received her last dose of study drug treatment.

- Patient (b) (6): 55F assigned to EU-Herceptin. Her first dose of study drug was (b) (6). On (b) (6) she had neutropenia, grade 2-3. She experienced grade 4 seizure on (b) (6), during the **neoadjuvant phase**, 134 days after study drug initiation. She was hospitalized and (b) (6) CT showed brain lesions. She died on (b) (6) of CNS metastases. Last dose of study drug was (b) (6). Study drug C1D1 (b) (6), C2D1 (b) (6), C3D1 (b) (6), C4D1 (b) (6). She completed 4 courses of neoadjuvant treatment and about 3 weeks after completing neoadjuvant treatment, she had a seizure and **documented CNS metastases**. Her death is counted as occurring during the neoadjuvant phase. Her death is not counted as treatment emergent as it occurred more than 30 days after she received her last dose of study drug treatment.
- Patient (b) (6): 52F assigned to EU-Herceptin/ABP 980. She experienced grade 4 acute prerenal failure and grade 4 gastrointestinal toxicity during the neoadjuvant phase, 46 days after her first dose of study drug and ultimately had resolution of these events. She continued on the study and during the **adjuvant phase**, 164 days after study drug initiation and 4 days after her most recent dose of ABP 980, she experienced grade 4 respiratory failure. She was hospitalized and intubated and died 1 day later of grade 5 **septic shock**.
- Patient (b) (6): 63F assigned to EU-Herceptin/ABP 980. She experienced grade 3 metastases to adrenals, bone, liver, and lung on (b) (6) during the **adjuvant phase**, 204 days after study drug initiation. CT on (b) (6) confirmed metastases. She was transferred to palliative care on (b) (6) and died on (b) (6) of **progressive disease** (officially reported as cardio-pulmonary insufficiency).
- Patient (b) (6): 34F assigned to EU-Herceptin/ABP 980. She experienced grade 1 radiation pneumonitis on November (b) (6) during the **adjuvant phase**, 321 days after study drug initiation. On January (b) (6), the patient was hospitalized for grade 3 radiation pneumonitis and grade 3 PCP pneumonia. The patient's screening test for HIV had been negative, but an enzyme-linked immunosorbent assay for HIV was positive on (b) (6). CD4 count on (b) (6) was $70 \times 10^6/L$. Patient died on (b) (6) of **PCP pneumonia**.

Reviewer's Comment: Narratives were reviewed for the patients who died. Three patients died of PD confirmed on imaging. One patient died of PCP pneumonia,

likely related to HIV/AIDS. Patient (b) (6) received ABP 980 in the neoadjuvant phase and died on study day 62 of sepsis from pneumonia. WBC count was 2570/mm³ and neutrophil count was 1979/mm³ with band neutrophil count of 283/mm³. This is likely related to paclitaxel, although ABP 980 could have contributed. Patient (b) (6) completed treatment with EU-Herceptin in the neoadjuvant phase. During the adjuvant phase, the patient experienced sudden onset grade 4 respiratory failure and died 1 day later. The cause of death was described as septic shock, although no information about laboratory results or treatment was provided to corroborate an infectious etiology as cause of death. Given the sudden onset of respiratory failure and death, pulmonary embolism is on the differential as cause of death.

7.3.2. Nonfatal Serious Adverse Events

Serious TEAEs from the neoadjuvant phase of 20120283 is listed in Table 25 below, with few patients experiencing events in both treatment arms.

Table 25: Serious TEAEs, Neoadjuvant Phase

MedDRA Term	ABP 980 n=364 (%)	EU-Herceptin n=361 (%)
Blood and lymphatic system disorders		
Febrile neutropenia	3 (0.8) ^{2,4}	0 (0.0)
Cardiac disorders		
Atrial fibrillation	1 (0.3)	0 (0.0)
Cardio-respiratory arrest	1 (0.3)	0 (0.0)
Sinus bradycardia	1 (0.3)	0 (0.0)
General disorders and administration site conditions		
Chest pain	1 (0.3)	0 (0.0)
Immune system disorders		
Hypersensitivity	1 (0.3) ³	0 (0.0)
Infections and infestations		
Cystitis	1 (0.3)	0 (0.0)
Incision site infection	1 (0.3)	0 (0.0)
Pneumonia	1 (0.3)	0 (0.0)
Pneumonia bacterial	1 (0.3)	0 (0.0)
Sepsis	1 (0.3) ²	0 (0.0)
Wound sepsis	0 (0.0)	1 (0.3)
Injury, poisoning and procedural complications		
Radius fracture	1 (0.3)	0 (0.0)
Subcutaneous haematoma	0 (0.0)	1 (0.3)
Tibia fracture	1 (0.3)	0 (0.0)
Wound	1 (0.3)	0 (0.0)
Investigations		
Alanine aminotransferase increased	0 (0.0)	1 (0.3) ⁵
Aspartate aminotransferase increased	0 (0.0)	1 (0.3) ⁵
White blood cell count decreased	1 (0.3) ⁴	0 (0.0)
Metabolism and nutrition disorders		
Decreased appetite	1 (0.3)	0 (0.0)
Psychiatric disorders		
Anxiety disorder	0 (0.0)	1 (0.3)
Reproductive system and breast disorders		
Breast haematoma	1 (0.3)	0 (0.0)
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	1 (0.3) ³	0 (0.0)
Vascular disorders		
Vena cava thrombosis	1 (0.3)	0 (0.0)

Source dataset: ADAE.xpt

¹ Patient (b) (6) is a 52F assigned to ABP 980/ABP 980. She started the neoadjuvant phase on (b) (6) and the adjuvant phase on (b) (6). On (b) (6) (study day 134), she experienced grade 4 atrial fibrillation and cardio-pulmonary arrest during the postoperative period of her breast margin excision surgery. She had no apparent neurological focalities and was admitted to the ICU. CT brain showed minimum acute cranial hemorrhage. The next day she was afebrile and had no leukocytosis and O2 saturation was 95%. On (b) (6) MRI brain showed no lesions. She was discharged on (b) (6) and had normal EKG and echo with NSR. Treatment medications included amiodarone. The investigators felt these events were unrelated to the study drug or paclitaxel.

