FDA Briefing Document

Oncologic Drugs Advisory Committee Meeting

July 13, 2017

BLA 761074

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

Applicant: Mylan Pharmaceuticals

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We bring the 351(k) BLA for MYL-1401O with the Applicant's proposed indications to this Advisory Committee to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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1. INTRODUCTION

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[1], 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):

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[2]

The purpose of the Oncologic Drugs Advisory Committee meeting is to discuss whether the totality of evidence presented support licensure of "MYL-1401O" as a biosimilar to US-Herceptin. This determination requires the following criteria to be met:

- "MYL-1401O" is highly similar to US-Herceptin, notwithstanding minor differences in clinically inactive components, and

[1] 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*).

[2] 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.

- There are no clinically meaningful differences between "MYL-1401O" and US-Herceptin.

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 and effectiveness of the reference product, and enables a biosimilar biological product to be licensed based on less than a full complement of product-specific preclinical and clinical data.

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.

To support a demonstration of biosimilarity, FDA recommends that applicants use a stepwise approach to developing the data and information needed. At each step, the applicant should evaluate the extent to which there is residual uncertainty about the biosimilarity of the proposed product to the reference product and identify next steps to try to address that uncertainty. The underlying presumption of an abbreviated development program is that a molecule that is shown to be analytically and functionally highly similar to a reference product is anticipated to behave like the reference product in the clinical setting(s). The stepwise approach should start with extensive structural and functional characterization of both the proposed biosimilar product and the reference product, as this analytical characterization

serves as the foundation of a biosimilar development program. Based on these results, an assessment can be made regarding the analytical similarity of the proposed biosimilar product to the reference product and the amount of residual uncertainty remaining with respect to both the structural/functional evaluation and the potential for clinically meaningful differences. Additional data, such as nonclinical and/or clinical data, can be tailored to address residual uncertainty(ies).

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

2.1. **The Reference Product**

The BPCI Act defines the "reference product" as the single biological product licensed under section 351(a) of the PHS Act against which a proposed biosimilar product is evaluated in a 351(k) application. In general, an applicant needs to provide information to demonstrate biosimilarity based on data directly comparing the proposed product with the reference product, in this case, US-Herceptin. 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.

As a scientific matter, the type of bridging data needed will always include data from analytical studies (e.g., structural and functional data) that directly compare all three products (i.e., the proposed biosimilar product, the reference product, and the non-US-licensed comparator product) and is likely to also include bridging clinical PK or PD study data for all three products.

3. DRAFT POINTS TO CONSIDER

1. Discussion Point 1: 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 Point 2: 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 Point 3: Please discuss whether there is adequate scientific justification to support licensure for all of the proposed indications.[3]

Voting Point 1:
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)?

4. CMC

Executive Summary

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.

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

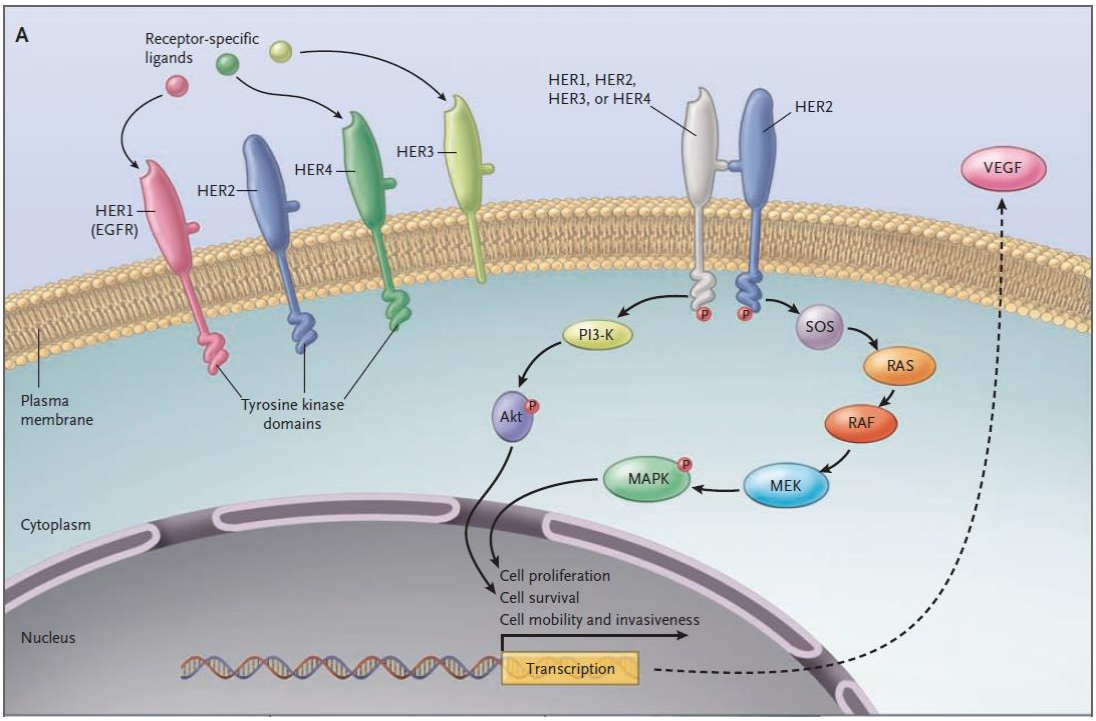
[3] Herceptin's indication for treatment in combination with cisplatin and capecitabine or 5-fluorouracil in patients with HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease, is protected by orphan drug exclusivity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

[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.

Pathophysiology of HER2 and Mechanism of Action of Trastuzumab

The HERs are a family of transmembrane tyrosine kinases that consists of the following known isoforms: HER1, HER2, HER3, and HER4 (also known as epidermal growth factor receptors ErbB-1, ErbB-2, ErbB-3, and ErbB-4). The receptors are composed of an extracellular binding domain, a lipophilic transmembrane domain, and an intracellular tyrosine kinase domain (with the exception of HER3). The HER family is known to regulate cell survival responses including, but not limited to, cell proliferation, adhesion, and differentiation. The activity of the HER family receptors is typically initiated by ligand binding, followed by homodimerization or heterodimerization, phosphorylation of tyrosine kinase residues, and downstream signal transduction; however, activation can also result from receptor mutation or overexpression. Of the four family members, the HER2 isoform is the preferred dimerization partner; however, it has no known ligand and can undergo ligand-independent dimerization and activation. Cleavage of the HER2 extracellular domain (shedding) results in a constitutively active phosphorylated signaling remnant (p95). Receptor dimerization leads to tyrosine kinase phosphorylation followed by activation of the PI3K/AKT survival pathway and the RAS/RAF/MEK/MAPK pathway. HER2 messenger RNA or protein overexpression and/or gene amplification occurs in over 20% of breast cancer and in gastric cancer, leading to the use of anti-HER2 therapy for these indications.

Figure 1. HER Activation



Source: Hudis 2007[4]

Trastuzumab is a humanized $IgG_1\kappa$ monoclonal antibody directed against an epitope on the extracellular juxtamembrane domain of HER2. Multiple mechanisms of action have been proposed for trastuzumab, including inhibition of HER2 receptor dimerization, increased destruction of the endocytic portion of the HER2 receptor, inhibition of extracellular domain shedding, and activation of cell-mediated immune defenses such as ADCC activity. Trastuzumab has not been shown to inhibit the dimerization of HER2 with the other isoforms; therefore, signaling through the other three receptor isoforms is maintained in the presence of the antibody. Studies have supported a mechanism by which trastuzumab is bound to the HER2 receptor and taken up by the target cell through endocytosis and subsequently degrades the receptor leading to a downregulation of downstream survival signaling, cell cycle arrest and apoptosis.[5] 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,[6] 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.[7] In addition, the initiation of ADCC activity plays a role in the mechanism of action of trastuzumab; it appears

[4] Hudis, C. New England Journal of Medicine, 2007, 357, 39-51.
[5] Nahta R, Esteva FJ. Oncogene, 2007, 26, 3637-3643.
[6] Pupa S, et. al., Oncogene, 1993, 8, 2917-2923.
[7] Hayes D, et. al., Clinical Cancer Research, 2001, 7, 2701-2711.

that natural killer (NK) cells are important mediators of ADCC activity in the context of trastuzumab-treated breast cancer.[8] Receptor-ligand binding between trastuzumab and HER2 lead to the recruitment of immune cells (e.g., NK cells, macrophages, neutrophils) that express FcγRIIIa or certain other Fc receptors. The effector cell Fc receptor binds to the Fc region of the antibody, triggering release of cytokines and recruitment of more immune cells. These immune cells release proteases that effectively lyse the HER2 expressing target cell, resulting in cell death. Trastuzumab has also been demonstrated to inhibit angiogenesis and proliferation by reducing the expression of pro-angiogenic proteins, such as vascular endothelial growth factor (VEGF) and the transforming growth factor beta (TGF-β) in a mouse model.[9]

MYL-1401O Manufacturing

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, presentation 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.

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

[8] Arnould L, et. al., British Journal of Cancer, 2006, 94, 2559-267.
[9] Wen X, et. al., Oncogene, 2006, 25, 6986-6996.

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 expiration dates of the US-Herceptin and EU-Herceptin lots included in the similarity assessment spanned approximately 6 years (2013 to 2019), and the MYL-1401O lots used for analysis were manufactured between 2011 and 2015.

The analytical similarity exercise included a comprehensive range of methods (listed in Table 1), which included orthogonal methods for the assessment of critical quality attributes. A number of 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.

