CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761074Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	*Electronic Stamp Date*
From	Laleh Amiri-Kordestani, M.D. (CDTL) Julia Beaver, M.D. (Division Director)
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	351(k) BLA 761074
Applicant	Mylan GmbH
Date of Submission	11/3/2016
BsUFA Goal Date	12/3/2017
Proprietary Name / Established (USAN) names	OGIVRI/Trastuzumab-dkst MYL-1401O Lyophilized Powder for Intravenous Infusion
Dosage forms / Strength	lyophilized powder for injection/420 mg per vial
Proposed Indication(s)	OGIVRI 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:	*Approval*

REVIEW TEAM

Clinical Reviewers: Suparna Wedam (efficacy), Jennifer Gao (safety)

Statistics: Lijun Zhang, Shenghui Tang (TL)

Pharm/Tox: Haw-Jyh Chiu and Todd Palmby (TL)

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Immunogenicity: Brian Janelsins and Rachel Novak (TL)

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Clinical Pharmacology: Brian Furmanski and Sarah Schrieber (TL)

CMC Statistics: Li Xing, Meiyu Shen, Yi Tsong (TL)

OBP Labeling: Vicky Borders-Hemphill

CDRH: Eunice Lee and Reena Philip

OSI: Lauren Iacono-Connor and Susan Thompson

OSIS: Hasan A. Irier, Makini K. Cobourne-Duval and Michael F. Skelly (TL)

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

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1. Introduction

On November 3, 2016, the Applicant submitted a biologics license application (BLA) under the 351(k) pathway of the Public Health Service Act for MYL-1401O, a proposed biosimilar to US licensed Herceptin (trastuzumab)[1]. The Applicant is seeking licensure of MYL-1401O 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

The analytical similarity program presented by the Applicant included the evaluation of the proposed biosimilar, MYL-1401O, US-licensed Herceptin, and EU-Herceptin. In the US, trastuzumab 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, trastuzumab is marketed only as a single-dose vial containing 150 mg of lyophilized drug product.

Based on the presentations approved in the US and EU at the time of development of MYL-1401O, the Applicant developed two MYL-1401O drug product presentations containing 420 mg and 150 mg of the lyophilized drug product. The Applicant is currently only seeking licensure of the 420 mg presentation. The Applicant provided analytical data to demonstrate comparability between the MYL-1401O 420 mg and 150 mg presentations to justify inclusion of both presentations in the analytical similarity assessment and to justify the relevance of

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

clinical data obtained using the MYL-1401O 150 mg presentation (for which the Applicant is not currently seeking licensure) to support a demonstration of biosimilarity and support licensure of the MYL-1401O 420 mg presentation.

The analytical similarity program consisted of two parts: 1) an analytical comparison between the proposed biosimilar and US-Herceptin to support the demonstration that the products are highly similar, and 2) analytical comparisons between MYL-1401O, US-Herceptin and EU-Herceptin to establish the analytical portion of the scientific bridge to justify the use of clinical and animal data generated using EU-Herceptin as the comparator.

The totality of analytical data support the determination that MYL-1401O is highly similar to US-Herceptin notwithstanding minor differences in clinically inactive components. In addition, the analytical portion of the scientific bridge between EU-Herceptin, US-Herceptin, and MYL-1401O was established, providing support for the use of nonclinical and clinical data generated with EU-Herceptin to support a demonstration of biosimilarity of MYL-1401O to US-Herceptin.

The pharmacokinetics and toxicity profile of MYL-1401O was compared head-to-head with EU-Herceptin via intravenous administration in cynomolgus monkeys. Overall, the animal studies provided in the BLA submission did not identify any safety concerns with MYL-1401O or differences in the PK or toxicity profile of MYL-1401O compared to EU-Herceptin in cynomolgus monkeys. The results of the animal studies demonstrated similarity in the safety and PK profiles of MYL-1401O to EU-Herceptin in cynomolgus monkeys and the Pharmacology and Toxicology discipline has not identified any residual uncertainties and has no outstanding issues.

The pharmacokinetic similarities of MYL-1401O, EU-Herceptin and US-Herceptin were evaluated in Study MYL-HER-1002. The results of this human pharmacokinetic similarity study support a demonstration of no clinically meaningful differences between MYL-1401O and US-Herceptin. The results of this study also established the pharmacokinetic component of the scientific bridge between EU-Herceptin, MYL-1401O, and US-Herceptin. Through analytical and pharmacokinetic data, the Applicant established an adequate scientific bridge between EU-Herceptin, MYL-1401O, and US-Herceptin to justify the relevance of clinical data generated using EU-Herceptin to support a demonstration of biosimilarity of MYL-1401O to US-Herceptin.