² Patient (b) (6) was a 72F randomized to ABP 980/ABP 980. Her first dose of study drug was (b) (6) and on (b) (6) (study day 42), experienced grade 3 febrile neutropenia and grade 4 sepsis with Staph capitis bacteremia. The study drug was withdrawn and the patient was discontinued from the study. She recovered from the AE on (b) (6).

³ Patient (b) (6) was a 66F randomized to ABP 980/ABP 980. Her first dose of study drug in the neoadjuvant phase was (b) (6) and in the adjuvant phase was (b) (6). On (b) (6) she received ABP 980, on (b) (6) she received paclitaxel, and on (b) (6) (neoadjuvant phase study day 82) she experienced grade 3 hypersensitivity and grade 4 dyspnea, with the dyspnea related to the hypersensitivity. The investigator felt the events were due to paclitaxel. The AE resolved on (b) (6).

⁴ Patient (b) (6) was a 47F randomized to ABP 980/ABP 980. Her first dose of study drug in the neoadjuvant phase was (b) (6) and in the adjuvant phase was (b) (6). On (b) (6) (study day 76 neoadjuvant phase) she experienced grade 4 febrile neutropenia, grade 4 WBC decrease, and grade 3 upper respiratory tract infection (URTI was categorized as event of interest and not serious adverse event). The febrile neutropenia and WBC decrease were felt related to paclitaxel and resolved on (b) (6) (she received G-CSF and antibiotics) and the URTI was resolved on (b) (6) and felt to be unrelated to study drug or paclitaxel.

⁵ Patient (b) (6) was a 58F randomized to EU-Herceptin/ABP 980. She received her first dose of study drug in the neoadjuvant phase on (b) (6) and in the adjuvant phase on (b) (6). She had multiple occurrences of AST and ALT elevation, with AST elevation on (b) (6) grade 3 and the other instances grade 1-2 and all occurring during the month of (b) (6) during the neoadjuvant phase when she received EU-Herceptin. The patient had resolution of all of her AST and ALT increase events by Oct 11, 2014. These events were felt to be related to study drug and related to paclitaxel.

Reviewer's Comment: Very few patients experienced serious TEAEs during the neoadjuvant phase. Narratives were reviewed of the patients who experienced multiple serious TEAEs and no safety concerns were noted.

Serious TEAEs from the adjuvant phase are listed in Table 26 below, with few patients experiencing events in both treatment arms.

Table 26: Serious TEAEs, Adjuvant Phase

MedDRA Term	ABP 980/ ABP 980 N=349 (%)	EU- Herceptin/ ABP 980 N=171 (%)	EU- Herceptin/ EU-Herceptin N=171 (%)
Cardiac disorders			
Ventricular extrasystoles	0 (0.0)	1 (0.6)	0 (0.0)
Gastrointestinal disorders			
Enterocolitis	1 (0.3)	0 (0.0)	0 (0.0)
Faecaloma	1 (0.3)	0 (0.0)	0 (0.0)
Gastric ulcer perforation	1 (0.3)	0 (0.0)	0 (0.0)
Pancreatitis acute	1 (0.3)	0 (0.0)	0 (0.0)
General disorders and administration site conditions			
Asthenia	1 (0.3)	0 (0.0)	0 (0.0)
Chest pain	1 (0.3)	0 (0.0)	0 (0.0)
Gait disturbance	1 (0.3)	0 (0.0)	0 (0.0)
Infections and infestations			
Pneumocystis jirovecii pneumonia	0 (0.0)	1 (0.6)	0 (0.0)
Pneumonia	0 (0.0)	0 (0.0)	2 (1.2)
Septic shock	0 (0.0)	1 (0.6)	0 (0.0)
Soft tissue infection	0 (0.0)	0 (0.0)	1 (0.6)
Urinary tract infection	1 (0.3)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications			
Drug dispensing error	1 (0.3)	0 (0.0)	0 (0.0)
Humerus fracture	1 (0.3)	0 (0.0)	0 (0.0)
Ligament sprain	1 (0.3)	0 (0.0)	0 (0.0)
Radiation pneumonitis	0 (0.0)	1 (0.6)	1 (0.6)
Upper limb fracture	0 (0.0)	1 (0.6)	0 (0.0)
Wound decomposition	1 (0.3)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders			
Back pain	1 (0.3)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer	0 (0.0)	1 (0.6)	0 (0.0)
Metastases to adrenals	0 (0.0)	1 (0.6)	0 (0.0)
Metastases to bone	0 (0.0)	1 (0.6)	0 (0.0)
Metastases to central nervous system	1 (0.3)	0 (0.0)	0 (0.0)
Metastases to liver	0 (0.0)	1 (0.6)	0 (0.0)
Metastases to lung	0 (0.0)	1 (0.6)	0 (0.0)