Table 1. Quality Attributes and Methods Used to Evaluate the Analytical Similarity of MYL-1401O, US-Herceptin and EU-Herceptin

Quality Attribute	Methods
Primary structure	• Peptide mass fingerprinting by liquid chromatography (LC) with electrospray (ESI) mass spectrometry (MS) detection • Intact molecular mass (LC-ESI-MS) • Reduced molecular mass (LC-ESI-MS)
Protein content	• Concentration [ultraviolet (UV) spectroscopy at 280 nm]
Higher order structure	• Near and far UV circular dichroism (CD) • Fourier transform infrared spectroscopy (FTIR) • Intrinsic fluorescence (IF) • LC-ESI-MS (disulfide bond characterization) • Differential scanning calorimetry (DSC) • Ellman's reagent (free cysteines)
Size Variants/Aggregates	• Size exclusion high performance liquid chromatography (SEC-HPLC) with UV detection • SEC with multi-angle light scattering (MALS) • Analytical ultracentrifugation sedimentation velocity (AUC) • Capillary Electrophoresis-Sodium Dodecyl Sulfate (CE-SDS, Reduced and Non-Reduced)
Charge and Hydrophobic variants	• Capillary isoelectric focusing (cIEF) • Cation exchange HPLC (CEX-HPLC) • Hydrophobic interaction chromatography (HIC-HPLC) • LC-ESI-MS (oxidation)
Glycosylation	• Normal phase (NP)-HPLC (glycan mapping) • Reverse phase (RP)-HPLC (afucosylation and sialic acid) • CE-SDS reduced (Non-glycosylated heavy chain) • Boronate affinity chromatography (glycation)
Potency	• HER2 binding assay by flow cytometry • Inhibition of proliferation bioassay • Antibody-dependent cellular cytotoxicity (ADCC) bioassay (PBMC as effector cells)
Fc-receptor binding and function	• FcγRIIIa V type binding affinity (Biacore) • FcγRIIIb binding affinity (Biacore) • FcγRIIa binding affinity (Biacore) • FcγRIIb binding affinity (Biacore) • FcγRIa binding affinity (Biacore) • FcRn binding affinity (Biacore) • Cellular dependent cytotoxicity (CDC) bioassay • C1q binding assay (ELISA)

Primary Structure

To support a demonstration that MYL-1401O is highly similar to US-Herceptin, it is expected that the expression construct for the proposed biosimilar product encodes the same primary amino acid sequence as US-Herceptin. To achieve this goal, expression constructs were designed to encode a protein sequence that matches US-Herceptin. This can be confirmed at the protein level by methods including a variety of MS approaches, as described below.

Peptide mapping

The primary structure assessments of MYL-1401O, US-Herceptin, and EU-Herceptin performed by peptide mapping with two different enzymes, demonstrated that the chromatographic profile (peptide map) and primary amino acid sequence of MYL-1401O match those of US-Herceptin and EU-Herceptin. No additional peptides or missing peptides were detected among the three products.

Further primary structure analysis

Additional assessments of primary structure, including molecular mass determination for the intact antibody and an evaluation under reducing conditions where the heavy chains (HC) and light chains (LC) of each molecule were assessed separately, were conducted for each product. The data show similar observed masses for MYL-1401O, US-Herceptin, and EU-Herceptin under reducing and non-reducing conditions, and the measured masses correlated with the expected molecular masses.

Trastuzumab has 16 disulfide bonds, including 12 intra-chain and 4 inter-chain linkages. Analysis by non-reduced peptide mapping using RP-HPLC-MS showed the presence of the same intra-chain and inter-chain disulfide bonds in all three products. The expected HC to LC inter-chain disulfide bond was not identified in any of the products using this method; however, free cysteine analysis identified no free cysteines in any of the products, indicating that the expected disulfide bonds are fully formed.

Protein Content

US-Herceptin is marketed in a multi-dose vial containing 420 mg of drug product with a protein concentration of 21 mg/ml upon reconstitution. The EU-Herceptin 150 mg presentation also has a reconstituted protein concentration of 21 mg/ml. The data confirm that the reconstituted protein concentrations in the MYL-1401O vials are similar to those of the US-Herceptin and EU-Herceptin vials. The MYL-1401O drug product manufacturing process was designed to match the protein content of US-Herceptin, within reasonable manufacturing tolerances. The recoverable protein amounts (420 mg) in the MYL-1401O and US-Herceptin vials are similar.

Higher Order Structure

The secondary and tertiary structures of the three products were evaluated using far and near UV CD, FTIR, DSC and IF. Proper folding is critical for the effective function and serum half-life of proteins.

Information regarding secondary structure (α-helix, β-sheet and random coil structures) was provided by the far UV CD spectroscopy and FTIR results, and information on tertiary structure was provided by the near UV CD and IF results. All four methods yielded overlapping spectra among the MYL-1401O, US-Herceptin, and EU-Herceptin lots evaluated.

DSC was used to measure the melting temperatures of the protein subunits. Quantitative analysis and representative thermograms demonstrate structural similarity among the three products.

Aggregates and Low Molecular Weight Species

Biopharmaceuticals typically contain low levels of protein aggregates at the time of release, and the levels often increase with the age of the product. They are measured for lot release and as part of long term stability studies, and are controlled by release requirements and expiry periods. Small amounts of aggregation are present in MYL-1401O, US-Herceptin, and EU-Herceptin. Aggregation is typically detected and quantified by SEC-HPLC. The average level of aggregates in US-Herceptin as quantified by the Applicant's SEC-HPLC assay was 0.47%, while the level in MYL-1401O was 0.30% and the level in EU-Herceptin was 0.46%; AUC data support these results. MYL-1401O has marginally lower levels of aggregates compared to US-Herceptin and EU-Herceptin, but the results were within a quality range established based on the US-Herceptin data (mean ± 3sd) or EU-Herceptin data (for the comparison of MYL-1401O to EU-Herceptin). Based on stability data, the difference in the average levels of aggregates is likely to be due to differences in the ages of the lots at the time of analysis. From a quality standpoint, aggregation may have implications for product immunogenicity or potency. Here, the aggregation levels observed and the identified differences do not preclude a demonstration that the products are highly similar and are not expected to have any clinical impact.

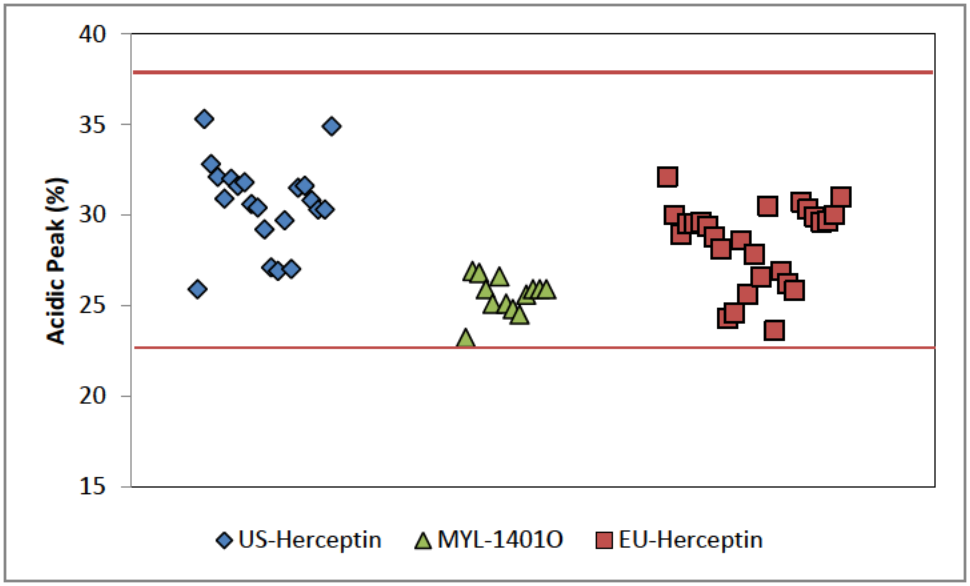
Low molecular weight species (LMWS), such as free HC or LC, incomplete combinations of HC and LC, and proteolyzed species, were evaluated using non-reduced and reduced CE-SDS. MYL-1401O total fragment and monomer levels were within the quality ranges established (mean ± 3sd); however, there were minor differences with respect to individual LMWS. Specifically, for LC, Fab/HC, and 2H1L variants, 8-17% of the MYL-1401O lots (1-2 lots) were outside the quality range established based on the US-Herceptin data. With the exception of the LC, these results met the expectation that 90% of the individual lots are within the quality range; however, for the LC, one of the US-Herceptin lots was also outside its established quality range. The levels of

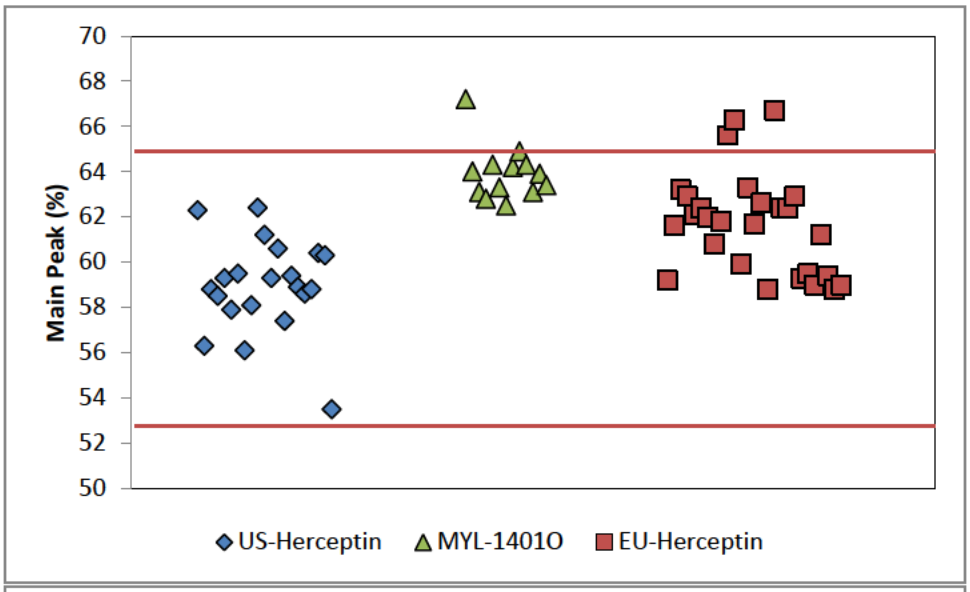
each of these variants were very low (<1% for LC and Fab/HC; <2% for 2H1L), and the differences do not preclude a demonstration that the products are highly similar and are not expected to have clinical impact.

