FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Oncologic Drugs Advisory Committee (ODAC) Meeting
FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503)
10903 New Hampshire Avenue, Silver Spring, Maryland
July 13, 2017

QUESTIONS

BLA 761074

"MYL-1401O", a proposed biosimilar to Herceptin (trastuzumab)

Applicant: Mylan GmbH

PROPOSED INDICATIONS:

1. Adjuvant breast cancer:

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

2. Metastatic breast cancer (MBC):

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

3. Metastatic gastric cancer:

    a. In combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease[1]

[1]Herceptin's indication for treatment in combination with cisplatin and capecitabine or 5-fluorouracil in patients with HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease, is protected by orphan drug exclusivity expiring on October 20, 2017. See the Orphan Drug Designations and Approvals database at http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm

QUESTIONS (cont.)

The Applicant (Mylan) has submitted a biologics license application (BLA) under section 351(k) of the Public Health Service Act (PHS Act) for MYL-1401O[2], a proposed biosimilar to US-Herceptin (trastuzumab). Genentech's BLA #103792 for Herceptin was initially licensed by FDA on September 25, 1998.

The Applicant is seeking licensure of MYL-1401O for the same indications as US-Herceptin (hereafter referred to as US-Herceptin).

Background. 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." A 351(k) application must contain, among other things, information demonstrating that the proposed product is biosimilar to a reference product based upon data derived from analytical studies, animal studies, and a clinical study or studies, unless FDA determines, in its discretion, that certain studies are unnecessary in a 351(k) application (see section 351(k)(2) of the PHS Act).

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 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 stand-alone 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.

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

[2]In this document, FDA generally refers to the Applicant's proposed product by the Applicant descriptor "MYL-1401O". FDA has not yet designated a nonproprietary name for the Applicant's proposed biosimilar product that includes a distinguishing suffix (see Guidance for Industry, *Nonproprietary Naming of Biological Products*).

QUESTIONS (cont.)

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 sufficient 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 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 results of the analytical similarity comparison show that for the critical functional assays [binding to human epidermal growth factor receptor 2 (HER2), inhibition of target cell proliferation, and antibody-dependent cellular cytotoxicity (ADCC) activity] MYL-1401O, US-Herceptin, and EU-Herceptin met the pre-defined statistical criteria for analytical similarity. These results support that MYL-1401O and US-Herceptin are highly similar. Minor differences observed in other quality attributes do not preclude a demonstration that MYL-1401O is highly similar to US-Herceptin, as the differences were determined not to have clinical impact. Therefore, the data presented supported both a demonstration that US-Herceptin and MYL-1401O are highly similar and the analytical portion of the scientific bridge between MYL-1401O, US-Herceptin and EU-Herceptin.

Pharmacology/Toxicology. 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.

QUESTIONS (cont.)

Clinical Pharmacology. The Applicant submitted Study MYL-HER-1002 which evaluated the pharmacokinetic (PK) similarities of MYL-1401O, EU-Herceptin and 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 between MYL-1401O, US-Herceptin and EU-Herceptin. The submitted clinical pharmacology study adequately demonstrated similarity of PK among MYL-1401O, US-Herceptin and EU-Herceptin. Study MYL-HER-1002 conducted in healthy subjects, using an IV administration route is considered sufficiently sensitive to detect clinically significant differences in PK among the products.

Immunogenicity. The incidence of immunogenicity for MYL-1401O and EU-Herceptin was compared in a multiple-dose, parallel-arm study in 493 patients with 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 pharmacokinetic endpoints was observed. A scientific bridge was established between MYL-1401O, EU-Herceptin and US-Herceptin, supporting the relevance of comparative data, including immunogenicity data, generated using EU-Herceptin to support a demonstration of no clinically meaningful differences between MYL-1401O and US-Herceptin. Similar immunogenicity results were observed in Study MYL-HER-3001 for MYL-1401O and EU-Herceptin. The data support a determination of no clinically meaningful differences in immunogenicity risk between MYL-1401O and US-Herceptin.

Efficacy and Safety. The Applicant submitted analytical and PK data to support a scientific bridge between MYL-1401O, EU-Herceptin, and US-Herceptin. 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. The FDA review of the data from this study supports the Applicant's conclusion that there are no clinically meaningful differences in terms of efficacy and safety between MYL-1401O and US-Herceptin.

Efficacy: 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.

Safety: The safety results of MYL-Her-3001 showed no meaningful differences between MYL-1401O and EU-Herceptin. The majority of cardiac adverse events were grade 1-2 and the majority of patients recovered in both groups.

Extrapolation. The Applicant seeks licensure for all indications for which US-Herceptin is licensed (listed in the Introduction section above). The MYL-1401O clinical program, however, provides clinical efficacy and safety data from a clinical program in patients with MBC. The evidence indicates that the extrapolation of biosimilarity to the indications for which the Applicant is seeking licensure is scientifically justified.

QUESTIONS (cont.)

QUESTIONS:

1. **DISCUSSION:** Please discuss whether the evidence supports a demonstration that "MYL-1401O" is highly similar to US-Herceptin, notwithstanding minor differences in clinically inactive components.

2. **DISCUSSION:** Please discuss whether the evidence supports a demonstration that there are no clinically meaningful differences between "MYL-1401O" and US-Herceptin in the studied condition of use.

3. **DISCUSSION:** Please discuss whether there is adequate scientific justification to support licensure for all of the proposed indications[3].

4. **VOTE:** 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)?

   Please explain the reasons for your vote.

[3]Herceptin's indication for treatment in combination with cisplatin and capecitabine or 5-fluorouracil in patients with HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease, is protected by orphan drug exclusivity expiring on October 20, 2017.