Nervous system disorders				
	Autonomic nervous system imbalance	1 (0.3)	0 (0.0)	0 (0.0)
	Headache	1 (0.3)	0 (0.0)	0 (0.0)
	Ischaemic stroke	1 (0.3)	0 (0.0)	0 (0.0)
Psychiatric disorders				
	Bipolar disorder	0 (0.0)	0 (0.0)	1 (0.6)
Reproductive system and breast disorders				
	Postmenopausal haemorrhage	0 (0.0)	0 (0.0)	1 (0.6)
Respiratory, thoracic and mediastinal disorders				
	Hydrothorax	0 (0.0)	0 (0.0)	1 (0.6)
	Pneumothorax	0 (0.0)	0 (0.0)	1 (0.6)
	Respiratory failure	0 (0.0)	1 (0.6)	0 (0.0)
Surgical and medical procedures				
	Hysterectomy	1 (0.3)	0 (0.0)	0 (0.0)
Vascular disorders				
	Deep vein thrombosis	0 (0.0)	0 (0.0)	1 (0.6)

Source: Day 120 Update ADAE.xpt

7.3.3. Dropouts and/or Discontinuations

The pre-specified safety withdrawal criteria are reasonable and included patient preference or withdrawal of consent, safety concerns (due to an AE, failure to follow contraception, protocol requirements), disease progression/recurrence, patient follows periodic abstinence, lost to follow-up, or decision by the investigator. Patient with clinically relevant cardiovascular side effects or clinically relevant ECG changes had to be withdrawn from the study.

Table 27 below lists the patients with treatment emergent AEs who were withdrawn from further treatment with the study drug, not including those who died on study (see Section 7.3.1 above for deaths on study). All were coded as unlikely related to the study drug, except for patient (b) (6) who received EU-Herceptin in the neoadjuvant phase and ABP 980 in the adjuvant phase. During cycle 4 of the adjuvant phase, she received ABP 980 on (b) (6) and on (b) (6) she experienced grade 3 ventricular hypokinesia. Her LVEF was 59% at screening, 43% on (b) (6) study day 177) and 33% on (b) (6) study day 184, end of study visit). The event is not resolved/not recovered.

Table 27: TEAEs Leading to Study Drug Withdrawal, Neoadjuvant Phase

Patient	Treatment (neoadjuvant/ adjuvant)	MedDRA Term	AE Grade
(b) (6)	EU-Herceptin/ Not Treated	Oedema peripheral ^{3, 4}	3
	ABP 980/ Not Treated	Vena cava thrombosis ^{2,3}	2
	ABP 980/ ABP 980	Metastases to central nervous system ^{2, 4}	3
	ABP 980/ Not Treated	Febrile neutropenia ² /Sepsis ^{2,3}	3/4
	EU-Herceptin/ Not Treated	Hypersensitivity ³	2
	EU-Herceptin/ ABP 980	Ventricular hypokinesia ⁴	3
	ABP 980/ ABP 980	Drug dispensing error ²	2
	ABP 980/ ABP 980	Soft tissue infection/wound dehiscence ⁴	2/2
	ABP 980/ ABP 980	Breast abscess	3
	ABP 980/ ABP 980	Humerus fracture ²	3
	EU-Herceptin/ EU-Herceptin	Hydrothorax ² /pneumonia ² / Pneumothorax ² /radiation pneumonitis ²	3
	ABP 980/ ABP 980	Ischaemic stroke ⁴	2
	ABP 980/ ABP 980	Metastases to central nervous system ⁴	3
	ABP 980/ Not Treated	Pneumonia bacterial ^{2,3}	4

Source dataset: ADAE.xpt

¹ Discontinued from the study

² Serious TEAE

³ Occurred during neoadjuvant phase

⁴ AE outcome not recovered

Reviewer's Comment: *There were relatively few patients who were discontinued from the study (5 total during the neoadjuvant phase of which 3 received ABP 980 and 2 received EU-Herceptin), not including those who died (patient deaths on study discussed in Section 7.3.1). These were well balanced between the various arms. Patient (b) (6) received EU-Herceptin/ABP 980 and experienced grade 3 ventricular hypokinesia in the adjuvant phase cycle 4, 176 days after study drug initiation on (b) (6). On (b) (6) at randomization the EF was 59%. On (b) (6) the EF was 43%. On (b) (6), the EF was 33%. The final dose of study drug was (b) (6) and the end of study was (b) (6). The patient was asymptomatic throughout. Given the patient received both EU-Herceptin and ABP 980, it is unclear which of the two agents, or if both, contributed to the asymptomatic decrease in EF. Overall there were no concerning safety findings.*

TEAEs leading to study drug withdrawal during the adjuvant phase are listed in Table 28 below.

Table 28: TEAEs Leading to Study Drug Withdrawal, Adjuvant Phase

MedDRA Term	ABP 980/ ABP 980 N=349 (%)	EU-Herceptin/ ABP 980 N=171 (%)	EU-Herceptin/ EU-Herceptin N=171 (%)
Ventricular hypokinesia	0 (0.0)	1 (0.6)	0 (0.0)
Gait disturbance	1 (0.3)	0 (0.0)	0 (0.0)
Breast abscess	1 (0.3)	0 (0.0)	0 (0.0)
Septic shock	0 (0.0)	1 (0.6)	0 (0.0)
Drug dispensing error	1 (0.3)	0 (0.0)	0 (0.0)
Wound dehiscence	1 (0.3)	0 (0.0)	0 (0.0)
Metastases to central nervous system	3 (0.9)	0 (0.0)	1 (0.6)
Headache	1 (0.3)	0 (0.0)	0 (0.0)
Ischaemic stroke	1 (0.3)	0 (0.0)	0 (0.0)
Seizure	0 (0.0)	0 (0.0)	1 (0.6)
Anxiety	0 (0.0)	0 (0.0)	1 (0.6)

Source dataset: Day 120 Update ADAE.xpt

7.3.4. Submission Specific Primary Safety Concerns

7.3.4.1. Treatment-Related TEAEs

A total of 725 patients from the safety population were treated in the neoadjuvant phase (364 ABP 980 and 361 EU-Herceptin). Table 29 below lists a summary of treatment-related TEAEs by grade during the neoadjuvant phase.