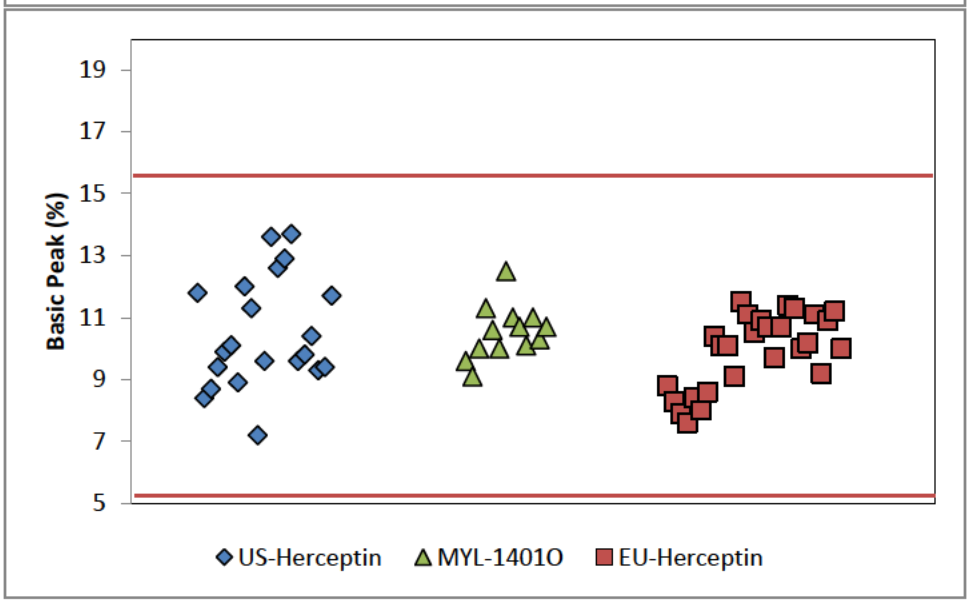
Charge Variants

Charge heterogeneity is commonly observed for monoclonal antibodies. The heterogeneity is derived from product variants that typically include deamidation, glycation, oxidation, heterogeneity of the cleavage of the C-terminal chain, and sialylation. These variants result in a complex charge profile. In cation exchange chromatography (CEX) and capillary isoelectric focusing (cIEF) assays, the charge profiles for MYL-1401O, US-Herceptin, and EU-Herceptin are resolved into three distinct groups: acidic peaks, basic peaks and the main peak. Although the results for most MYL-1401O lots were within the quality range criteria calculated (mean ± 3sd), some differences in the levels of acidic peak group and main peak were observed among the three products. Specifically, MYL-1401O generally had lower levels of acidic peaks and higher levels of main peak with respect to US-Herceptin and EU-Herceptin (Figure 2). No significant differences were observed in the levels of basic peaks among the three products. The quality range criteria developed by the Applicant using US-Herceptin results are depicted by the red lines in Figure 2 and other figures presented below. cIEF analyses also revealed small differences in charge variants.

Figure 2. Comparison of Charge Variant Profile Peak Levels for MYL-1401O, US-Herceptin and EU-Herceptin by CEX







Source: FDA analysis of the Applicant 351(k) BLA submission

To evaluate the nature of the observed differences, the Applicant performed characterization studies. These studies suggest that the difference in the levels of the acidic and main peaks may be due, in part, to differences in deamidation at LC asparagine 30 (Asn30), which is in the complementarity-determining region (CDR). All three molecules exhibited Asn30 deamidation; however, in fractions highly enriched in acidic variants, the cumulative amount of Asn30 deamidation was greater in US-Herceptin and EU-Herceptin lots than in MYL-1401O. However, the highly enriched acidic fractions that contain high levels of deamidated Asn30 were shown to have similar levels of ADCC activity among the products, suggesting that the differences observed in acidic peaks have minimal effect on target binding and, subsequently, potency. The magnitude of the acidic variant differences driven by Asn30 deamidation is not expected to

impact immunogenicity or PK.

A small decrease in the levels of basic peaks and increase in the level of main peak in MYL-1401O lots relative to US-Herceptin and EU-Herceptin may be related to a lower level of C-terminal lysine in MYL-1401O. Differences in C-terminal lysine levels for products administered via intravenous infusion are considered to not have clinical impact, because this amino acid is expected to be cleaved shortly after infusion into patients.

In addition to the minor differences in levels of charge variants, two additional peaks were detected in the MYL-1401O IEC chromatograms; one peak is in the acidic region, and one peak is in the basic region. The characterization data provided indicate that the basic variant is related to oxidation at methionine 255 (Met 255) and that the acidic variant is related to Asn30 deamidation. These peaks are not well resolved but appear to be present at extremely low levels. Given the amounts and nature of these variants (i.e., the identified modifications are not different than those found in US-Herceptin) they are not expected to have clinical impact and do not preclude a determination of highly similar.

Additionally, product variants were evaluated by separation of the molecules using HIC. The HIC analysis showed minor differences among the three products; these differences were similar in magnitude to those identified using IEX-HPLC and cIEF and likely result from the same variants. Oxidation at M255, located in the Fc region of the HC, and glycation were also evaluated, and the data show that MYL-1401O lots were within the range of variability observed in the US-Herceptin and EU-Herceptin lots.

Glycosylation

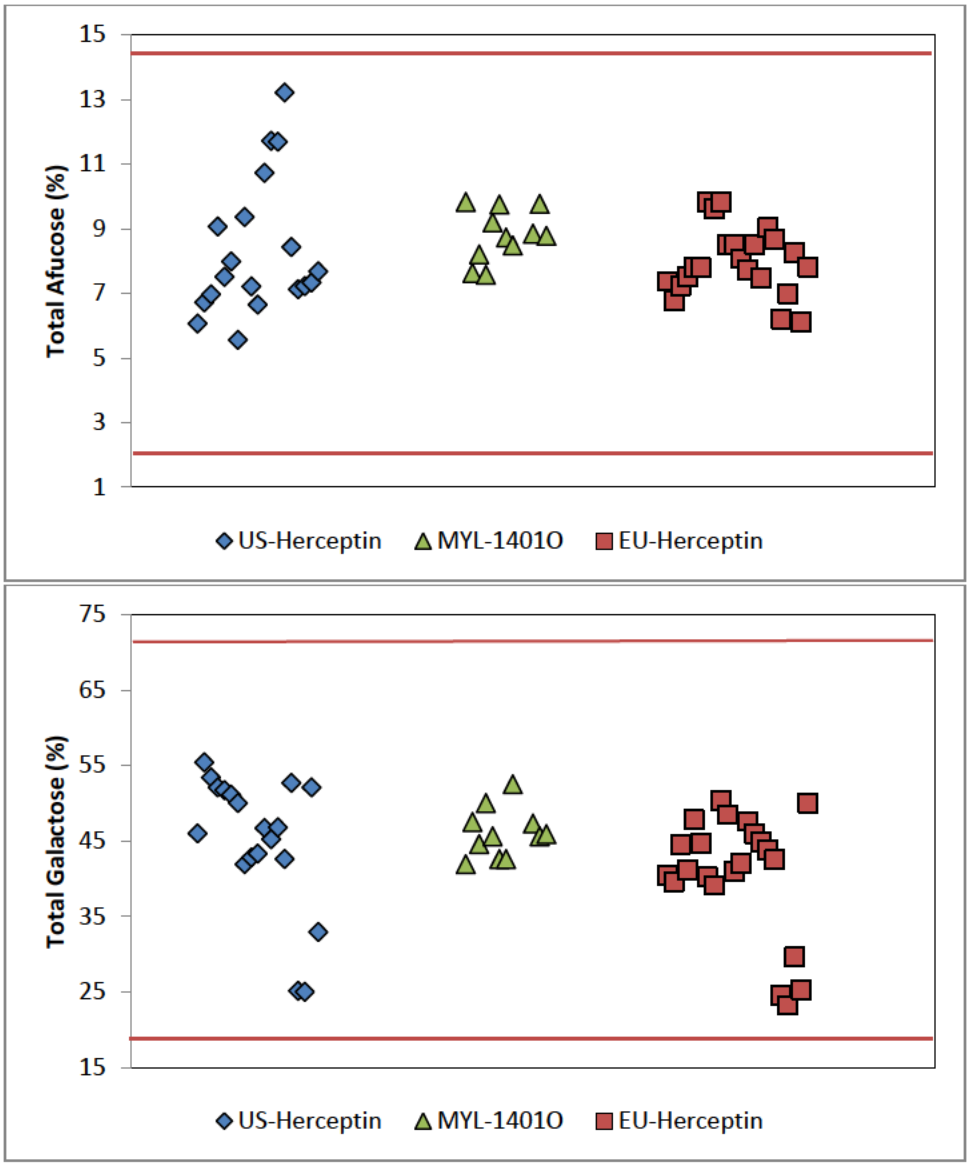
Trastuzumab is a glycoprotein containing one N-glycan in the Fc region of each HC of the molecule. Antibody glycosylation is typically heterogeneous and is variable among antibody products and, to some extent, among lots of a specific product. NP-HPLC, RP-HPLC (with and without MS) and CE-SDS reduced were used to determine the content of various glycoforms. Altogether, 13 N-glycan groups were identified; the most abundant forms were G0F and G1F.

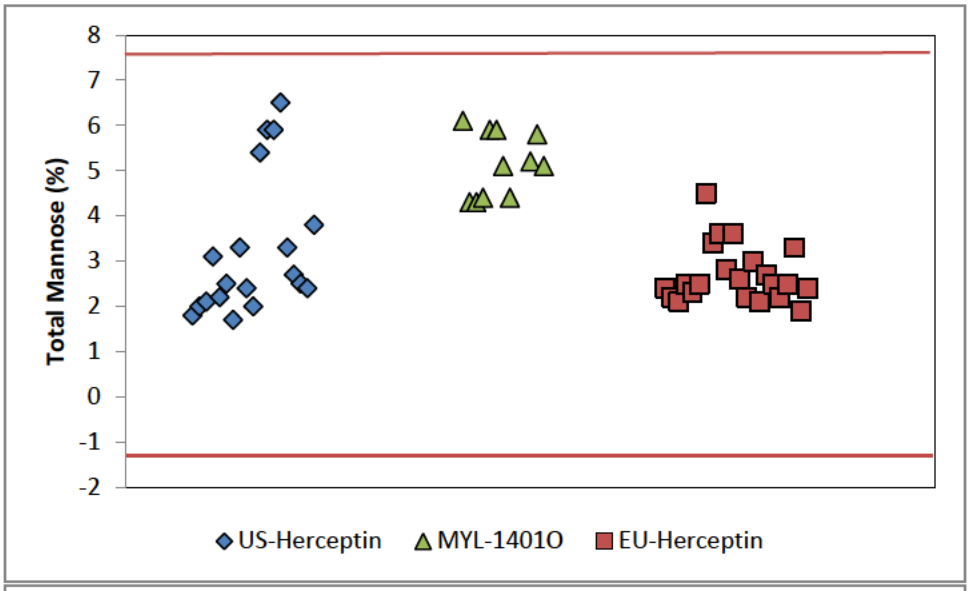
Glycoforms containing fucose at the base of the biantennary structure can influence the Fc three-dimensional structure and lower the binding affinity of the molecule to Fc receptors such as FcγRIIIa. Other differences in glycosylation, such as in levels of high mannose and sialylation, can influence the PK profile of the molecule[10].