Anti-drug antibodies were measured in study MYL-Her-3001 comparing MYL-1401O to EU-Herceptin. The data indicate that there is no increase in immunogenicity risk for MYL-1401O when compared to EU-Herceptin, which supports the demonstration of no clinically meaningful differences to US-Herceptin.

The results of the clinical development program indicate that the Applicant's data support a determination of no clinically meaningful differences between MYL-1401O and US-Herceptin in terms of safety and efficacy in the indication studied (metastatic breast cancer). Specifically, the 90% confidence intervals for the overall response rate ratio between MYL-1401O and EU-Herceptin are within the equivalence margins. The safety analyses in MYL-Her-3001, which

compared MYL-1401O and EU-Herceptin in HER2 positive metastatic breast cancer patients, did not show any meaningful differences in safety between arms.

The Applicant provided adequate scientific justification for extrapolation of data to support licensure of the adjuvant breast cancer and metastatic gastric cancer indications.

In considering the totality of the evidence, the data submitted by the Applicant show that MYL-1401O 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 MYL-1401O and US-Herceptin in terms of safety, purity, and potency.

2. Background

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

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

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

The 'totality of the evidence' submitted by the Applicant should be considered when evaluating whether an Applicant has adequately demonstrated that a proposed product meets the statutory standard for biosimilarity to the reference product. Such evidence generally includes comparative structural and functional characterization, animal study data, human PK and, if applicable, pharmacodynamics (PD) data, clinical immunogenicity data, and other clinical safety and effectiveness data.

In general, an Applicant needs to provide information to demonstrate biosimilarity based on

data directly comparing the proposed biosimilar product with the US-licensed reference product. 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

- April 25, 2012
  During this Pre-IND 113682 Biosimilar meeting FDA advised Mylan that a phase 1 bridging study would be required to show bioequivalence between Bmab-200 and US-licensed Herceptin. FDA also provided advice regarding the design of a clinical trial.

- October 21, 2015
  During this Biosimilar Biological Product Development Type 2 meeting Mylan discussed with the Agency their pharmacokinetic data from the "Phase 1 bioequivalence trial," MYL-Her-1002, and the protocol and statistical analysis plan for the proposed trial, MYL-Her-3001.

- September 1, 2016
  During this Biological Product Development Type 2 and 4 meeting Mylan discussed with the Agency their clinical development program which consisted of 2 clinical studies in healthy subjects, 1 confirmatory efficacy and safety study in patients with metastatic breast cancer conducted globally, and 1 supportive PK, efficacy, and safety study in patients with breast cancer conducted in India with the Bmab-200 formulation and sought FDA advice regarding their 351(k) BLA submission plan.

3. CMC/Device

Source: CMC/Quality/Micro/Facilities Review Team (Kristen Nickens, Sarah Kennett, Brian Janelsins, Rachel Novak, Kathleen Clouse, Lakshmi Narasimhan, Maria Candauchacon, Patricia Hughes, Michael Shanks, Laura Fontan, Peter Qui and Vicky Borders-Hemphill) and ODAC briefing document

Final Product Quality Team Recommendation: Approval

General product quality considerations

MYL-1401O is a humanized recombinant IgG1 monoclonal antibody of the kappa isotype consisting of two identical heavy chains (HCs), which are glycosylated at asparagine (Asn) residue 300, and two identical light chains (LCs). The relative molecular mass of MYL-1401O is 1480 (b) (4) Da. MYL-1401O consists of 1328 amino acids, with LCs and HCs comprised of 214 and 450 amino acids, respectively.

MYL-1401O is produced using a mammalian cell line expanded in bioreactor cultures followed by a drug substance purification process that includes various steps designed to isolate and purify the protein product. Residual levels of process-related impurities (e.g., host cell proteins [HCP], host cell DNA [HCD], and those specific to the MYL-1401O manufacturing process) were evaluated as part of the MYL-1401O drug substance in-process and release testing. The data provided demonstrated that the MYL-1401O drug substance manufacturing process sufficiently reduces the impurities to very low levels (e.g., ppm for HCP and pg/ml for HCD).

The MYL-1401O drug product was developed as a multi-dose vial containing 420 mg of lyophilized powder, to reflect the same strength, dosage form and route of administration as US-Herceptin (420 mg).

The manufacturing process for MYL-1401O drug substance was scaled-up over the course of development, and comparability studies between the scales demonstrated consistency of the product. The drug product manufacturing process remained essentially the same. The drug product intended for commercial use was demonstrated to be analytically comparable to the drug product manufactured for clinical use, and combined data were included in the analytical similarity assessment.