Table 29: Treatment-Related TEAEs by Grade, Neoadjuvant Phase

Adverse Event Grade	ABP 980 n=364 (%)	EU-Herceptin n=361 (%)
1	42 (11.5)	48 (13.3)
2	32 (8.8)	27 (7.5)
3	2 (0.5)	2 (0.6)
4	0 (0.0)	3 (0.8)

Source dataset: ADAE.xpt

Reviewer's Comment: The treatment-related TEAEs in the neoadjuvant phase were well balanced between the two study drugs without safety concerns. The majority were grade 1-2 in severity. Of the 3 patients who had grade 4 AEs, all receive EU-Herceptin:

- **Neutropenia:** patients (b) (6) (14 days after study drug initiation) and (b) (6) (18 days after study drug initiation)
- **Gastrointestinal toxicity and acute prerenal failure:** patient (b) (6) (see section 7.3.1)

Table 30 below lists a summary of treatment-related TEAEs by grade during the adjuvant phase.

Table 30: Treatment-Related TEAEs by Grade, Adjuvant Phase

Adverse Event Grade	ABP 980/ ABP 980 n=349 (%)	EU-Herceptin/ ABP 980 n=171 (%)	EU-Herceptin/ EU-Herceptin n=171 (%)
1	87 (24.9)	33 (9.5)	32 (9.2)
2	30 (8.6)	16 (4.6)	7 (2.0)
3	2 (0.6)	3 (0.9)	1 (0.3)
4	1 (0.3) ¹	0 (0.0)	0 (0.0)

Source dataset: Day 120 Update ADAE.xpt

¹ Patient (b) (6) had grade 4 neutropenia during the adjuvant phase, 180 days after study drug initiation. Her ANC nadir was 470 and she had a dose delay and the event was resolved 10 days after the nadir. She did not experience fevers.

Reviewer's Comment: The treatment-related TEAEs in the adjuvant phase were mostly grade 1-2. There were more treatment-related TEAEs in the ABP 980/ABP 980 arm compared to the other two, primarily due to neutropenia, leukopenia, anemia, and thrombocytopenia (total hematologic cases below):

- **ABP 980/ABP 980 = 35 (10.0%)**
- **EU-Herceptin/ABP 980 = 9 (5.3%)**
- **EU-Herceptin/EU-Herceptin = 9 (5.3%)**

Only one patient had grade 4 TEAE, which was neutropenia and resolved without concomitant fevers. These differences in grade 1-2 toxicity incidences are unlikely to have clinical significance.

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 no pregnancies reported in study 20120283. Cardiac toxicities, pulmonary toxicities, and infusion reactions are discussed below.

7.3.4.2.1 Cardiac Toxicity

Table 31 below lists the cardiac TEAEs during the neoadjuvant phase for study 20120283. The majority were grade 1-2 in severity and felt by the Investigator to be unlikely related to the study drug. No patient required dose modification or were discontinued from the study due to these AEs. Only one patient had a serious cardiac AE of cardio-respiratory arrest from which she fully recovered and occurred post-surgery (see Table 25 above for full narrative explanation).

Table 31: Cardiac Toxicities, Neoadjuvant Phase

Patient	Neoadjuvant Treatment	MedDRA Term	AE Grade
(b) (6)	ABP 980	Cardiac failure	1
	ABP 980	Cardiac failure	1
	ABP 980	Cardiac failure	1
	ABP 980	Cardiac failure chronic	2
	ABP 980	Cardiac failure chronic	2
	ABP 980	Cardiac failure chronic	1
	ABP 980	Cardio-respiratory arrest	4
	ABP 980	Cardiotoxicity	1
	ABP 980	Cardiotoxicity	1
	ABP 980	Left ventricular dysfunction	1
	EU-Herceptin	Cardiac failure congestive	1
	EU-Herceptin	Cardiomyopathy	1
	EU-Herceptin	Congestive cardiomyopathy	1
	EU-Herceptin	Diastolic dysfunction	1
	EU-Herceptin	Left ventricular hypertrophy	1

Source dataset: ADAE.xpt

¹ Only patient with serious cardiac TEAE. Refer to Table 25 above for discussion of her AE and outcome.

² Cardiac TEAEs felt possibly related to the study drug.

Reviewer's Comment: During the neoadjuvant phase, there were more patients in the ABP 980 arm who experienced cardiac TEAEs than in the EU-Herceptin arm (ABP 980 10 pts and 3.2% vs EU-Herceptin 5 pts and 1.6%). However, the overall incidence in both arms was low within the expected incidence level for the reference product US-Herceptin.

Table 32 below lists the cardiac TEAEs during the adjuvant phase for study 20120283 (not including data from the Day 120 Safety Update). The majority were grade 1-2 and none were identified as serious.

- Patient (b) (6): received EU-Herceptin/ABP 980 and experienced grade 3 ventricular hypokinesia felt possibly related to the study drug had the drug withdrawn and was discontinued from the trial. She was a 60F who started the neoadjuvant phase on (b) (6) and during cycle 4 of the adjuvant phase, she experienced grade 3 ventricular hypokinesia described as diffuse left ventricular hypokinesia. Her baseline EF was 59% on (b) (6). On (b) (6) her EF was 43%. On (b) (6) her EF was 33%. The patient was clinically asymptomatic. She was discontinued from the study and her current AE status is not resolved.
- Patient (b) (6): 49F randomized to EU-Herceptin/EU-Herceptin. She received her first dose of adjuvant treatment on (b) (6) and on (b) (6), she experienced grade 3 cardiomyopathy described as myocardiodystrophy. Her final dose of study drug had been administered (b) (6) and she completed all 10 adjuvant cycles. The cardiomyopathy was medically managed. Her EF at baseline was 63%, remained >60% throughout the study, and at the end of study on (b) (6), it was 42%. The patient completed the study.