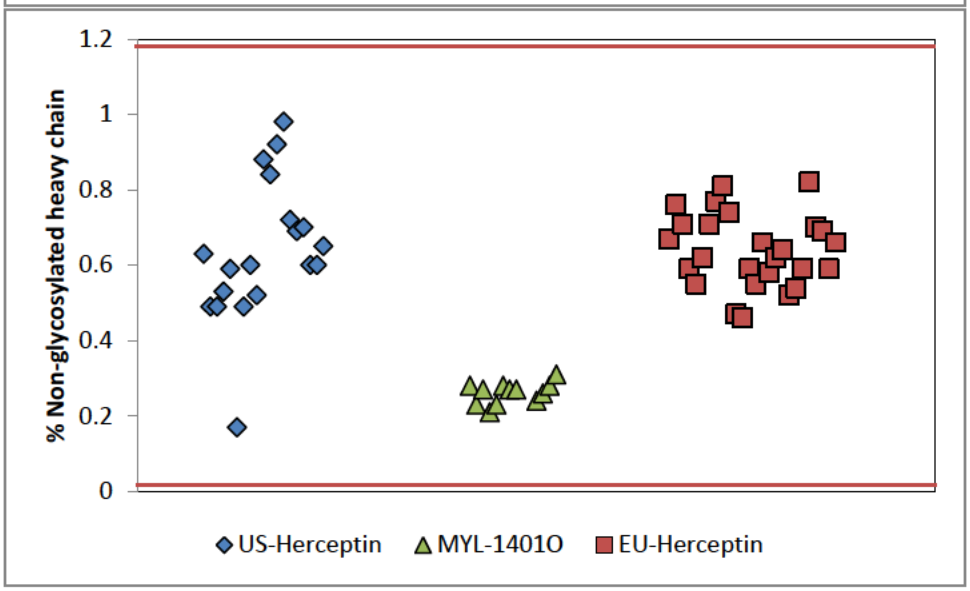
Differences were observed in the amount of various glycoforms present among the three products as shown in Figure 3 below.

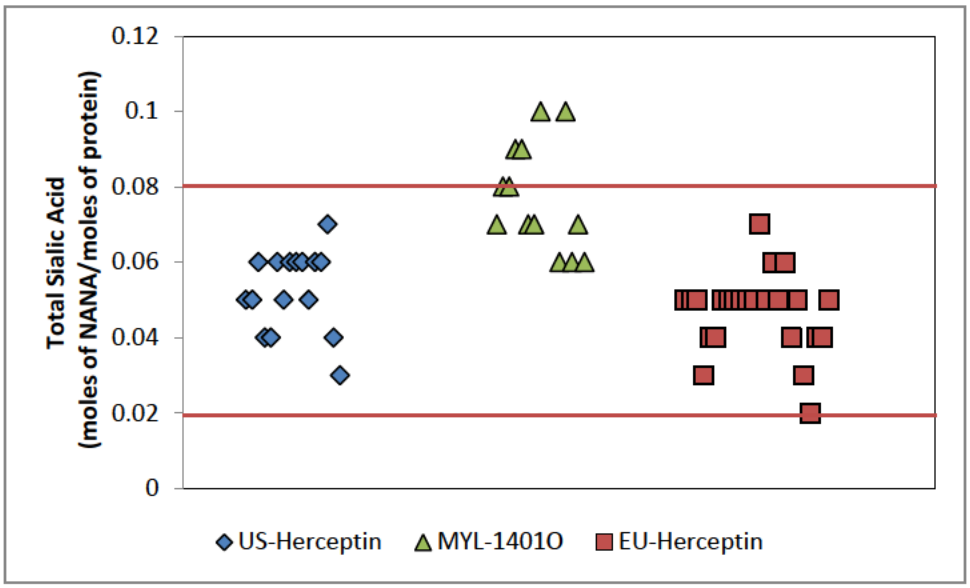
[10] Liu, L. J Pharma Sci. 2015 Jun; 104(6):1866-84.

Figure 3. Comparison of Glycan Profile for MYL-1401O, US-Herceptin and EU-Herceptin




Total Mannose (%)
8
7
6
5
4
3
2
1
0
-1
-2
US-Herceptin
MYL-1401O
EU-Herceptin


% Non-glycosylated heavy chain
1.2
1
0.8
0.6
0.4
0.2
0
US-Herceptin
MYL-1401O
EU-Herceptin



Source: FDA analysis of the Applicant351(k) BLA submission

The Applicant evaluated glycosylation using NP-HPLC and utilized an RP-HPLC-MS method as an orthogonal method for evaluating afucosylation. Total levels of afucosylated isoforms were determined from MYL-1401O, US-Herceptin and EU-trastuzumab lots assessed using NP-HPLC by calculating the sum of glycan structures lacking core fucose, including high mannose glycans (Man 5 and Man 6). The NP-HPLC analysis shows similar afucosylation levels among the three products; the RP-HPLC-MS data support these results.

High mannose and sialylated glycan structures can alter the PK of a molecule through binding to cell surface mannose binding proteins and through reduced FcRn binding, respectively. Differences in the levels of high mannose forms (Man 5 and Man 6) and sialic acid were noted among the products. Specifically, 31% of MYL-1401O lots were outside the sialic acid quality range criteria calculated using the US-Herceptin data (mean ± 3sd), and while the lots were within the quality range criteria, MYL-1401O generally had higher levels of mannose compared to the majority of the US-Herceptin and EU-Herceptin lots. Although there are differences in the sialic acid levels, the levels are extremely low among all three products (no more than 0.10 mol/mol). MYL-1401O lots with minor differences in glycosylation with respect to the US-Herceptin lots were included among those used in clinical studies. Residual uncertainty about biosimilarity that resulted from the differences in high mannose and sialylated glycans is adequately addressed by data that showed no impact of these differences on PK. These differences do not preclude a demonstration that the products are highly similar.

The lack of glycosylation in the Fc region of the HC of an antibody has been correlated with loss of effector function, increased aggregation, and structural changes. MYL-1401O had lower levels of non-glycosylated heavy chain (NG-HC) compared to US-Herceptin and EU-Herceptin. Lower NG-HC is not a concern from the safety perspective, because a lack of glycosylation

correlates with a reduction in Fc receptor binding and effector function. Because effector function is a primary mechanism of action of trastuzumab, the lower levels of NG-HC in MYL-1401O could potentially impact product efficacy. However, the overall levels of NG-HC were very low (<1%) among the three products, and given the ADCC activity and FcγRIIIa binding results discussed below, these differences do not preclude a determination that MYL-1401O and US-Herceptin are highly similar.

Biological Activity

A number of bioassays were designed and qualified to evaluate potential trastuzumab functions including binding of HER2, inhibition of proliferation, and ADCC activity. The data are reported relative to the Applicant's in-house MYL-1401O reference material.

HER2 binding

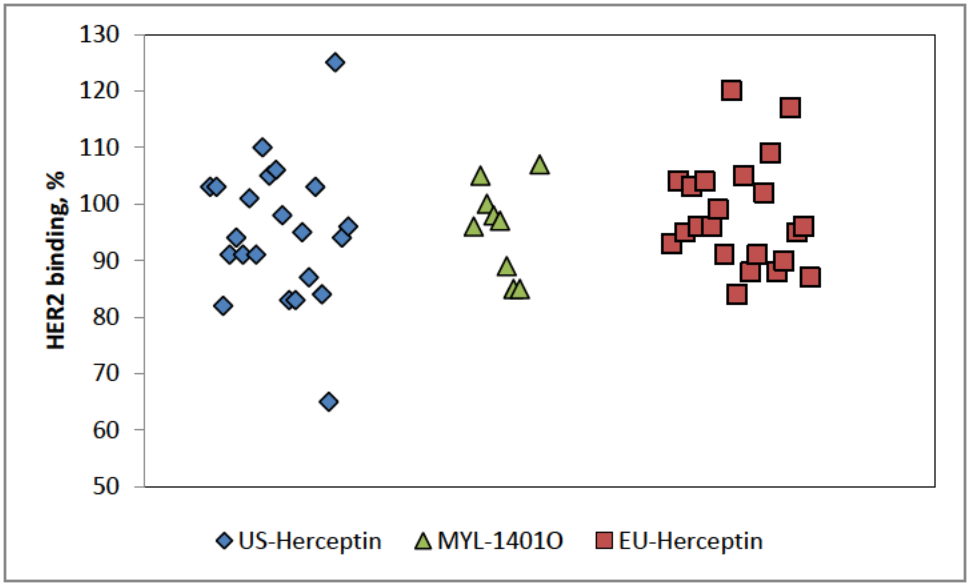
HER2 binding was assessed using a flow cytometry method. SKBR3 cells, which are human breast cancer cells that overexpress HER2, were incubated with increasing concentrations of MYL-1401O, US-Herceptin, or EU-Herceptin. During the incubation the antibody binds to the HER2 expressed on the surface of the breast cancer cells. The bound antibodies are detected using fluorescently tagged secondary antibody that specifically recognizes the Fc region of the trastuzumab molecule and can be quantified by flow cytometry. A comparison of the relative HER2 binding of MYL-1401O, US-Herceptin, and EU-Herceptin was carried out with 9 to 22 lots of each product (Table 2 and Figure 4). Because of the criticality of the HER2 binding attribute, these data were subjected to a statistical analysis using equivalence testing. The HER2 binding activity of MYL-1401O would be considered statistically equivalent to the HER2 binding activity of US-Herceptin if the 90% confidence interval (CI) of the mean difference in HER2 binding between MYL-1401O and US-Herceptin is entirely within the equivalence acceptance criterion calculated using the Applicant's US-Herceptin HER2 binding data. Similarly, the binding activity of MYL-1401O was compared to an equivalence acceptance criterion calculated using the EU-Herceptin data, and the binding activity of EU-Herceptin was compared to an equivalence acceptance criterion calculated using the US-Herceptin data. Equivalence testing results for the HER2 binding data for MYL-1401O, US-Herceptin, and EU-Herceptin are shown in Table 3.