OBP recommended one CMC post-marketing commitment:

- Perform a method validation study to confirm the suitability of the FcγRIIIa-V_{158} surface plasmon resonance (SPR) binding assay for use as a potency assay for drug substance and drug product lot release and stability testing. The final study results will be submitted to the BLA.

Microbiology reviews

Dr. Reyes Candau-Chacon (DS microbiology review) recommended approval of the BLA from a microbial control and microbiology product quality perspective.

Lakshmi Rani Narasimhan (DP microbiology review) recommended approval of the BLA from a sterility assurance and microbiology product quality perspective.

Facilities review/inspection

A pre-licensure inspection (PLI) of (b) (4) was conducted by Reyes Candau-Chacon (Lead Inspector), Lakshmi Narasimhan (DMA), Michael Shanks (DIA), Sarah Kennett (OBP), and Kristen Nickens (OBP). An eight-item Form FDA 483 was issued at the end of the inspection (b) (4)

(b) (4)

(b) (4) Following the response provided by the Applicant, the inspection outcome was VAI.

Following this PLI, a surveillance inspection was conducted by FDA Office of Regulatory Affairs (ORA) from (b) (4) The outcome was VAI, however to address the observations, multiple CAPAs were required, including (b) (4) The responses provided in November 2017, confirmed that corrective actions related to (b) (4) were complete and acceptable and that the BLA is recommended for approval from a facilities perspective.

Analytical similarity assessment

The analytical similarity assessment was performed to demonstrate that MYL-1401O and US-Herceptin are highly similar, notwithstanding minor differences in clinically inactive components, and to establish the analytical portion of the scientific bridge among MYL-1401O, US-Herceptin, and EU-Herceptin to justify the relevance of the comparative clinical and non-clinical data generated using EU-Herceptin. The similarity assessments were based on pairwise comparisons of the analytical data generated by the Applicant or their contract laboratory using several lots of each product. The FDA performed confirmatory statistical analyses of the data submitted, which included results from an assessment of up to 16 lots of MYL-1401O, 28 lots of US-Herceptin, and 38 lots of EU-Herceptin. All lots of each product were not included in every assessment; the number of lots analyzed in each assay was determined by the Applicant based on the availability of test material at the time of analysis, orthogonal analytical techniques, variability of the analytical method, method qualification, and use of a common internal reference material.

The analytical similarity tests included a comprehensive range of methods, which included orthogonal methods for the assessment of critical quality attributes. Several assays were designed to specifically assess the potential mechanisms of action of trastuzumab, including Fc-mediated functions. All methods were validated or qualified prior to the time of testing and were demonstrated to be suitable for the intended use.

The MYL-1401O drug product was evaluated and compared to US-Herceptin and EU-Herceptin using a battery of biochemical, biophysical, and functional assays, including assays that addressed each major potential mechanism of action. The analytical data submitted support the conclusion that MYL-1401O is highly similar to US-Herceptin. The amino acid sequences of MYL-1401O and US-Herceptin are identical. A comparison of the secondary and tertiary structures and the impurity profiles of MYL-1401O and US-Herceptin support the conclusion that the two products are highly similar. HER2 binding, inhibition of proliferation, and ADCC activity, which reflect the presumed primary mechanisms of action of US-Herceptin, were determined to be equivalent.

Some tests indicate that subtle shifts in glycosylation (sialic acid, high mannose, and NG-HC) exist and are likely an intrinsic property of the MYL-1401O product due to the manufacturing process. High mannose and sialic acid containing glycans can impact PK, while NG-HC is associated with loss of effector function through reduced FcγRIIIa binding and reduced ADCC activity. However, FcγRIIIa binding was similar among products and ADCC activity was equivalent among products. The differences related to the increases in total mannose forms and sialic acid and decreases in NG-HC were addressed by the ADCC assay results, supporting similar levels of ADCC activity between the products and by the PK similarity between MYL-1401O and US-Herceptin. Additional subtle differences in size and charge related variants were detected; however, these variants generally remain within the quality range criteria. Further, the data submitted by the Applicant support the conclusion that MYL-1401O and US-Herceptin can function through the same mechanisms of action for the indications for which Herceptin is currently approved, to the extent that the mechanisms of action are known or can reasonably be determined. Thus, based on the extensive comparison of the functional, physicochemical, protein and higher order structure attributes, MYL-1401O is highly similar to US-Herceptin, notwithstanding minor differences in clinically inactive components.

In addition, the three pairwise comparisons of MYL-1401O, US-Herceptin and EU-Herceptin establish the analytical component of the scientific bridge among the three products to justify the relevance of comparative data generated from clinical and non-clinical studies that used EU-Herceptin to support a demonstration of biosimilarity of MYL-1401O to US-Herceptin.