Table 32: Cardiac Toxicities, Adjuvant Phase

MedDRA Term	ABP 980/ ABP 980 N=349 (%)	EU-Herceptin/ ABP 980 N=171 (%)	EU-Herceptin/ EU-Herceptin N=171 (%)
Atrial fibrillation	1 (0.3)	0 (0.0)	1 (0.3)
Atrial tachycardia	1 (0.3)	0 (0.0)	2 (0.6)
Cardiac failure	2 (0.6)	1 (0.3)	1 (0.3)
Cardiomegaly	1 (0.3)	0 (0.0)	0 (0.0)
Cardiomyopathy	0 (0.0)	0 (0.0)	1 (0.3)
Cardiotoxicity	0 (0.0)	0 (0.0)	1 (0.3)
Congestive cardiomyopathy	1 (0.3)	0 (0.0)	0 (0.0)
Diastolic dysfunction	0 (0.0)	0 (0.0)	2 (0.6)
Dilatation atrial	0 (0.0)	0 (0.0)	1 (0.3)
Dilatation ventricular	0 (0.0)	0 (0.0)	1 (0.3)
Electrocardiogram QT prolonged	0 (0.0)	0 (0.0)	1 (0.3)
Heart rate increased	1 (0.3)	0 (0.0)	0 (0.0)
Left atrial dilatation	2 (0.6)	0 (0.0)	0 (0.0)
Left ventricular dysfunction	2 (0.6)	0 (0.0)	1 (0.3)
Left ventricular hypertrophy	2 (0.6)	1 (0.3)	1 (0.3)
Mitral valve incompetence	5 (1.4)	1 (0.3)	2 (0.6)
Mitral valve prolapse	1 (0.3)	0 (0.0)	0 (0.0)
Myocardial ischaemia	1 (0.3)	0 (0.0)	0 (0.0)
Myocarditis	1 (0.3)	0 (0.0)	0 (0.0)
Palpitations	2 (0.6)	2 (0.6)	0 (0.0)
Systolic dysfunction	2 (0.6)	0 (0.0)	1 (0.3)
Tachycardia	1 (0.3)	2 (0.6)	1 (0.3)
Transaminases increased	1 (0.3)	0 (0.0)	0 (0.0)
Tricuspid valve incompetence	1 (0.3)	0 (0.0)	0 (0.0)
Ventricular extrasystoles	1 (0.3)	1 (0.3)	0 (0.0)
Ventricular hypokinesia	1 (0.3)	1 (0.3)	2 (0.6)

Source dataset: Day 120 Update ADAE.xpt

Reviewer's Comment: Adjuvant phase cardiac AEs were primarily grade 1-2 in severity. Four patients had grade 3 toxicities, all possibly related to the study drug:

- Patient (b) (6): EU-Herceptin/ABP 980, had grade 3 ventricular hypokinesia that was not serious but the study drug was stopped and the patient was discontinued from the study. The AE is not resolved. An IR was sent on 12/20/17 requesting an update on the AE status, but no additional information was available.

- **Patient (b) (6): EU-Herceptin/ABP 980, had ventricular extrasystoles that was serious, the patient continued on study and recovered from the AE.**
- **Patient (b) (6): EU-Herceptin/EU-Herceptin, had cardiomyopathy that was not serious. She completed the study. An IR was sent on 12/20/17 requesting an update on the AE status, but no additional information was available.**
- **Patient (b) (6): EU-Herceptin/ABP 980, had cardiac failure that was not serious, the patient completed the study. Her LVEF was 64% at screening, decreased to a low of 52% on study days 209 and 302, and was 53% at the end of study on study day 391, which was within the normal range.**

7.3.4.2.2 Pulmonary Toxicity and Infusion Reactions

Table 33 below lists the frequency of treatment-emergent pulmonary toxicities and infusion reactions during the neoadjuvant phase. These were infrequent overall and primarily grade 1-2 in severity. Except for the patients discussed below, for the majority of patients, AEs did not require changes in dose of the study drug, AEs did not result in study discontinuation, patients recovered from their AEs, AEs were not considered serious:

- Patient (b) (6) received ABP 980 and had grade 3 hypersensitivity considered serious. This patient was discussed in Table 18 above.
- Patient (b) (6) received ABP 980 and had grade 4 cardio-respiratory arrest considered serious. This patient was discussed above.
- Patient (b) (6) received EU-Herceptin and had grade 3 drug hypersensitivity the same day the study drug was initiated on day 1 of the study, felt likely related to paclitaxel and not the study drug. Ultimately the patient withdrew consent after the neoadjuvant phase and discontinued from the study.
- Patient (b) (6) received EU-Herceptin and had the study drug withdrawn and discontinued from the study due to grade 2 hypersensitivity, but this was felt to be related to paclitaxel and not the study drug.
- Patient (b) (6) received EU-Herceptin and initiated treatment on (b) (6). On (b) (6) during the neoadjuvant phase (C4D21) the patient had grade 1 pulmonary fibrosis, described as pneumosclerosis. This was felt to be unrelated to the study drug or paclitaxel and the patient went on to complete the adjuvant phase of the study.

Table 33: Pulmonary Toxicities and Infusion Reactions, Neoadjuvant Phase

MedDRA Term	ABP 980 N=364 (%)	EU-Herceptin N=361 (%)
Acute interstitial pneumonitis	1 (0.3)	0 (0.0)
Acute respiratory failure	0 (0.0)	1 (0.3)
Cardio-respiratory arrest	1 (0.3)	0 (0.0)
Drug hypersensitivity	3 (0.8)	3 (0.8)
Hypersensitivity	3 (0.8)	2 (0.6)
Infusion related reaction	8 (2.2)	2 (0.6)

Source dataset: ADAE.xpt

Reviewer's Comment: *There are no safety concerns noted for pulmonary toxicities and infusion reactions during the neoadjuvant phase.*

Table 34 below lists the frequency of treatment-emergent pulmonary toxicities and infusion reactions during the adjuvant phase.