Table 2. Descriptive Statistics for the HER2 Binding Data

Product	Number of batches	Sample mean, %	Sample standard deviation, %	Min, %	Max, %
MYL-1401O	9	96	8.0	85	107
US-Herceptin	22	95	12.0	65	125
EU-Herceptin	22	98	9.0	84	120

Source: FDA analysis of data from the Applicant 351(k) BLA submission

Figure 4. Comparative Potency (Flow Cytometry) of MYL-1401O, US-Herceptin and EU-Herceptin to Human HER2



Source: FDA analysis of data from the Applicant 351(k) BLA submission

Table 3. Equivalence Testing Results for the HER2 Binding

Comparison	# of lots	Mean difference	90% CI for mean difference	Equivalence margin	Equivalent
MYL-1401O vs. US	(9, 22)	0.008	(-0.065, 0.081)	(-0.184, 0.184)	Yes
MYL-1401O vs. EU	(9, 22)	-0.021	(-0.084, 0.043)	(-0.141, 0.141)	Yes
EU vs. US	(22, 22)	0.029	(-0.027, 0.084)	(-0.184, 0.184)	Yes

Source: FDA analysis of data from the Applicant 351(k) BLA submission

The statistical equivalence analyses shown in Table 3 support the conclusion that MYL-1401O is highly similar to US-Herceptin. Further, these analyses support the analytical component of the scientific bridge among US-Herceptin, EU-Herceptin, and MYL-1401O to justify the relevance of

comparative data generated from clinical and nonclinical studies that used EU-Herceptin.

Inhibition of proliferation

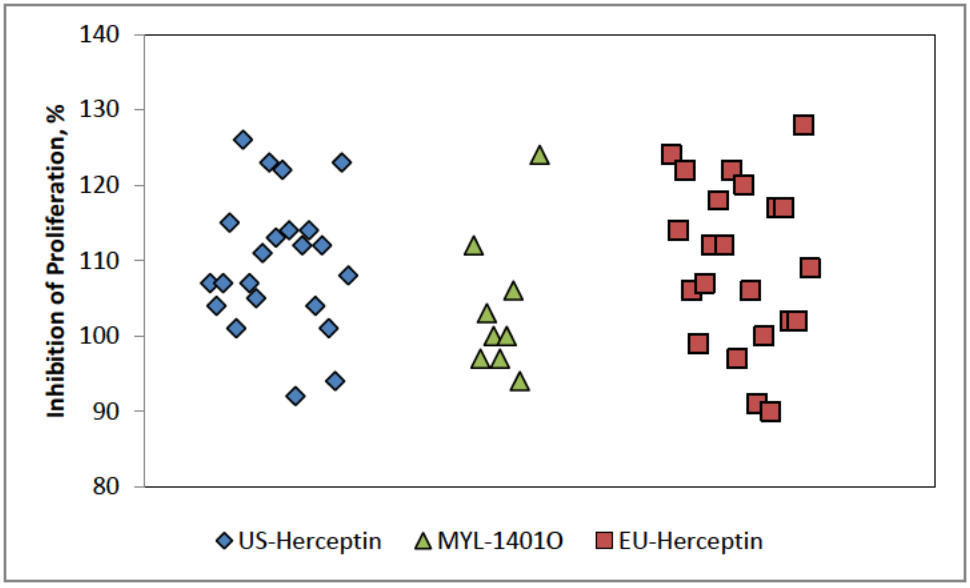
One mechanism of action of trastuzumab is the inhibition of proliferation of HER2 expressing cells. This mechanism of action was evaluated using an in vitro inhibition of proliferation bioassay employing SKBR3 cells. This assay measures the ability of trastuzumab to inhibit cell proliferation based on the metabolic activity of the cells before and after treatment with the antibody. Potency is quantified using a fluorescent detection reagent. A comparison of the relative potency of MYL-1401O, US-Herceptin, and EU-Herceptin was carried out with 9 to 22 lots of each product (Table 4 and Figure 5). Because of the criticality of this attribute, these data were subjected to a statistical analysis using equivalence testing. The MYL-1401O capacity for inhibition of proliferation (potency) would be considered statistically equivalent to the potency of US-Herceptin if the 90% CI of the mean difference in potency between MYL-1401O and US-Herceptin is entirely within the equivalence acceptance criterion calculated from the Applicant's US-Herceptin inhibition of proliferation data. Similar analyses were performed for the other pairwise comparisons. Equivalence testing results for the MYL-1401O, US-Herceptin, and data are shown in Table 5.

Table 4. Descriptive Statistics for the Inhibition of Proliferation Data

Product	Number of batches	Sample mean, %	Sample standard deviation, %	Min, %	Max, %
MYL-1401O	9	104	9.0	94	124
US-Herceptin	22	110	9.0	92	126
EU-Herceptin	22	110	11.0	90	128

Source: FDA analysis of data from the Applicant 351(k) BLA submission

Figure 5. Comparative Potency (Inhibition of Proliferation) of MYL-1401O, US-Herceptin and EU-Herceptin



Source: FDA analysis of data from the Applicant 351(k) BLA submission

Table 5. Equivalence Testing Results for the Inhibition of Proliferation

Comparison	# of lots	Mean difference	90% CI for mean difference	Equivalence margin	Equivalent
MYL-1401O vs. US	(9, 22)*	-0.061	(-0.130, 0.007)	(-0.134, 0.134)	Yes
MYL-1401O vs. EU	(9, 22)*	-0.061	(-0.134, 0.012)	(-0.161, 0.161)	Yes
EU vs. US	(22, 22)	0.000	(-0.050, 0.050)	(-0.134, 0.134)	Yes

Source: FDA analysis of data from the Applicant 351(k) BLA submission
* The 90% CI is adjusted for the sample size imbalance.

The statistical equivalence analyses shown in Table 5 support the conclusion that MYL-1401O is highly similar to US-Herceptin. Further, these analyses support the analytical component of the

scientific bridge among US-Herceptin, EU-Herceptin, and MYL-1401O to justify the relevance of comparative data generated from clinical and nonclinical studies that used EU-Herceptin.

ADCC

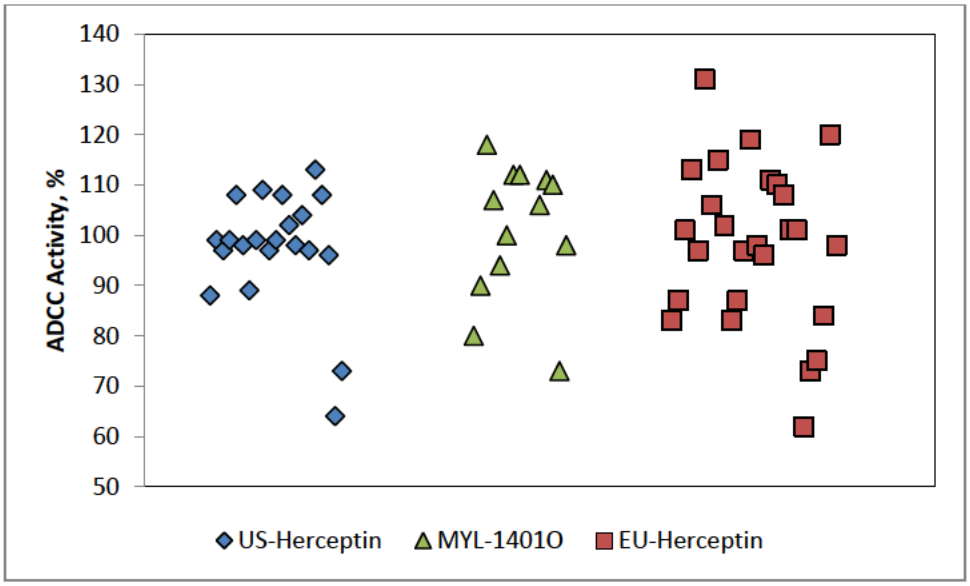
ADCC was assessed using SKBR3 HER2 overexpressing cells as target cells and peripheral blood mononuclear cells (PBMC) as effector cells. SKBR3 cells were pre-incubated with serial dilutions of antibody followed by incubation with PBMCs. The addition of MYL-1401O, US-Herceptin and EU-Herceptin to the cell culture will induce ADCC activity, which is measured by release of proteases that are quantified using a luminescent detection reagent. A comparison of the relative ADCC activity of MYL-1401O, US-Herceptin, and EU-Herceptin was carried out with 13 to 26 lots of each product (Table 6 and Figure 6). Because of the criticality of this attribute, these data were subjected to a statistical analysis using equivalence testing. The ADCC activity of MYL-1401O would be considered statistically equivalent to the ADCC activity of US-Herceptin if the 90% CI of the mean difference in activity between MYL-1401O and US-Herceptin is entirely within the equivalence acceptance criterion calculated from the Applicant's US-Herceptin data. Similar analyses were performed for the other pairwise comparisons. Equivalence testing results for the MYL-1401O, US-Herceptin, and EU-Herceptin ADCC data are shown in Table 7.

Table 6. Descriptive Statistics for the ADCC Data

Product	Number of batches	Sample mean, %	Sample standard deviation, %	Min, %	Max, %
MYL-1401O	13	101	13.0	73	118
US-Herceptin	21	97	12.0	64	113
EU-Herceptin	26	98	16.0	73	131

Source: FDA analysis of data from the Applicant 351(k) BLA submission

Figure 6. Comparative Potency by ADCC of MYL-1401O, US-Herceptin and EU-Herceptin



Source: FDA analysis of data from the Applicant 351(k) BLA submission

Table 7. Equivalence Testing Results for ADCC activity

Comparison	# of lots	Mean difference	90% CI for mean difference	Equivalence margin	Equivalent
MYL-1401O vs. US	(13, 21)*	0.035	(-0.043, 0.113)	(-0.173, 0.173)	Yes
MYL-1401O vs. EU	(13, 26)*	0.025	(-0.012, 0.090)	(-0.240, 0.240)	Yes
EU vs. US	(26, 21)	0.010	(-0.058, 0.078)	(-0.173, 0.173)	Yes

Source: FDA analysis of data from the Applicant 351(k) BLA submission
* The 90% CI is adjusted for the sample size imbalance.

The statistical equivalence analyses shown in Table 7 support the conclusion that MYL-1401O is highly similar to US-Herceptin. Further, these analyses support the analytical component of the scientific bridge among US-Herceptin, EU-Herceptin, and MYL-1401O to justify the relevance of comparative data generated from clinical and nonclinical studies that used EU-Herceptin.

Fc Function

Complement dependent cytotoxicity (CDC) activity

The Fc region of an antibody HC contains amino acid residues that can interact with complement C1q to mediate CDC. In CDC, the complement system is activated when C1q interacts with antibodies bound to cell surface targets, which initiates a biological cascade that ultimately results in pore formation in the target cell membrane. CDC is not currently understood to be a mechanism of action of trastuzumab; however, a comparison of C1q binding and CDC activity was performed based on the capacity of IgG1 molecules to perform this function. The C1q binding activity of MYL-1401O, US-Herceptin, and EU-Herceptin was evaluated using an enzyme-linked immunosorbent assay (ELISA). The relative binding activities were similar among the three products. CDC activity was evaluated using an in vitro assay in which SKBR3 cells were incubated with increasing concentrations of MYL-1401O, US-Herceptin, or EU-Herceptin in the presence or absence of human plasma as a source of complement. CDC activity was measured using a fluorescent marker sensitive to the presence of cell death components released upon cell lysis. No difference in CDC activity of MYL-1401O, US-Herceptin and EU-Herceptin was observed.