Reviewer Comment: I concur with CMC/OBP review team's conclusion that data support a demonstration of biosimilarity of MYL-1401O to US-Herceptin.
There were a substantial number of errors in the data and information presented in the original BLA submission. Where these errors impacted the review time of the application or the manufacturing and controls for future lots of MYL-1401O, Mylan was requested to make corrections to the BLA. A major amendment was needed for this application due to these issues.

CDRH

A CDRH consult was obtained to comment on the product label for BLA 761074, under sections 1.1, 1.2, and 1.3, regarding the statement for the companion diagnostic. Per CDRH reviewers (Drs. 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." In the revised label received on July 10, 2017, Mylan removed reference to a companion diagnostic. In response, the Applicant was informed that since a companion diagnostic was considered essential to the safe and effective use of Herceptin, a companion diagnostic is essential to the safe and effective use of Ogivri. The Applicant was requested to provide a rationale for why the approved companion diagnostics for trastuzumab could serve as companion diagnostics for Ogivri. The Applicant provided a response and reinserted the companion diagnostic wording to the drug label on July

19, 2017. CDRH reviewers concluded that Mylan's response explaining why it believes the approved companion diagnostics for trastuzumab could serve as companion diagnostics for Ogivri is adequate. Moreover, for purposes of the HER-2 tests approved as companion diagnostics for trastuzumab, CDRH believes that reference to trastuzumab in the device labeling includes not only Herceptin but also products determined to be biosimilar to Herceptin.

4. Nonclinical Pharmacology/Toxicology

Source: Pharmacology and Toxicology Review (Drs. Haw-Jyh Chiu and Todd Palmby)

Final Pharmacology/Toxicology Team Recommendations: Approval.

Two nonclinical animal studies were submitted in support of this BLA: (1) a single-dose comparative pharmacokinetic (PK) study in cynomolgus monkeys comparing MYL-1401O to EU-Herceptin and (2) a 4-week, repeat-dose toxicity and toxicokinetic study in cynomolgus monkeys comparing MYL-14010 to EU-Herceptin.

Overall, based on the nonclinical studies provided in this BLA submission, there was no evidence to indicate potential clinical safety concerns associated with MYL-1401O administration. There were no toxicity findings in animals treated with either MYL-1401O or EU-Herceptin. The toxicokinetic profile of MYL-1401O was comparable to that of EU-Herceptin.

In summary, the animal studies provided in the BLA submission did not identify differences in the PK or toxicity profile of MYL-1401O compared to EU-Herceptin in cynomolgus monkeys. Since the Applicant used a non-US-licensed comparator (EU-Herceptin) in nonclinical studies, the Applicant provided a bridge to demonstrate the similarity between EU-Herceptin and US-Herceptin. Results from comparative analytic data (refer to the CMC section of this document for details) provided the necessary bridge between MYL-1401O, EU-Herceptin and US-Herceptin to justify the relevance of the results of the animal studies conducted using EU-Herceptin to a demonstration of biosimilarity of MYL-1401O to US-Herceptin. From the perspective of the Pharmacology and Toxicology discipline, the results of these animal studies were adequate to demonstrate similarity in the safety and PK profiles of MYL-1401O to EU-Herceptin in cynomolgus monkeys. No residual uncertainties have been 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 MYL-1401O and EU-Herceptin in cynomolgus monkeys, and that the relevance of the results of animal studies with EU-Herceptin to the determination of biosimilarity of MYL-1401O to US-Herceptin was justified by an appropriate scientific bridge comprised of comparative analytic data for MYL-1401O, EU-Herceptin and US-Herceptin.

5. Clinical Pharmacology

Source: Clinical Pharmacology Review (Drs. Brian D. Furmanski, Sarah J. Schrieber and Nam Atiqur Rahman) and ODAC briefing document

Final Clinical Pharmacology Team Recommendations: Approval

The objectives of the clinical pharmacology program were to evaluate the pharmacokinetic (PK) similarity between MYL-1401O and US-Herceptin and to support the scientific bridge between MYL-1401O, US-Herceptin and EU- Herceptin. The Applicant submitted Study MYL-HER-1002 which evaluated the PK similarities of MYL-1401O, EU-Herceptin and US-Herceptin.