Table 34: Pulmonary Toxicities and Infusion Reactions, Adjuvant Phase

MedDRA Term	ABP 980/ ABP 980 N=349 (%)	EU-Herceptin/ ABP 980 N=171 (%)	EU-Herceptin/ EU-Herceptin N=171 (%)
Adverse drug reaction	1 (0.3)	0 (0.0)	0 (0.0)
Infusion related reaction	10 (2.9)	1 (0.6)	1 (0.6)
Acute interstitial pneumonitis	1 (0.3)	0 (0.0)	0 (0.0)
Interstitial lung disease	0 (0.0)	0 (0.0)	1 (0.6)
Pneumonitis	1 (0.3)	0 (0.0)	0 (0.0)
Pulmonary fibrosis	1 (0.3)	1 (0.6)	0 (0.0)

Source dataset: Day 120 Update ADAE.xpt

Reviewer's Comment: *There were more infusion related reactions in the ABP 980/ABP 980 arm during the adjuvant phase, but these were all grade 1-2 and unlikely to have clinical significance. Only one patient (b) (6), who received EU-Herceptin/ABP 980, had a grade 4 toxicity of respiratory failure and was discussed in Table 24 above.*

7.4. Supportive Safety Results

7.4.1. Common Adverse Events

Common TEAEs during the neoadjuvant phase seen in $\geq 5\%$ of patients in any group are shown in Table 35 below.

Table 35: Common TEAEs (≥5% any group) in the Neoadjuvant Phase

MedDRA Term		ABP 980 N=364 (%)	EU-Herceptin N=361 (%)
Blood and lymphatic system disorders	Anaemia	40 (11.0)	37 (10.2)
	Leukopenia	21 (5.8)	16 (4.4)
	Neutropenia	53 (14.6)	45 (12.5)
Gastrointestinal disorders	Diarrhoea	23 (6.3)	19 (5.3)
	Nausea	21 (5.8)	18 (5.0)
General disorders and administration site conditions	Asthenia	54 (14.8)	59 (16.3)
	Fatigue	17 (4.7)	15 (4.2)
Investigations	Alanine aminotransferase increased	15 (4.1)	17 (4.7)
Musculoskeletal and connective tissue disorders	Arthralgia	63 (17.3)	55 (15.2)
	Bone pain	12 (3.3)	29 (8.0)
	Myalgia	32 (8.8)	31 (8.6)
	Pain in extremity	10 (2.7)	16 (4.4)
Nervous system disorders	Neuropathy peripheral	50 (13.7)	43 (11.9)
	Paraesthesia	17 (4.7)	21 (5.8)
	Peripheral sensory neuropathy	25 (6.9)	22 (6.1)
Respiratory, thoracic and mediastinal disorders	Epistaxis	17 (4.7)	5 (1.4)
Skin and subcutaneous tissue disorders	Alopecia	19 (5.2)	23 (6.4)
Vascular disorders	Hypertension	18 (4.9)	15 (4.2)

Source dataset: ADAE.xpt

Reviewer's Comment: TEAEs seen in ≥5% of patients in any treatment group were well balanced with no meaningful differences in the neoadjuvant phase.

Common TEAEs during the adjuvant phase seen in ≥5% of patients in any group are shown in Table 36 below.

Table 36: Common TEAEs (≥5% any group) in the Adjuvant Phase

MedDRA Term		ABP 980/ ABP 980 N=349 (%)	EU- Herceptin/ ABP 980 N=171 (%)	EU- Herceptin/ EU- Herceptin N=171 (%)
Blood and lymphatic system disorders	Anaemia	17 (4.9)	10 (2.9)	7 (2.0)
	Neutropenia	25 (7.2)	6 (1.7)	10 (2.9)
General disorders and administration site conditions	Asthenia	18 (5.2)	10 (2.9)	7 (2.0)
Injury, poisoning and procedural complications	Radiation skin injury	37 (10.6)	16 (4.6)	17 (4.9)
Musculoskeletal and connective tissue disorders	Arthralgia	20 (5.7)	9 (2.6)	9 (2.6)

Source dataset: Day 120 Update ADAE.xpt

Reviewer's Comment: *There were more neutropenia and radiation skin injury seen in the ABP 980/ABP 980 arm. These were primarily grade 1-2 in toxicity. The radiation skin injury is unlikely to be related to the study drug. One patient (b) (6) who received ABP 980/ABP 980 experienced two instances of neutropenia, one grade 3 and one grade 4, and recovered from both. Patient (b) (6) who received ABP 980/ABP 980 had two instances of grade 3 neutropenia from which she recovered. One other patient who received ABP 980/ABP 980 (patient (b) (6)) and one who received EU-Herceptin/ABP 980 (patient (b) (6)) also had grade 3 neutropenia and both recovered. Overall these differences are unlikely to be meaningful.*

7.4.2. Laboratory Findings

Trastuzumab is not known to cause significant laboratory abnormalities. The laboratory changes were reviewed from the original BLA submission CSR and the Day 120 Safety Update. Grade 3 and higher laboratory changes during the neoadjuvant and adjuvant phases of the safety population are shown below in Table 37 and Table 38 below.