Binding to Fc Receptors

The Fc receptors, FcγRI, FcγRII, FcγRIII and FcRn, are diverse in structure and cell type expression. The predominant Fc receptor type on NK cells is FcγRIII (a or b forms), while other leukocytes express a broader range of Fc receptors. FcγRI and FcγRII isoforms may contribute to effector function, depending on the effector cell type at the site of disease. The neonatal Fc receptor, FcRn, plays an important role in IgG homeostasis, by binding the Fc region in a pH dependent manner and protecting the molecule from lysosomal degradation, thus prolonging the half-life of the molecule. Therefore, binding to both Fcγ receptors and FcRn was assessed using surface plasmon resonance (SPR)-based assays. Small differences were noted in the binding kinetics of MYL-1401O, US-Herceptin, and EU-Herceptin to FcγRIa, FcγRIIa, FcγRIIb/c, FcγRIIIa V158, FcγRIIIb and FcRn. SPR-based assays generally have relatively high amounts of variability. Residual uncertainty about biosimilarity that resulted from the differences in binding kinetics is adequately addressed by data that showed no impact of these differences on ADCC and PK. The differences in Fc receptor binding among MYL-1401O, US-Herceptin, and EU-Herceptin were determined not to preclude a demonstration that MYL-1401O and US-Herceptin are highly similar.

Comparative Stability Studies

The Applicant evaluated the stability of MYL-1401O, US-Herceptin, and EU-Herceptin in several

studies, including evaluations of thermal stability at 25°C for 6 months and at 40°C for 3 months and forced degradation studies using exposure to light, low and high pH, and oxidizing conditions. The products were evaluated both as a lyophilized powder and following reconstitution. Accumulation of high and low molecular weight species (SEC-HPLC and CE-SDS reducing and non-reducing), changes in charge variants (CEX-HPLC), loss of function (HER2 binding and/or FcγRIIIa binding), conformational changes (CD and IF), and protein concentration (UV detection) were evaluated. The stability patterns of the three products were similar in all studies.

Conclusions on Analytical Similarity Assessment

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 residual uncertainties related to the increases in total mannose forms and sialic acid and decreases in NG-HC were addressed by the ADCC similarity and by the PK similarity between MYL-1401O and US-Herceptin as discussed in the section on Clinical Pharmacology below. 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.

5. PHARMACOLOGY/TOXICOLOGY

Executive Summary

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.

Conclusion

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.

6. CLINICAL PHARMACOLOGY

Executive Summary

The objectives of the clinical pharmacology program are to evaluate the pharmacokinetic 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 pharmacokinetic (PK) similarities of MYL-1401O, EU-Herceptin and US-Herceptin.

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. Additional considerations on the use of data generated using non-US-approved comparator product are provided in section 2, (under "The Reference Product") above.

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.

Description of Clinical Pharmacology Study

The PK of MYL-1401O following IV administration has been characterized in a study using US-Herceptin and EU-Herceptin as the comparator products. A summary of the pivotal PK study, including PK endpoints is provided below.

MYL-HER-1002 was a single-dose, randomized, double-blind, 3-arm, parallel-group study designed to compare the pharmacokinetic profiles of MYL-1401O (n = 42), US-Herceptin (n = 37) and EU-Herceptin (n = 41) administered as a single 8 mg/kg intravenous infusion over 90 minutes to healthy male volunteers (N=120). The pre-defined PK endpoints were $AUC_{0-\infty}$, AUC_{0-t}, and C_{Max}.

Based on the Guidance for Industry entitled, "Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product," a single-dose, parallel group design is appropriate for trastuzumab because the product has a long half-life (ranging from 2 to 12 days) and avoids repeated exposures that can lead to an increased immune response and affect the PK similarity assessments. A study in healthy subjects is considered safe and more sensitive compared with that in patients with potentially confounding factors such as underlying disease, concomitant medications, and other factors. Lastly, the selected dose of 8 mg/kg is clinically meaningful and based on an approved dose for trastuzumab.

Results of Clinical Pharmacology Study

Study MYL-HER-1002 Pharmacokinetic Results

In Study MYL-HER-1002, the 90% CIs for the ratios of the geometric mean of $AUC_{0-\infty}$, AUC_{0-t} and C_{Max} in pairwise comparisons between MYL-1401O, US-Herceptin and EU-Herceptin were within the pre-specified limits of 80% to 125% for PK similarity, as summarized in Table 8 and depicted

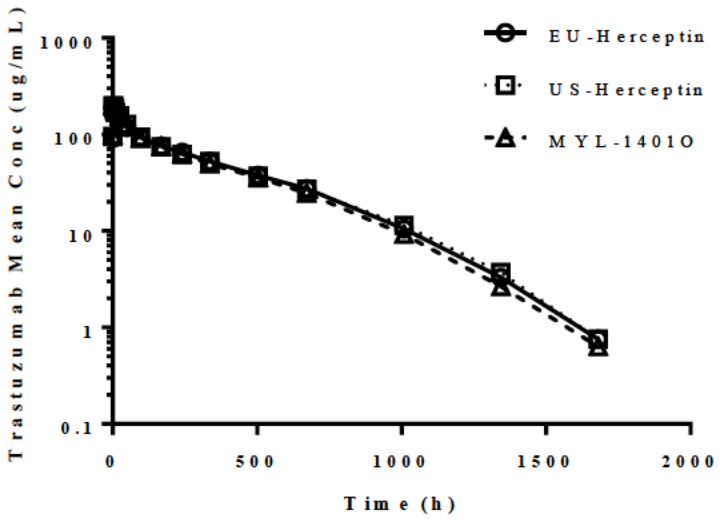
in Figure 7. These data establish the PK similarity between MYL-1401O and US-Herceptin. The data also establish the PK component of the scientific bridge to justify the relevance of the comparative clinical data generated using EU-Herceptin (Study MYL-HER-3001) to support a demonstration of the biosimilarity of MYL-1401O to US-Herceptin.

Table 8. Statistical analyses of PK parameters in Study MYL-HER-1002

Comparison	Geometric Mean Ratio (90% CI)		
	C_{Max}	AUC_{0-t}	AUC_{0-Inf}
US-Herceptin vs MYL-1401O	101.1 (95.8-106.4)	95.7 (89.7-101.8)	95.2 (89.3-101.5)
EU-Herceptin vs MYL-1401O	104.0 (98.8-109.4)	96.7 (90.9-102.9)	96.6 (90.7-102.8)
US-Herceptin vs EU-Herceptin	97.1 (92.2-102.4)	98.9 (92.7-105.3)	98.5 (92.4-105.1)

Source: FDA analysis of data from MYL-1401O 351(k) BLA submission

Figure 7. PK profiles following a single 8 mg/kg IV dose of MYL-1401O, US-Herceptin or EU-Herceptin in healthy subjects in Study MYL-HER-1002



Source: FDA analysis of data from MYL-1401O 351(k) BLA submission

Clinical Pharmacology Summary

Overall, 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.

7. IMMUNOGENICITY

Executive Summary

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. Therefore, the data indicates that there is no increase in immunogenicity risk for MYL-1401O as compared to EU-Herceptin, which supports the demonstration of no clinically meaningful differences to US-Herceptin.

Discussion

Background. Immune responses against therapeutic biological products can negatively impact the safety, efficacy, and pharmacokinetics of the product. Often, immune responses to therapeutic biologics are measurable in the form of anti-drug antibodies (ADA) that can be detected in serum following exposure to the drug. Therefore, immunogenicity assessment for therapeutic biological products focuses on measuring ADA. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of ADA positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of ADA in the studies described below with the incidence of ADA in other studies or to other products may be misleading.

The Applicant established an adequate bridge between MYL-1401O, EU-Herceptin and US-Herceptin, to justify the relevance of immunogenicity data obtained using EU-Herceptin to support a demonstration of no clinically meaningful differences between MYL-1401O and US-Herceptin.

Methods. The development of anti-drug antibodies was monitored in study MYL-HER-3001 a multiple-dose, parallel arm design clinical study that allowed for a comparative assessment of immunogenicity between MYL-1401O and EU-Herceptin. The study design, patient population, treatment, and immunogenicity sampling schedule of the study is summarized in Table 9.

Table 9. Immunogenicity sampling in Study for MYL-1401O

Study ID	Design	Route	Number	Population	Dose/ Schedule	Sampling
MYL-HER-3001	Parallel	Intravenous	MYL-1401O (N=247) EU-Herceptin (N=246)	Metastatic Breast Cancer	Loading dose: 8 mg/kg; Maintenance Dose: 6 mg/kg every three weeks	Pre-dose weeks 0 (baseline), 6, 12, 18, 24, 36, and 48

Source: Summary based on information from the Applicant 351(k) BLA submission

Serum samples were tested for ADA using a tiered strategy as recommended by FDA (Guidance for Industry: Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products. CDER, CBER, and CDRH. April 2016). A screening assay was used to test all samples. Samples deemed positive in the screening assay were then tested in a confirmatory assay to confirm that the binding was specific for the product. FDA determined that based on the Applicant's ADA assessment, including the specific assay capabilities for detection of ADA, the results observed from Study MYL-HER-3001, and what is publicly known about the incidence and nature of both ADA and neutralizing ADA to trastuzumab, that an evaluation of neutralizing ADA was not necessary to further inform on the immunogenicity assessment of MYL-1401O.

Results. The results of the multiple-dose, parallel-arm comparative clinical study MYL-HER-3001 are summarized in Table 10.

Table 10. Immunogenicity results for Study MYL-HER-3001

Product	N	Treatment-induced ADA
MYL-1401O	222	3.2%
EU-Herceptin	210	3.3%

Source: FDA analysis of data from the Applicant 351(k) BLA submission

There was no impact of immunogenicity on PK parameters from Study MYL-HER-3001 (data not shown).

Immunogenicity Conclusion

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.

8. CLINICAL OUTCOMES

Executive Summary

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 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.

