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RESEARCH**

APPLICATION NUMBER:

761073Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	<i>Electronic Stamp Date</i>
From	Jennifer Gao, MD (Acting CDTL, DOP1) Laleh Amiri-Kordestani, MD (Associate Director, DOP1)
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	BLA 761073
Applicant	Amgen
Date of Submission	July 28, 2017; resubmitted December 28, 2018
BsUFA Goal Date	June 28, 2019
Proprietary Name	ABP 980 (also referred to as Kanjinti by the applicant) ¹
Nonproprietary Name	trastuzumab-anns ¹
Dosage Form(s) and Strengths	For Injection: 420 mg lyophilized powder in a multiple-dose vial for reconstitution
Applicant Proposed Indication(s)/Population(s)	<p>Adjuvant Breast Cancer KANJINTI is indicated for adjuvant treatment of HER2-overexpressing node positive or node negative (ER/PR negative or with one high risk feature) breast cancer</p> <ul style="list-style-type: none"> • 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. <p>Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.</p> <p>Metastatic Breast Cancer KANJINTI is indicated:</p> <ul style="list-style-type: none"> • 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. <p>Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.</p> <p>Metastatic Gastric Cancer KANJINTI is indicated, 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.</p> <p>Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.</p>
Recommendation on Approval	<p>¹ For purposes of this review, the proposed product is referred to by the applicant's descriptor ABP 980, which was the name used to refer to this product during development. The proposed proprietary name (Kanjinti) and proposed nonproprietary name (trastuzumab-anns) are not to be used until the application is approved.</p>

Regulatory Action	
<p>Recommended Indication(s)/Population(s)</p>	<p>Adjuvant Breast Cancer KANJINTI is indicated for adjuvant treatment of HER2-overexpressing node positive or node negative (ER/PR negative or with one high risk feature) breast cancer</p> <ul style="list-style-type: none"> • 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. <p>Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.</p> <p>Metastatic Breast Cancer KANJINTI is indicated:</p> <ul style="list-style-type: none"> • 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. <p>Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.</p> <p>Metastatic Gastric Cancer KANJINTI is indicated, 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.</p> <p>Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.</p>

1. Background

On July 28, 2017, the applicant submitted biologics license application (BLA) 761073 under section 351(k) of the Public Health Service Act (PHS Act) for ABP 980, a proposed biosimilar to US-licensed Herceptin (trastuzumab; henceforth referred to as US-Herceptin)². At that time, the applicant sought licensure of ABP 980 for the same indications for which US-Herceptin has been previously approved, namely for adjuvant treatment of breast cancer, metastatic breast cancer, and metastatic gastric cancer. During the review of the initial submission for ABP 980, the FDA concluded that data supported a demonstration of biosimilarity, but issued a complete response (CR) letter to the applicant on May 25, 2018 on the basis of manufacturing facility deficiencies. At the FDA pre-license inspections (PLI) conducted (b) (4) the inspectors identified multiple deficiencies related to cGMP, including (b) (4)

On December 28, 2018, the applicant submitted responses to address deficiencies identified in the CR letter in their BLA (761073) Class 2 Resubmission. With the Class 2 Resubmission, the applicant no longer sought the licensure for the following indications: metastatic gastric cancer indication or single agent treatment of HER2+ breast cancer using the every 3 week dosing regimen.

However, on March 4, 2019, the applicant notified FDA that it was updating the indications for which it was seeking licensure to include all of the indications for which US-Herceptin was previously approved and submitted revised labeling. The applicant's updated requested indications are the same as those that have been previously approved for the reference product US-Herceptin:

Adjuvant breast cancer:

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:

² In this document, any reference to "US-Herceptin" is a 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".

- 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.

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.”

In the US, US-Herceptin is approved as a multi-dose vial containing 420 mg of lyophilized drug product and as a single-dose vial containing 150 mg of lyophilized drug product. In the EU, EU-Herceptin is marketed only as a single-dose vial containing 150 mg of lyophilized drug product. The applicant developed ABP 980 as a 420 mg lyophilized powder in a multiple-dose vial for reconstitution. The applicant is currently only seeking licensure of the 420 mg multiple-dose vial.

To support the demonstration that ABP 980 is highly similar to US-Herceptin, the applicant evaluated and compared ABP 980 to US-Herceptin using biochemical, biophysical, and functional assays, including assays that addressed each potential mechanism of action. 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 a demonstration that ABP-980 is highly similar to US-Herceptin. The analytical data supported the determination that ABP 980 is highly similar to US-Herceptin, notwithstanding minor differences in clinically inactive components. The sponsor also performed analytical comparisons of ABP 980, US-Herceptin and EU-Herceptin to establish the analytical portion of the scientific bridge to support the relevance of clinical data generated using EU-Herceptin as the comparator to the assessment of biosimilarity. The immunogenicity assays used to evaluate anti-drug antibodies in comparative immunogenicity study provided in support of this BLA are adequately validated.