Evidence of PK similarity was demonstrated between MYL-1401O and US-licensed Herceptin, as well as the PK portion of the scientific bridge between MYL-1401O, US-licensed Herceptin, and EU-approved Herceptin. The 90% CI of the geometric mean ratio for each product pairwise comparison for the primary pre-specified PK endpoint of AUC0-inf fell within the pre-specified margin of 80 to 125%. Study MYL-HER-1002 was a single-dose, randomized, double-blind, 3-arm, parallel group study in 120 healthy male subjects designed to determine the PK similarity of MYL-1401O, US-Herceptin and EU-Herceptin following a single 8 mg/kg intravenous (IV) dose. The 90% confidence intervals (CI) for all three pairwise comparisons of $AUC_{0-\infty}$, $AUC_{0-t,}$ and C_{Max} were within the pre-specified limits of 80 – 125%. The results of the study established the PK similarity between MYL-1401O and the US-Herceptin and provide the PK element of the scientific bridge to justify the relevance of the comparative data generated using EU-Herceptin in Study MYL-HER-3001 to support a demonstration of biosimilarity to US-Herceptin. Overall, Study MYL-HER-1002 supports a demonstration of PK similarity between MYL-1401O and US-Herceptin, as well as the scientific bridge among MYL-1401O, US-Herceptin and EU-Herceptin.

Immunogenicity

The incidence of immunogenicity for MYL-1401O and EU-Herceptin was compared in a multiple-dose, parallel-arm study in 493 patients with metastatic breast cancer (MYL-HER-3001). 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, the data indicates that there is no increase in immunogenicity risk for MYL-1401O as compared to EU-Herceptin, which supports the demonstration that there are no clinically meaningful differences between MYL1401O and US-licensed Herceptin.

Reviewer Comment: I concur with clinical pharmacology team's conclusion that the submitted clinical pharmacology study adequately demonstrated similarity of PK among MYL-1401O, US-Herceptin and EU-Herceptin. The evidence of PK similarity supports a

demonstration of no clinically meaningful differences between MYL-1401O and US-Herceptin. Also, the PK similarity data establish the PK component of the scientific bridge to justify the relevance of the comparative clinical data generated using EU-Herceptin to support a demonstration of the biosimilarity of MYL-1401O to US-Herceptin. The immunogenicity data indicate that there is no increase in immunogenicity risk for MYL-1401O when compared to EU-Herceptin, which supports a demonstration of no clinically meaningful differences between MYL-1401O and US-Herceptin.

6. Clinical Microbiology

Not applicable.

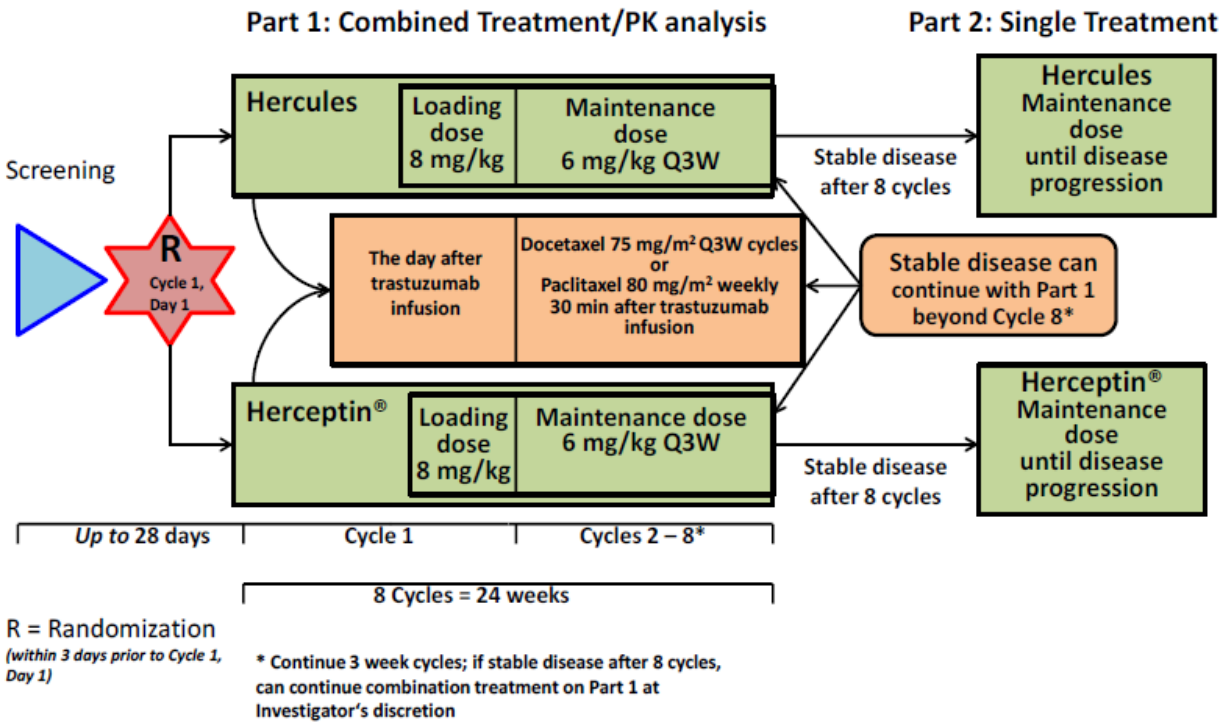
7. Clinical/Statistical- Efficacy

Source: Combined Clinical/Stat Review (Drs. Suparna Wedam, Jennifer Gao, Lijun Zhang and Shenghui Tang) and ODAC briefing document