Discussion

Study Description

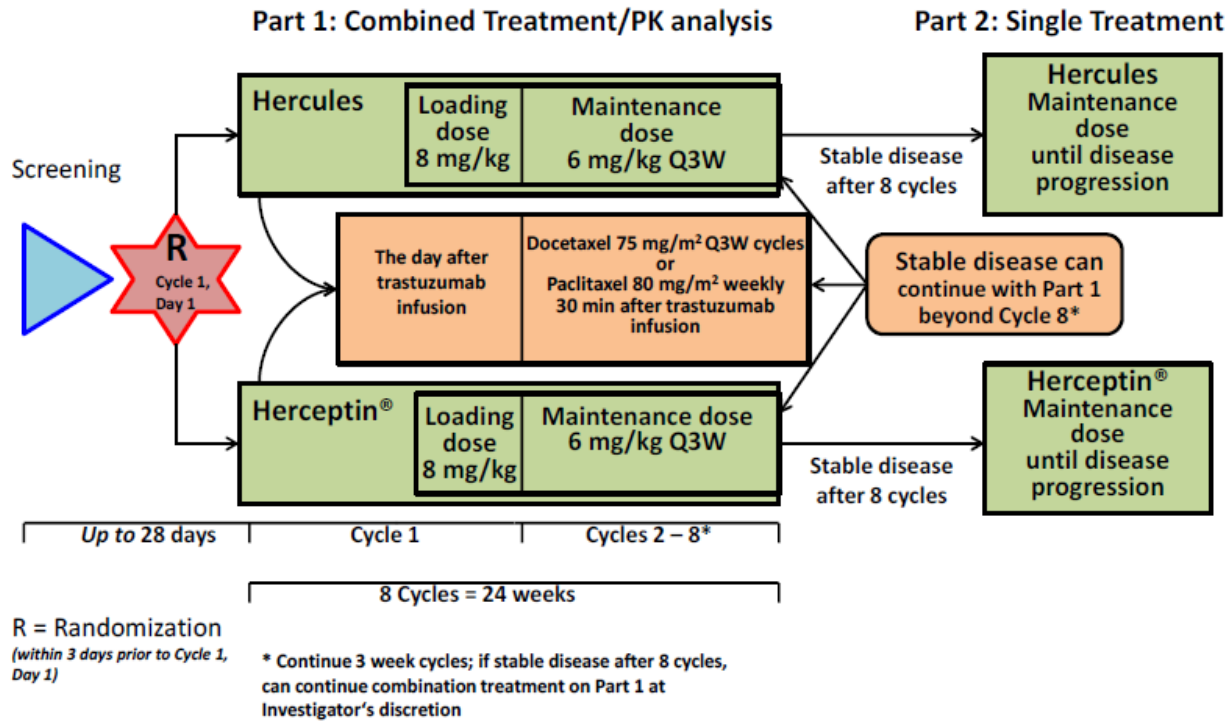
The Applicant submitted data from one clinical study which assessed the efficacy and safety of MYL-1401O compared to EU-Herceptin: Study MYL-Her-3001. This was a two-part, multicenter, double-blind, randomized, parallel-group study. Untreated HER2-positive MBC patients were randomized 1:1 to either MYL-1401O 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 $\geq$ 2 years), ER/PR status (positive or negative), and type of taxane received (paclitaxel or docetaxel).

Part 1: MYL-1401O or EU-Herceptin plus a taxane were administered for a minimum of 8 cycles.

Part 2: Patients with at least stable disease in Part 1 were allowed to continue with single agent MYL-1401O or EU-Herceptin.

Patients continued on treatment until disease progression or toxicity.

Figure 8. MYL-Her-3001 Study Schema



Source: Study protocol Figure 1

8.1. Analysis of Clinical Efficacy

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.

Sample size determination

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).

Selection of Equivalence Margin

The equivalence margin was derived using a fixed-effect meta-analysis of data from three randomized trials comparing taxane and trastuzumab combination versus taxane alone.[11] [12] [13] To be consistent with the current study population, only the IHC3+ and/or FISH positive patient populations were included in the conducted meta-analysis. The treatment effect of trastuzumab in each historical study and the results of the meta-analysis are summarized in Table 11. From the meta-analysis, the estimated treatment effect (ORR ratio, trastuzumab + taxane vs. taxane) and its 95% CI was 1.92 (1.54, 2.39). To maintain 50% of the treatment effect (i.e., the lower bound of the 95% CI: 1.54), the equivalence region was calculated to be from 0.81 to 1.24.

Table 11. Meta-Analysis Results based on Data from 3 Randomized Trials

Trial[a]	Trastuzumab + Taxane ORR (n/N)	Taxane ORR (n/N)	ORR Ratio[b] (95% CI)
Gasparini[12]	85% (33/39)	48% (20/42)	1.78 (1.26, 2.51)
Marty[11]	61% (56/92)	34% (32/94)	1.79 (1.29, 2.48)
Slamon[13]	49% (33/68)	17% (13/77)	2.87 (1.65, 5.00)
Meta-Analysis (Fixed-effect model)	--	--	1.92 (1.54, 2.39)

[a] IHC3+ and/or FISH positive patients from 3 randomized trials
[b] ORR Ratio: ORR of (Trastuzumab + Taxane) / ORR of Taxane
n/N= number of responders/number of total patients in the treatment arm
Source: Study SAP Appendix A Table 1

Analysis Populations

The following are the definitions for the analysis populations.

- Intent-to-treat (ITT) 1 population: patients randomized into the study under Protocol Amendment 2 (first line treatment for MBC only) and beyond. The primary efficacy analysis was conducted in ITT1.
- ITT2 population: all patients randomized on to study.
- Per Protocol (PP) population: a subset of patients in the ITT1 population who met the following criteria:
    - Received the treatment to which they were randomized,
    - The absence of any major protocol violations in Part 1 which precluded the evaluation of the patient

[11] Marty. et al. J Clin Oncol., 2005, 4265-74.
[12] Gasparini. et al. Breast Cancer Res Treat., 2007, Vol.101, 355-365.
[13] Slamon. et al. N Engl J Med., 2001, 783-92.

- Had at least 1 post-baseline tumor assessment if a progression disease; and at least 2 if CR, PR, or SD,
- Had received at least 2 complete cycles of treatment; however, if a progression, death, or discontinuation occurred before the end of the first 2 cycles, the patient was retained in the PP population.

Statistical Analysis for Primary Endpoints

The primary objective of the study was to support that there are no clinical differences between MYL-1401O compared to EU-Herceptin based on ORR at Week 24 (Part 1).

Missing Data Handling Strategies

For the analysis of the primary endpoint, ORR, if a patient qualified for inclusion into an efficacy analysis population (i.e., ITT1, ITT2, and PP) but had no post-randomization centrally reviewed evaluation, the patient was categorized as a non-responder.

Efficacy Analysis Results

The ITT1 population consisted of a total of 458 patients (230 in the MYL-1401O arm and 228 in the Herceptin arm) who were randomized into the study under Protocol Amendment 2 and beyond. Nineteen patients (7 in the MYL-1401O arm and 12 patients in the EU-Herceptin arm) of the ITT1 population were not included in the PP population per the pre-specified criteria. The ITT2 population included all 500 patients randomized on to the study (249 in the MYL-1401O arm and 251 in the EU-Herceptin arm).

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 (Table 12). 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.

Table 12. ORR per Central Review at Week 24, ITT1 Population

	MYL-1401O + Taxane (N=230)	EU-Herceptin + Taxane (N=228)
Complete response (CR), n (%)	4 (2)	0
Partial response (PR), n (%)	157 (68)	146 (64)
Stable disease (SD), n (%)	48 (21)	49 (21)
Progressive disease (PD), n (%)	9 (4)	20 (9)
N/A, n (%)	12 (5)	13 (6)
Overall response rate, n (%)	161 (70%)	146 (64%)
Ratio of ORR (MYL-1401O vs. EU-Herceptin)	1.09	
90% CI	(0.98, 1.22)	

Source: FDA analysis of data from the Applicant 351(k) BLA submission

A supportive analysis of ORR was performed in the PP population. In the PP population, the ORR was 71% and 67% in the MYL-1401O and the EU-Herceptin arm, respectively. The ratio of ORR was 1.06 (90% CI: 0.96, 1.18). Similar results were observed in the ITT2 population.

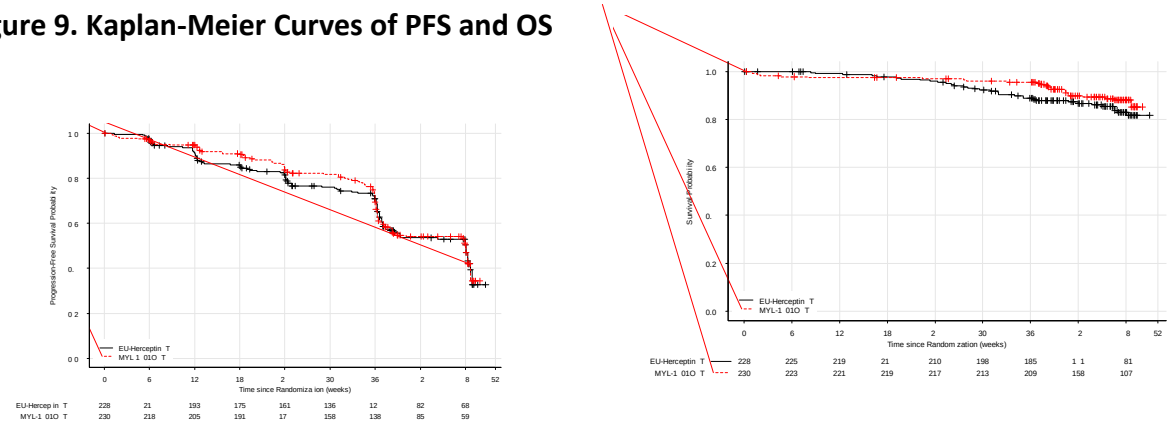
Results of PFS per central review and OS at Week 48 in the ITT1 population are summarized in Table 13. Figure 9 shows Kaplan-Meier curves for PFS and OS.