Table 37: Safety Population Grade 3+ Laboratory Changes, Neoadjuvant Phase

Laboratory Parameter	ABP 980 (N = 364) n (%)	Trastuzumab (N = 361) n (%)
Hematology		
Leukocytes	4 (1.1)	2 (0.6)
Neutrophils	18 (4.9)	15 (4.2)
Lymphocytes (decreased)	16 (4.4)	20 (5.5)
Hemoglobin (decreased)	1 (0.3)	2 (0.6)
Serum Chemistry		
Sodium (hypernatremia)	1 (0.3)	3 (0.8)
Sodium (hyponatremia)	1 (0.3)	4 (1.1)
Potassium (hyperkalemia)	1 (0.3)	1 (0.3)
Potassium (hypokalemia)	1 (0.3)	1 (0.3)
Glucose (hypoglycemia)	0 (0.0)	1 (0.3)
Alkaline phosphatase	0 (0.0)	1 (0.3)
Aspartate aminotransferase	0 (0.0)	2 (0.6)
Alanine aminotransferase	2 (0.5)	3 (0.8)
Gamma-glutamyl transferase	8 (2.2)	10 (2.8)

Note: For each laboratory parameter, subjects were counted only once even if the subject had multiple grade ≥ 3 results for that parameter.

Source: Study 20120283 CSR Table 41

Table 38: Safety Population Grade 3+ Laboratory Changes, Adjuvant Phase

Laboratory Parameter	ABP 980/ ABP 980 (N = 349) n (%)	Trastuzumab/ Trastuzumab (N = 171) n (%)	Trastuzumab/ ABP 980 (N = 171) n (%)
Hematology			
Leukocytes	1 (0.3)	2 (1.2)	1 (0.6)
Neutrophils	4 (1.1)	0 (0.0)	3 (1.8)
Lymphocytes (decreased)	38 (10.9)	17 (9.9)	14 (8.2)
Lymphocytes (increased)	0 (0.0)	0 (0.0)	0 (0.0)
Hemoglobin (decreased)	1 (0.3)	0 (0.0)	1 (0.6)
Hemoglobin (increased)	0 (0.0)	0 (0.0)	0 (0.0)
Platelet	1 (0.3)	0 (0.0)	0 (0.0)
Serum Chemistry			
Sodium (hypernatremia)	3 (0.9)	0 (0.0)	1 (0.6)
Sodium (hyponatremia)	3 (0.9)	3 (1.8)	4 (2.3)
Potassium (hyperkalemia)	1 (0.3)	1 (0.6)	1 (0.6)
Potassium (hypokalemia)	3 (0.9)	2 (1.2)	0 (0.0)
Glucose (hypoglycemia)	1 (0.3)	0 (0.0)	0 (0.0)
Creatinine	0 (0.0)	0 (0.0)	0 (0.0)
Bilirubin	0 (0.0)	0 (0.0)	0 (0.0)
Albumin	0 (0.0)	0 (0.0)	0 (0.0)
Alkaline Phosphatase (ALP)	1 (0.3)	0 (0.0)	0 (0.0)
Aspartate Aminotransferase (AST)	1 (0.3)	0 (0.0)	1 (0.6)
Alanine Aminotransferase (ALT)	1 (0.3)	1 (0.6)	0 (0.0)
Gamma Glutamyl Transferase	3 (0.9)	2 (1.2)	3 (1.8)

Note: For each laboratory parameter, subjects were counted only once even if the subject had multiple grade ≥ 3 results for that parameter. Only subjects who received at least 1 dose of investigational product in the adjuvant phase were included in the population for this summary.

Source: Day 120 Update CSR, Table 29

Reviewer's Comment: Laboratory changes during the neoadjuvant and adjuvant phases were infrequent in both treatment groups with no safety concerns noted.

7.4.3. Vital Signs

Changes in vital signs for the safety population during the neoadjuvant phase and adjuvant phase were reviewed for heart rate, systolic blood pressure, and diastolic blood pressure were minimal in both treatment groups.

Reviewer's Comment: No safety concerns noted.

7.4.4. Electrocardiograms (ECGs)

Limited ECG data was collected for study 20120283. ECG data was collected at screening and during the study, ECG could be repeated for quality reasons or if the investigator felt it was indicated for safety reasons. There was no systematic collection of ECG after screening.

Reviewer's Comment: While there is little ECG data available for study 20120283, trastuzumab is not known to cause significant ECG changes and therefore, this is unlikely to impact the overall safety of ABP 980.

7.4.5. Special Safety Studies/Clinical Trials

No special safety studies were conducted.

7.4.6. Immunogenicity

Table 39 below lists the immunogenicity findings during the neoadjuvant phase of study 20120283. These were relatively few and no patient had neutralizing antibodies.

Table 39: Safety Population Immunogenicity During the Neoadjuvant Phase

Variable	ABP 980 (N = 364) n (%)	Trastuzumab (N = 361) n (%)
Subjects with an on-study result (N1) ^a	363	360
Total antibody incidence [n (%)] ^b		
Binding antibody positive anytime	2 (0.6)	5 (1.4)
Neutralizing antibody positive anytime	0 (0.0)	0 (0.0)
Subjects with a result at baseline (N2)	357	350
Pre-existing antibody incidence [n (%)] ^c		
Binding antibody positive at or before baseline	0 (0.0)	3 (0.9)
Neutralizing antibody positive at or before baseline	0 (0.0)	0 (0.0)
Subjects with a postbaseline result (N3)	355	351
Developing antibody incidence [n (%)] ^d		
Binding antibody positive postbaseline with a negative or no result at baseline	2 (0.6)	2 (0.6)
Transient ^e	2 (0.6)	0 (0.0)
Neutralizing antibody positive postbaseline with a negative or no result at baseline	0 (0.0)	0 (0.0)
Transient ^e	0 (0.0)	0 (0.0)

Note: Baseline was defined as the last non-missing assessment taken before the first dose of investigational product.

^a Subjects considered on-study after signing informed consent

^b Percentages were calculated as $n/N1 \times 100$.