Final Clinical/Statistical Team Recommendations: Approval

The Applicant submitted one comparative clinical study MYL-Her-3001 with a multicenter, randomized, double-blinded, parallel group design to assess the efficacy and safety of MYL-1401O compared to EU-Herceptin to support a demonstration of no clinically meaningful differences between MYL-1401O and US-Herceptin (see figure 1 below).

Figure 1. MYL-Her-3001 Study Schema



Source: Study protocol Figure 1

This was a two-part, multicenter, double-blind, randomized, parallel-group study. Untreated HER2-positive MBC patients were randomized 1:1 to either MYL-1401O or EU-Herceptin in combination with a taxane (paclitaxel or docetaxel). Patients were stratified by: time of tumor progression to metastatic disease from primary diagnosis (<2 years vs ≥ 2 years), ER/PR status (positive or negative), and type of taxane received (paclitaxel or docetaxel).

The primary endpoints for the comparative clinical study were:

- Part 1: To compare the independently assessed best overall response rate (ORR) at Week 24 with MYL-1401O plus taxane versus EU-Herceptin plus taxane in patients who have not received previous first-line treatment for HER2+ MBC.

- Part 2: To descriptively compare the safety, immunogenicity, and tolerability profile of single-agent MYL-1401O and EU-Herceptin and to compare the immunogenicity of MYL- 1401O and EU-Herceptin.

To provide at least 80% power to demonstrate equivalence between MYL-1401O and EU-Herceptin on the primary ORR analysis (ratio of ORR) with the pre-defined equivalence margin of (0.81, 1.24), a sample size of 410 patients (205 per treatment group) was required. Accounting for a 10% attrition rate, the sample size was increased to 456. This sample size calculation assumed that the ORR would be approximately 69% in both treatment arms and the ORR ratio of MYL-1401O to EU-Herceptin was to be analyzed with a two-sided 90% CI (i.e., alpha controlled ≤ 0.05).

The primary analysis of ORR was based on the ratio of ORRs per central review at Week 24 in the ITT1 population. The ORR in the MYL-1401O arm was 70% and 64% in the EU-Herceptin arm. The ORR ratio (MYL-1401O: EU-Herceptin) was 1.09 with a 90% CI of (0.98, 1.22), which was within the pre-defined equivalence region of (0.81, 1.24). The difference of ORR between the two arms was 6.0% (90% CI: -1.3%, 13.2%). At the Week 48 cut off, the median duration of response was 9.7 months for both treatment arms.

In summary, the 90% confidence interval for the ratio of ORR between MYL-1401O and EU-Herceptin in MYL-Her-3001 study is within the equivalence margins**.** Results from sensitivity analyses were consistent and agree with the primary analysis result.

Reviewer Comment: I concur with clinical team's conclusion that the submitted clinical study demonstrated no differences in terms of efficacy between MYL-1401O and EU-Herceptin. As the Applicant established an appropriate scientific bridge comprised of comparative PK and analytical data for MYL-1401O, EU-Herceptin and US-Herceptin (please see sections 3, 4 and 5), the efficacy results of Study MYL-Her-3001 support a demonstration of no clinically meaningful differences between MYL-1401O and US-Herceptin.

8. Safety

Source: Combined Clinical/Stat Review (Dr Jennifer Gao) and ODAC briefing document

The safety population in the randomized comparative clinical study MYL-Her-3001 consisted of all patients (n=493) who received at least one dose of study drug. The frequency of TEAEs, serious events, and events leading to discontinuation of study drug had no meaningful differences between the treatment arms. Major events of interest which are listed as Black Box Warnings in the prescribing information for US-Herceptin include cardiomyopathy, infusion reactions, pulmonary toxicity, and embryo-fetal toxicity. There were no reports of embryo-fetal toxicity in MYL-Her-3001. Most cardiac adverse events were grade 1-2 and most patients recovered in both groups. The safety results of MYL-Her-3001 showed no meaningful differences between MYL-1401O and EU-Herceptin.