The clinical pharmacology study 20130117 demonstrated similarity of PK among ABP 980, US-Herceptin, and EU-Herceptin, which established the PK portion of the scientific bridge and supported a demonstration of no clinically meaningful differences between ABP 980 and US-Herceptin. In addition, the results from the applicant’s comparative clinical study 20120283 supported a demonstration of no clinically meaningful differences between ABP 980 and US-

Herceptin. Together, the totality of the data thus supported the demonstration of biosimilarity of ABP 980 to US-Herceptin. The applicant also provided adequate scientific justification for extrapolation of data and information to support licensure of ABP 980 under Section 351(k) as a biosimilar for the conditions of use for which US-Herceptin has been previously approved and for which the applicant sought licensure. For additional details about the data and information in the applicant’s original submission used to support a demonstration that APB-980 is biosimilar to US-Herceptin, refer to the Dr. Amiri-Kordestani’s Cross-Discipline Team Leader Review filed in DARRTS on May 25, 2018.

2. Product Quality

Discipline		Reviewer	Team Leader
Stat-Product Quality (CMC)		Yu-Yi Hsu	Meiyu Shen
OBP	DP/DS	Lei Zhang	Patrick Lynch
Microbio Quality	Drug Product	Jessica Hankins	Reyes Candau-Chacon
	Drug Substance	Jessica Hankins	
OBP-Labeling		Vicky Borders-Hemphill	
Facilities		Wayne Seifert	Zhihao Qiu
RBPM		Andrew Shiber	

The product quality deficiencies described in the CR letter dated May 25, 2018 have been adequately addressed by the applicant in the resubmission. The Office of Pharmaceutical Quality (OPQ) recommends approval of STN 761073 for ABP 980 manufactured by Amgen, Inc. The data submitted in the application resubmission are adequate to support the conclusion that the manufacture of Kanjinti is well-controlled and leads to a product that is safe, pure and potent. The analytical similarity data submitted in the application, including the resubmission, demonstrate that ABP 980 is highly similar to US-Herceptin. A sufficient analytical component of the three-way scientific bridge was established to support the relevance of clinical data generated from studies with EU-Herceptin as a comparator to the demonstration of biosimilarity. Therefore, OPQ recommends that this product be approved for human use under conditions specified in the package insert.

Adequate descriptions of equipment, facilities, utilities, environmental controls, and cleaning and contamination control strategy were provided for ABP 980 DS manufacture at (b) (4) Immunex Rhode Island Corporation (FEI: 3003359885); and DP at Amgen Technology Ireland UC, (FEI: 3002808497). ABP 980 DP manufacture will be conducted within the Amgen Technology Ireland ADL-PM2 manufacturing suite. The final dosage form for the 420 mg multiple-dose vial consists of a 50 mL (b) (4) glass vial, with 20 mm (b) (4) stopper, and aluminum flip off dust cover. All proposed manufacturing and testing facilities are acceptable based on their current acceptable CGMP compliance status and recent relevant inspectional coverage. The facility reviewers recommend approval from a facility standpoint.

Key changes made by the applicant during this review cycle are included in the OPQ

Application Team Lead Review for BLA 761073 filed in Panorama on June 1, 2019.

3. Nonclinical Pharmacology/Toxicology

Refer to the CDTL review filed in DARRTS on May 25, 2018.

4. Clinical Pharmacology

Refer to the CDTL review filed in DARRTS on May 25, 2018.

5. Clinical Microbiology

Refer to the CDTL review filed in DARRTS on May 25, 2018.

6. Clinical/Statistical-Efficacy

Refer to the CDTL review filed in DARRTS on May 25, 2018.

7. Safety

Refer to the CDTL review filed in DARRTS on May 25, 2018 and the clinical review dated May 21, 2018 also filed in DARRTS. The resubmission included the Periodic Benefit-Risk Evaluation Report (PBRER)/Periodic Safety Update Report (PSUR) #1, covering the reporting period of May 16, 2018 to September 24, 2018. Overall, 585 patients have been exposed to ABP 980 since the beginning of the development program. No new safety signals have been identified by the applicant and no significant actions were taken for safety reasons.

8. Advisory Committee Meeting

An advisory committee meeting was not held for this application.

9. Pediatrics

The Agency has determined at this time that no pediatric studies will be required under the Pediatric Research Equity Act (PREA) for the applicant's BLA. Refer to memo filed in DARRTs on June 12, 2019.

10. Other Relevant Regulatory Issues

Refer to the CDTL review filed in DARRTS on May 25, 2018.

11. Labeling

Prescribing Information

The draft labeling submitted by the applicant to BLA 761073 on June 10, 2019 is adequate from a review perspective.

12. Recommendations

Recommended Regulatory Action

All deficiencies included in the May 25, 2018 CR letter have been adequately addressed by the applicant. 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 support a demonstration that there are no clinically meaningful differences between ABP 980 and US-Herceptin in terms of safety, purity and potency; therefore, we recommend approval of BLA 761073 for ABP 980 as a biosimilar to US-Herceptin for the following indications for which US-Herceptin is currently licensed and for which Amgen is seeking licensure:

Adjuvant Breast Cancer

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

- as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
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Metastatic Gastric Cancer

KANJINTI is indicated, 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.

Risk Evaluation and Management Strategies (REMS)

A REMS is not indicated.

Postmarketing Requirements (PMRs) and Commitments (PMCs)
Postmarketing requirements and commitments were not indicated.

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/

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06/12/2019 02:00:50 PM

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06/12/2019 02:06:20 PM