^c Percentages were calculated as $n/N2 \times 100$.

^d Percentages were calculated as $n/N3 \times 100$.

^e Negative result at the subject's last timepoint tested within the study period.

Source: Study 20120283 CSR Table 42

Table 40 below lists the immunogenicity findings for the adjuvant phase.

Table 40: Safety Population Immunogenicity During the Adjuvant Phase

Preferred Term	ABP 980/ ABP 980 (N = 349)	Trastuzumab/ Trastuzumab (N = 171)	Trastuzumab/ ABP 980 (N = 171)
Subjects with an on-study result (N1)	349	171	171
Total antibody incidence [n (%)] ^a			
Binding antibody positive anytime	2 (0.6)	2 (1.2)	4 (2.3)
Neutralizing antibody positive anytime	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with a result before first IP dose in adjuvant phase (N2)	349	171	171
Pre-existing antibody incidence [n (%)] ^b			
Binding antibody positive before adjuvant phase	2 (0.6)	2 (1.2)	3 (1.8)
Neutralizing antibody positive before adjuvant phase	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with a result after first IP dose in adjuvant phase (N3)	345	170	167
Developing antibody incidence [n (%)] ^c			
Binding antibody positive during adjuvant phase with negative or no result before adjuvant phase	0 (0.0)	0 (0.0)	1 (0.6)
Transient ^d	0 (0.0)	0 (0.0)	1 (0.6)
Neutralizing antibody positive during adjuvant phase with negative or no result before adjuvant phase	0 (0.0)	0 (0.0)	0 (0.0)
Transient ^d	0 (0.0)	0 (0.0)	0 (0.0)

Note: Only subjects who received at least 1 dose of investigational product during the adjuvant phase are included in the population for this summary.

^a Percentages are calculated as n/N1* 100.

^b Percentages are calculated as n/N2* 100.

^c Percentages are calculated as n/N3* 100.

^d Negative result at the subject's last time point tested during adjuvant phase.

Source: Day 120 Update CSR Table 31

Reviewer's Comment: No patient had neutralizing antibody positivity. Overall no concerning immunogenicity findings. Please refer to Dr. Chih-Jung Hsu's review for BLA 761073 for further details.

7.5. Other Safety Explorations

None

7.6. Additional Safety Evaluations

7.6.1. Human Carcinogenicity

Table 41 below lists the treatment emergent neoplasms throughout the study.

Table 41: Treatment Emergent Neoplasms

MedDRA Term	ABP 980/ ABP 980 N=349 (%)	EU- Herceptin/ ABP 980 N=171 (%)	EU- Herceptin/ EU-Herceptin N=171 (%)
Breast cancer	0 (0.0)	1 (0.3)	0 (0.0)
Haemangioma of liver	0 (0.0)	1 (0.3)	0 (0.0)
Lipoma of breast	0 (0.0)	0 (0.0)	1 (0.3)
Metastases to adrenals	0 (0.0)	1 (0.3)	0 (0.0)
Metastases to bone	0 (0.0)	1 (0.3)	0 (0.0)
Metastases to central nervous system	3 (0.9)	0 (0.0)	1 (0.3)
Metastases to liver	0 (0.0)	1 (0.3)	0 (0.0)
Metastases to lung	0 (0.0)	1 (0.3)	0 (0.0)
Papilloma	1 (0.3)	0 (0.0)	0 (0.0)
Uterine leiomyoma	3 (0.9)	2 (0.6)	3 (0.9)
Xanthogranuloma	1 (0.3)	0 (0.0)	0 (0.0)

Source dataset: Day 120 Update ADAE.xpt

Reviewer's Comment: *Trastuzumab products are not known to cause secondary malignancies. Overall the incidence of neoplasms was low with no meaningful differences between the treatment arms.*

7.6.2. Human Reproduction and Pregnancy Data

There was no reported ABP 980 exposure in pregnant women in 20120283. There have been no reported embryo-fetal toxicities.

Reviewer's Comment: *No safety concerns noted.*

7.6.3. Pediatrics and Assessment of Effects on Growth

There were no ABP 980 exposure in pediatric patients in study 20120283.

Reviewer's Comment: *No safety concerns noted.*

7.6.4. Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no study drug overdoses in 20120283. The highest dose of study drug given was 8 mg/kg, which is the same as the loading dose.

Reviewer's Comment: *No safety concerns noted.*

7.7. Additional Submissions / Safety Issues

None

8. Postmarket Experience

ABP 980 is not marketed in any country. There is no postmarketing 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**
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- 10: Marty, et al., Journal of Clinical Oncology, 2005, 4265-4274**
- 11: Slamon, et al., New England Journal of Medicine, 2001, 365, 783-792**
- 12: Baselga, et al., New England Journal of Medicine, 2012, 366, 109-119**
- 13: Gianni, et al., Lancet, 2010, 375, 377-384**
- 14: Buzdar et al., 2007, Clinical Cancer Research, 2007, 13, 228-233**
- 15: Guidance for Industry: Pathological Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval, October 2014, <https://www.fda.gov/downloads/drugs/guidances/ucm305501.pdf>, Accessed May 21, 2018**

9.2. Labeling Recommendations

The following changes were made to the Kanjinti 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. “Kanjinti” refers to ABP 980
- 2. Highlights of Prescribing Information
 - a. Product name changed to “Kanjinti”
 - b. Full product title changed to “Kanjinti (trastuzumab-anns)”
 - c. Added description of biosimilar and biosimilarity of Kanjinti
- 3. Section 1 Indications and Usage
 - a. The following wording used *“Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.”*
- 4. Section 8 Use in Specific Populations
 - a. “Pregnancy Exposure Registry and Pharmacovigilance Program” section removed

9.3. Advisory Committee Meeting

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

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/s/

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