Reviewer Comment: The comparative safety results obtained in Study HYL-Her-3001, for which EU-Herceptin was the comparator, support a demonstration of no clinically meaningful differences between MYL-1401O and US-Herceptin because the Applicant established an appropriate scientific bridge comprised of comparative PK and analytical data for MYL-1401O, EU-Herceptin and US-Herceptin. I concur with clinical team's conclusion that the submitted clinical study adequately supports a finding that there are no clinically meaningful differences in terms of safety between MYL-1401O and US-Herceptin.

9. Considerations for Extrapolation of Biosimilarity

Source: Combined Clinical/Stat Review (Drs. Suparna Wedam, Jennifer Gao) and ODAC briefing document

The Applicant seeks licensure for all indications for which US-Herceptin is licensed. However, the MYL-1401O clinical program, provides clinical efficacy and safety data from a clinical program in patients with MBC.

The Applicant has submitted the following scientific justifications for extrapolation of data to support a demonstration of biosimilarity in the other indications for which the Applicant is seeking licensure:

- The mechanism of action (MOA) of trastuzumab on human tumor cells that overexpress HER2 includes inhibition of proliferation and antibody-dependent cellular cytotoxicity. This MOA is independent of the disease setting.
- Demonstration that MYL-1401O is highly similar to US-Herceptin based on extensive analytical characterization data.
- Similar pharmacokinetics was demonstrated between MYL-1401O and US-Herceptin in healthy subjects. A similar PK profile would be expected between MYL-1401O and US-Herceptin across the other indications for use.
- In MYL-Her-3001, the frequency of anti-drug antibody formation was low and there were no notable differences between MYL-1401O and EU-Herceptin. A sufficient scientific bridge was established to justify the use of clinical data generated with EU-Herceptin to support a demonstration of biosimilarity of MYL-1401O to US-Herceptin. Accordingly, similar immunogenicity would be expected between MYL-1401O and US-Herceptin in other indications of use.
- Similar clinical safety and efficacy profile was demonstrated between MYL-1401O and EU-Herceptin in HER2 positive metastatic breast cancer patients. A sufficient scientific bridge was established to justify the use of clinical data generated with EU-Herceptin to support a demonstration of biosimilarity of MYL-1401O to US-Herceptin. Accordingly, similar safety and efficacy would be expected between MYL-1401O and US-Herceptin. As analytical and PK similarity was demonstrated between MYL-1401O and US-Herceptin, a similar safety and efficacy profile would be expected in other indications for use.

As described in the Guidance for Industry: "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009", if a biological product meets the statutory requirements for licensure as a biosimilar product under section 351(k) of the PHS Act based on, among other things, data derived from a clinical study or studies sufficient to demonstrate safety, purity, and potency in an appropriate condition of use, the potential exists for that product to be licensed for one or more additional conditions of use for which the reference product is licensed.

Reviewer Comment: I concur with clinical team's conclusion that the evidence indicates that the extrapolation of data, including clinical data, to support licensure for the non-studied indications for which the Applicant is seeking licensure is scientifically justified.

10. Advisory Committee Meeting

This application was discussed during the afternoon session of ODAC meeting on July 13, 2017. The committee discussed the totality of evidence for analytical similarity, clinical similarity, and extrapolation to support licensure for all proposed indications (HER2-positive breast cancer in the adjuvant and metastatic settings and metastatic HER2-positive gastric cancer). The committee members agreed that the evidence supports a demonstration that MYL-1401O is highly similar to Herceptin, notwithstanding minor differences in clinically inactive components, and that the evidence supports a demonstration that there are no clinically meaningful differences between MYL-1401O and Herceptin in the studied condition of use. Ultimately, the committee voted unanimously (16-0) YES to the voting question "Does the totality of the evidence support licensure of MYL-1401O as a biosimilar product to US-Herceptin for the following indications for which US-Herceptin is licensed and for which the Applicant is eligible for licensure (HER2-positive breast cancer in the metastatic and adjuvant settings)?" (At the time of the ODAC meeting on July 13, 2017, Herceptin's gastric cancer indication was protected by orphan drug exclusivity, expiring on October 20, 2017. The voting question was limited to licensure of MYL-1401O for the adjuvant and metastatic breast cancer indications.)

11. Pediatrics

Mylan 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 July12th, 2017 and concurred with the plan for a full waiver. The minutes were entered to DARRTS on August 10th, 2017.

12. Other Relevant Regulatory Issues

Application Integrity Policy (AIP)
The application contained statements from Mylan and Biocon 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

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 MYL-Her-1001, MYL-Her-1002 and MYL-Her-3001. The Applicant has stated that none of the clinical investigators involved with the MYL-1401O studies have financial interests or arrangements to disclose as defined in 21 CFR 54.2(f).