Table 13. Results of PFS per Central Review and OS at Week 48, ITT1 Population

	MYL-1401O + Taxane (N=230)	EU-Herceptin + Taxane (N=228)
PFS per central review		
Number of PFS events	102 (44%)	102 (45%)
Median (95% CI), months	11.1 (8.8, 11.2)	11.1 (8.6, 11.2)
Unstratified HR (95% CI)	0.97 (0.74, 1.28)	
Stratified HR (95% CI)*	0.95 (0.71, 1.25)	
OS		
Number of deaths	25 (11%)	34 (15%)
Median (95% CI), months	NR	NR
Unstratified HR (95% CI)	0.67 (0.40, 1.13)	
Stratified HR (95% CI)*	0.61 (0.36, 1.04)	

*Stratified by assigned taxane, time of tumor progression to metastatic disease from primary diagnosis, and tumor endocrine status. Eighteen patients with one or more stratification factor data missing in CRFs were not included in the stratified analysis.
NR=Not Reached
Source: FDA analysis of data from the Applicant 351(k) BLA submission

Figure 9. Kaplan-Meier Curves of PFS and OS



PFS OS

Source: FDA analysis of data from the Applicant 351(k) BLA submission

8.2. Analysis of Clinical Safety

Methods

The safety population in the randomized comparative clinical study consisted of all patients (n=493) who received at least one dose of study drug. The safety assessments presented below are from Parts 1 and 2 of the study.

Results

An overview of the frequency of treatment-emergent adverse events (TEAEs) is shown in Table 14 for MYL-Her-3001. There were more patients with treatment-related TEAEs who received MYL-1401O compared to EU-Herceptin.

Table 14. Frequency of treatment-emergent adverse events (TEAEs) in MYL-Her-3001

MEDRA Term	MYL-1401O N=247 N (%)	EU-Herceptin N=246 N (%)
Patients with all grade TEAEs	241 (97.6)	239 (97.2)
Patients with Grade ≥3 TEAEs	161 (65.2)	162 (65.2)
Patients with serious TEAEs	97 (39.3)	91 (37.0)
Patients with treatment-related TEAEs	103 (41.7)	88 (35.8)
Patients with TEAEs leading to withdrawal from study	9 (3.6)	9 (3.7)

Source: FDA analysis of data from the Applicant 351(k) BLA submission

Common treatment-emergent adverse events seen in ≥5% of patients in any group are shown in Table 15 below.

Table 15. Frequency of common treatment-emergent adverse events (≥5% in any group) in MYL-Her-3001

MEDRA Term	MYL-1401O N=247 N (%)	EU-Herceptin N=246 N (%)	TOTAL N=493 N (%)
Anaemia	41 (16.6)	44 (17.9)	85 (17.2)
Leukopenia	43 (17.4)	53 (21.5)	96 (19.5)
Neutropenia	142 (57.5)	133 (54.1)	275 (55.8)
Diarrhoea	52 (21.1)	51 (20.7)	103 (20.9)
Nausea	51 (20.6)	38 (15.4)	89 (18.1)
Vomiting	27 (10.9)	24 (9.8)	51 (10.3)
Asthenia	56 (22.7)	41 (16.7)	97 (19.7)
Fatigue	30 (12.1)	37 (15.0)	67 (13.6)
Oedema peripheral	38 (15.4)	31 (12.6)	69 (14.0)
Peripheral swelling	11 (4.5)	13 (5.3)	24 (4.9)
Pyrexia	24 (9.7)	33 (13.4)	57 (11.6)
Upper respiratory tract infection	18 (7.3)	5 (2.0)	23 (4.7)
Urinary tract infection	24 (9.7)	18 (7.3)	42 (8.5)
Infusion related reaction	17 (6.9)	12 (4.9)	29 (5.9)
Alanine aminotransferase increased	22 (8.9)	22 (8.9)	44 (8.9)
Aspartate aminotransferase increased	16 (6.5)	24 (9.8)	40 (8.1)
Decreased appetite	22 (8.9)	25 (10.2)	47 (9.5)
Hyperglycaemia	15 (6.1)	19 (7.7)	34 (6.9)
Arthralgia	33 (13.4)	14 (5.7)	47 (9.5)
Bone pain	21 (8.5)	14 (5.7)	35 (7.1)
Myalgia	25 (10.1)	23 (9.3)	48 (9.7)
Headache	24 (9.7)	29 (11.8)	53 (10.8)
Neuropathy peripheral	31 (12.6)	30 (12.2)	61 (12.4)
Peripheral sensory neuropathy	32 (13.0)	36 (14.6)	68 (13.8)
Cough	19 (7.7)	18 (7.3)	37 (7.5)
Dyspnoea	16 (6.5)	18 (7.3)	34 (6.9)
Alopecia	143 (57.9)	135 (54.9)	278 (56.4)
Nail disorder	17 (6.9)	22 (8.9)	39 (7.9)
Rash	22 (8.9)	25 (10.2)	47 (9.5)

Source: FDA analysis of data from the Applicant 351(k) BLA submission

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. Events in these categories are shown in Tables 16 and 17 below. There were no reports of embryo-fetal

toxicity in MYL-Her-3001.

Table 16. Cardiac treatment-emergent adverse events (TEAEs) of special interest in MYL-Her-3001

MEDRA Term	MYL-1401O N=247 N (%)			EU-Herceptin N=246 N (%)		
	Total	Resolved	Grade ≥3	Total	Resolved	Grade ≥3
Cardiac failure[a,b]	6 (2.4)	3 (1.2)	3	2 (0.8)	2 (0.8)	0
Cardiomyopathy	1 (0.4)	1 (0.4)	0	1 (0.4)	0 (0.0)	0
Cardiotoxicity	2 (0.8)	2 (0.8)	0	0 (0.0)	0 (0.0)	0
Carditis	1 (0.4)	0 (0.0)	1	0 (0.0)	0 (0.0	0
Congestive cardiomyopathy	0 (0.0)	0 (0.0)	0	1 (0.4)	1 (0.4)	0
Left ventricular dysfunction	2 (0.8)	2 (0.8)	2	4 (1.6)	3 (1.2)	1
Left ventricular failure	0 (0.0)	0 (0.0)	0	1 (0.4)	0 (0.0)	0
Metabolic cardiomyopathy[a]	1 (0.4)	0 (0.0)	0	3 (1.2)	1 (0.4)	0
Ejection fraction decreased[a, c]	16 (6.5)	12 (4.9)	1	8 (3.3)	5 (2.0)	1
Myocardial fibrosis	1 (0.4)	0 (0.0)	0	0 (0.0)	0 (0.0)	0

Source: FDA analysis of data from the Applicant 351(k) BLA submission

[a] Eight patients (6 MYL-1401O and 2 EU-Herceptin) had ejection fraction decreased on more than one occasion. One patient who received MYL-1401O experienced both cardiac failure and metabolic cardiomyopathy.

[b] Of the three patients who received MYL-1401O and experienced grade ≥3 cardiac failure, 2 had resolution of their adverse event. One patient died from cardiac and respiratory failure with admission lower extremity ultrasound showing right femoral popliteal vein thrombosis.

[c] The patient who received MYL-1401O had resolution of their adverse event. The adverse event outcome of patient who received EU-Herceptin is unknown.

Table 17. Pulmonary and infusion reaction treatment-emergent adverse events of special interest in MYL-Her-3001

MEDRA Term	MYL-1401O N=247 N (%)	EU-Herceptin N=246 N (%)
Anaphylactic reaction	2 (0.8)	0 (0.0)
Drug hypersensitivity	1 (0.4)	1 (0.4)
Hypersensitivity	5 (2.0)	7 (2.8)
Infusion related reaction	17 (6.9)	12 (4.9)
Pneumonitis	4 (1.6)	2 (0.8)
Pulmonary fibrosis	1 (0.4)	0 (0.0)

Source: FDA analysis of data from the Applicant 351(k) BLA submission

The number of deaths in each treatment group is shown in Table 18 below.

Table 18. Treatment-Emergent Deaths in MYL-Her-3001

	MYL-1401O N=247	EU-Herceptin N=246	
	Docetaxel (%)	Docetaxel (%)	Paclitaxel (%)
Total Deaths	6 (2.4)	3 (1.2)	1 (0.4)

Source: FDA analysis of data from the Applicant 351(k) BLA submission

Two additional patients died in Part 1 of the study. Patient 190841 received MYL-1401O plus paclitaxel and per investigator died of disease progression. Patient 131328 received EU-Herceptin plus docetaxel and per investigator died of disease progression.

Conclusion

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.

9. CONSIDERATIONS FOR EXTRAPOLATION OF BIOSIMILARITY

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.

FDA has determined that it may be appropriate for a biosimilar product to be licensed for one or more conditions of use (e.g., indications) for which the reference product is licensed, based on data supporting a demonstration of biosimilarity, including data from clinical studies performed for another condition of use. This concept is known as extrapolation. As described in the Guidance for Industry: "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009", if a biological product meets the statutory requirements for licensure as a biosimilar product under section 351(k) of the PHS Act based on, among other things, data derived from a clinical study or studies sufficient to demonstrate safety, purity, and potency in an appropriate condition of use, the potential exists for that product to be licensed for one or more additional conditions of use for which the reference product is licensed. The Applicant needs to provide sufficient scientific justification for extrapolation, which should address, for example, the following issues for the tested and extrapolated conditions of use:

- The mechanism(s) of action (MOA), if known or can reasonably be determined, in each condition of use for which licensure is sought,
- The pharmacokinetics (PK) and bio-distribution of the product in different patient populations,
- The immunogenicity of the product in different patient populations,
- Differences in expected toxicities in each condition of use and patient population,
- Any other factor that may affect the safety or efficacy of the product in each condition of use and patient population for which licensure is sought.

As a scientific matter, the FDA has determined that differences between conditions of use with respect to the factors addressed in a scientific justification for extrapolation do not necessarily preclude extrapolation.

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

- The mechanism of action (MOA) of trastuzumab on human tumor cells that overexpress HER2 includes inhibition of proliferation and antibody-dependent cellular cytotoxicity (ADCC). 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 (PK) 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. 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.

In aggregate, the evidence indicates that the extrapolation of biosimilarity to the indications for which the Applicant is seeking licensure is scientifically justified.

10. SUMMARY

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 scientific bridge between EU-Herceptin, US-Herceptin, and MYL-1401O was established, supporting 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 results of the pharmacokinetic similarity study support a demonstration of no clinically meaningful differences between MYL-1401O and US-Herceptin.

Anti-drug antibodies were measured in 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. 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.

In considering the totality of the evidence and the established scientific bridge between EU-Herceptin, MYL-1401O, and US-Herceptin, 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 the safety, purity, and potency of the product.

FDA requests discussion at the Oncologic Drugs Advisory Committee meeting to obtain feedback and insights on whether the totality of evidence presented supports licensure of MYL-1401O as a biosimilar to US-Herceptin. This determination requires the following criteria to be

met:

- MYL-1401O is highly similar to US-Herceptin, notwithstanding minor differences in clinically inactive components, and
- There are no clinically meaningful differences between MYL-1401O and US-Herceptin.