Bioequivalence Inspections

Hasan A. Irier and Michael F. Skelly (TL) from the Office of Study Integrity and Surveillance (OSIS) conducted an inspection of bioanalytical portions of the clinical studies conducted by (b) (4) At the closing of inspection, no Form FDA 483 was issued at the site (there were no direct regulatory violations or instances of inaccurate reporting in these method validations and studies).

A memo from Makini K. Cobourne-Duval from OSIS reported that an inspection of the clinical portion of the study for BLA 761074 was conducted at WCCT Global LLC, Cypress, CA by ORA investigator, Yvonne T. LaCour during March 2017. Based on the information in the EIR, the OSIS reviewer recommended accepting the clinical portion of study MYL-HER 1002 (BLA 761074) for further Agency (FDA) review.

Clinical Inspections

Lauren Iacono-Connors, Susan Thompson (Team Leader) and Kassa Ayalew (Branch Chief) from OSI completed the clinical inspection summary (CIS) on June 2, 2017. FDA selected three clinical sites, and a CRO for audit. There were no significant inspectional findings for these 3 clinical investigators and CRO. OSI review concluded that the data from Study MYL-Her 3001 submitted to the Agency in support of BLA 761074, appear reliable based on available information.

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 December 9, 2016, that concluded that the proposed proprietary name, Ogivri, was acceptable.

Tingting Gao and Chi-Ming (Alice) Tu from OMEPRM completed a review (dated June 30, 2017) that determined that the suffix dkst for the non-proprietary name is acceptable (trastuzumab-dkst).

Tingting Gao and Chi-Ming (Alice) Tu completed a review dated August 4, 2017, that defined recommendations relating to carton and container and product labeling. Majority of the recommendations were incorporated in revised product labeling.

Pediatric and Maternal Health

The division of Pediatric and Maternal Health (DPMH) was consulted to determine whether Ogivri labeling should have similar labeling to Herceptin related to a pregnancy exposure registry and pregnancy pharmacovigilance program. Dr. Miriam Dinatale (DPMH reviewer) stated that because the risks of oligohydramnios have been adequately characterized in the Herceptin labeling, DPMH has determined that the Herceptin pregnancy registry and pregnancy pharmacovigilance program are no longer necessary for Herceptin and are therefore not necessary for Ogivri.

13. Labeling

Proposed labeling submitted by Mylan 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 MYL-1401O -specific information as well as to comply with current labeling practices.

14. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

The Applicant is seeking licensure for indications that are the same as those licensed for US-Herceptin. The Applicant is seeking licensure for the indication studied in its clinical program – metastatic breast cancer – as well as for the adjuvant breast cancer and metastatic gastric cancer indications, which have not been directly studied in the MYL-1401O clinical program. The data submitted to the BLA from the clinical development program of MYL-1401O support a demonstration of no clinically meaningful differences between MYL-1401O and US-licensed Herceptin. In addition, the Applicant provided adequate scientific justification for extrapolation of data to support licensure of the adjuvant breast cancer and metastatic gastric cancer indications. The Applicant demonstrated that MYL-1401O is highly similar to US-Herceptin based on extensive analytical data and that MYL-1401O has no clinically meaningful differences from US-Herceptin based on similar pharmacokinetics effects, immunogenicity, efficacy, and safety. The Applicant provided justification to support extrapolating all the data in the application to support licensure of other indications (adjuvant breast cancer and metastatic gastric cancer).
I recommend approval of the 351(k) BLA 761074 for MYL-1401O to receive licensure as a biosimilar product to Herceptin for each of the following indications for which Herceptin is currently licensed and for which Mylan is seeking licensure:

Adjuvant Breast Cancer

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

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

Metastatic Breast Cancer

Ogivri is indicated:

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

Metastatic Gastric Cancer

Ogivri 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.

Risk Benefit Assessment

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 must be met to establish biosimilarity, but the foundation of the data demonstrating biosimilarity is extensive structural and functional characterization to support a demonstration that the products are highly similar.

The data submitted to the 351(k) BLA support a demonstration of biosimilarity for MYL-1401O. A demonstration that MYL-1401O is highly similar to US-licensed 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 MYL-1401O as a biosimilar to US-licensed Herceptin under section 351(k) of the PHS Act. Because MYL-1401O is biosimilar to Herceptin, MYL-1401O is considered to have a favorable risk-benefit profile for all requested conditions of use.

Recommendation for Postmarketing Risk Evaluation and Management Strategies

None.

Recommendation for other Postmarketing Requirements and Commitments

I concur with the post-marketing commitment described in Section 3 of this review.

Recommended Comments to Applicant

None.

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/s/

LALEH AMIRI KORDESTANI
11/30/2017

JULIA A BEAVER
12/01/2017